Seventh Edition

Kendig's Disorders of the Respiratory Tract in Children

Chernick
Boat
Wilmott
Bush

SAUNDERS
ELSEVIER

SAUNDERS
ELSEVIER

1600 John F. Kennedy Boulevard
Suite 1800
Philadelphia, PA 19103-2899

KENDIG'S DISORDERS OF THE RESPIRATORY TRACT IN CHILDREN
ISBN-13: 978-0-7216-3695-5
ISBN-10: 0-7216-3695-0

First Edition 1967. Second Edition 1972. Third Edition 1977. Fourth Edition 1983.
Fifth Edition 1990. Sixth Edition 1998.

Library of Congress Cataloging-in-Publication Data

Kendig's disorders of the respiratory tract in children/[edited by] Victor Chernick ...
[et al.].—7th ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 0-7216-3695-0
1. Pediatric respiratory diseases. I. Title: Disorders of the respiratory tract in children.
II. Chernick, Victor. III. Kendig, Edwin L., 1911–2003
[DNLM: 1. Respiratory Tract Diseases—Child. 2. Respiratory Tract Diseases—Infant.
WS 280 K331 2006]
RJ431.K42 2006
618.92′2—dc22 2005056103

Acquisitions Editor: *Todd Hummel*
Senior Developmental Editor: *Kim J. Davis*
Senior Project Manager: *Joan Sinclair*
Design Direction: *Ellen Zanolle*

Printed in the United States of America.

Last digit is the print number: 9 8 7 6 5 4 3 2 1

Dedication

The seventh edition of this book is dedicated to Dr. Edwin Lawrence Kendig, Jr., who died suddenly on February 18, 2003. It was his vision that resulted in the publication of the first edition nearly 40 years ago.

Born in 1911 in Victoria, Virginia, he graduated from the Hampden-Sydney College in 1932, where he was awarded the Gammon Cup for character, scholarship, and athletics. In 1936 he graduated from the University of Virginia School of Medicine, after which he trained in pediatrics at Bellevue Hospital (New York), Johns Hopkins Hospital (Baltimore), and Babies Hospital (Wrightsville Beach, North Carolina).

Dr. Kendig then settled in Richmond, Virginia, where he enjoyed a long and distinguished academic career with a special interest in childhood tuberculosis and sarcoidosis. He had the foresight to realize the unique nature of, and the need for research in, the field of pulmonary disease in children. In addition to his work on this book, renamed *Kendig's Disorders of the Respiratory Tract in Children* beginning with the fifth edition, Dr. Kendig contributed to academic pediatrics at the local, national, and international levels. Indeed, his name became synonymous with the subspecialty of pediatric pulmonology.

A retired professor of pediatrics at the Virginia Commonwealth University's Medical College of Virginia Hospitals, Dr. Kendig was also past president of the Virginia State Board of Medicine, the Virginia Pediatric Society, the Richmond Academy of Medicine, and the American Academy of Pediatrics. For two decades, he served as an official examiner for the American Board of Pediatrics, where he spent 13 years lobbying for the creation of a sub-board of pediatric pulmonology finally instituted in 1986.

Internationally, Dr. Kendig was well known not only for his work on this text but also for his many years of service as a member of the standing committee of the International Pediatric Association. During his career, Dr. Kendig was honored with many tributes, including the Abraham Jacobi Award from the American Academy of Pediatrics and the Distinguished Service Award from the American Medical Association. In 2003 the Medical College of Virginia created the Edwin Lawrence Kendig, Jr., Professorship for Pediatric Pulmonary Diseases.

This textbook is Dr. Kendig's legacy to the subspecialty of pediatric pulmonology. We will miss his wise counsel and his dedication to excellence.

Victor Chernick

Thomas F. Boat

Robert W. Wilmott

Andrew Bush

Contributors

Robin Michael Abel, BSc, MBBS, PhD, FRCS (Eng Paeds)
Consultant Paediatric and Neonatal Surgeon, Hammersmith Hospital, London, United Kingdom
Congenital Lung Disease

Steven H. Abman, MD
Professor, Department of Pediatrics, University of Colorado School of Medicine; Director, Pediatric Lung Center, The Children's Hospital, Denver, Colorado
Bronchopulmonary Dysplasia

Mutasim N. Abu-Hasan, MD
Assistant Professor of Clinical Pediatrics, Pediatric Allergy and Pulmonary Division, Pediatrics, University of Iowa College of Medicine, Iowa City, Iowa
Asthma in the Preschool Child

Najma N. Ahmed, MD, MSc, FRCPC
Assistant Professor, Department of Pediatrics, IWK Health Centre, Halifax, Nova Scotia, Canada
Nonpulmonary Manifestations of Cystic Fibrosis

Daniel R. Ambruso, MD
Professor, Department of Pediatrics, University of Colorado School of Medicine; Pediatric Hematologist, Departments of Pediatric Hematology, Oncology, and Bone Marrow Transplantation, The Children's Hospital; Associate Medical Director and Director of Research, Bonfils Blood Center, Denver, Colorado
Chronic Granulomatous Disease of Childhood

Raouf S. Amin, MD
Professor of Pediatrics, Department of Pediatrics, University of Cincinnati College of Medicine; Professor of Pediatrics, Department of Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Chronic Respiratory Failure; Hypersensitivity Pneumonitis and Eosinophilic Pulmonary Diseases

Robert J. Arceci, MD, PhD
Director and King Fahd Professor of Pediatric Oncology, Department of Oncology, Johns Hopkins University, Baltimore, Maryland
Histiocytic Disorders of the Lung

M. Innes Asher, MD, ONZM, BSc, MBChB, FRACP
Chair in Pediatrics and Head of Department, Department of Pediatrics, Faculty of Medical and Health Sciences, University of Auckland; Paediatric Respiratory Specialist, Respiratory Department, Starship Children's Health, Auckland District Health Board, Auckland, New Zealand
Epidemiology of Asthma

Ian M. Balfour-Lynn, BSc, MD, MBBS, FRCP, FRCPCH, FRCS (Ed), DHMSA
Consultant in Paediatric Respiratory Medicine, Department of Paediatrics, Royal Brompton Hospital, London, United Kingdom
Acute Infections Producing Upper Airway Obstruction

Peter J. Barnes, DM, DSc, FRCP
Professor and Head of Respiratory Medicine, National Heart and Lung Institute, Imperial College; Honorary Consultant Physician, Royal Brompton Hospital, London, United Kingdom
Biology and Assessment of Airway Inflammation

Robyn J. Barst, MD
Professor of Pediatrics, Department of Pediatric Cardiology, Columbia University College of Physicians and Surgeons; Attending Pediatrician, Department of Pediatric Cardiology, Morgan Stanley Children's Hospital of New York Presbyterian Medical Center; Director, Pulmonary Hypertension Center, New York Presbyterian Medical Center, New York, New York
Childhood Pulmonary Arterial Hypertension

Leslie L. Barton, MD
Professor of Pediatrics and Director of Pediatric Residency Program, Department of Pediatrics, University of Arizona School of Medicine; University of Arizona Health Sciences Center; Department of Pediatrics, Tuscon, Arizona
Atypical Pneumonias in Children

Pierre-Yves Berclaz, MD, PhD
Assistant Professor, Division of Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Rare Childhood Lung Disorders: α_1-Antitrypsin Deficiency, Pulmonary Alveolar Proteinosis, and Pulmonary Alveolar Microlithiasis

Thomas F. Boat, MD
Professor and Chair, Department of Pediatrics, University of Cincinnati College of Medicine; Director, Cincinnati Children's Research Foundation; Physician-in-Chief, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Pulmonary Hemorrhage and Hemoptysis

Itzhak Brook, MD, MSc
Professor of Pediatrics, Georgetown University School of Medicine, Washington, D.C.
Lung Abscess and Pulmonary Infections Due to Anaerobic Bacteria

James W. Brooks, MD
Emeritus Professor of Surgery, Cardiothoracic Division, Virginia Commonwealth University Health System/Medical College of Virginia; Medical College of Virginia Hospital, Richmond, Virginia
Tumors of the Chest; Disorders of the Respiratory Tract Due to Trauma

Andrew Bush, MB, BS (Hons), MA, MD, FRCP, FRCPCH
Professor of Paediatric Respirology, Department of Paediatric Respiratory Medicine, Imperial College at National Heart and Lung Institute; Consultant Paediatric Chest Physician, Department of Paediatrics, Royal Brompton Hospital, London, United Kingdom
Congenital Lung Disease

Michael R. Bye, MD
Professor of Clinical Pediatrics, Department of Pediatrics, Columbia University; Acting Director, Pediatric Pulmonary Medicine, Department of Pediatrics, Pulmonary Medicine Section, Morgan Stanley Children's Hospital of New York Presbyterian, New York, New York
Lung Injury from Hydrocarbon Aspiration and Smoke Inhalation

Emmanuel Canet, MD, PhD
Director, Research Institute, Servier, Suresnes, France
Chest Wall Function and Dysfunction

Todd C. Carpenter, MD
Associate Professor of Pediatrics, Division of Pediatric Critical Care Medicine, University of Colorado Health Sciences Center; The Children's Hospital, Department of Pediatrics, Denver, Colorado
Acute Respiratory Failure

Robert G. Castile, MD, MS
Professor of Pediatrics, College of Medicine and Public Health, The Ohio State University; Staff Physician, Department of Pediatrics, Children's Hospital, Columbus, Ohio
Pulmonary Function Testing in Children

Anne B. Chang, MBBS, FRACP, MPHTM, PhD
Associate Professor, Department of Paediatrics and Child Health, University of Queensland; Doctor of Respiratory Medicine, Royal Children's Hospital, Brisbane, Queensland, Australia
Bronchiectasis

Victor Chernick, MD, FRCPC
Professor Emeritus, Department of Pediatrics, University of Manitoba; Active Staff, Children's Hospital of Winnipeg, Winnipeg, Manitoba, Canada
The Functional Basis of Respiratory Disease; Pneumonia Secondary to Varicella and Measles

Lyn S. Chitty, PhD, MRCOG
Senior Lecturer, Department of Clinical and Molecular Genetics, Institute of Child Health; Fetal Medicine Unit, Elizabeth Garrett Anderson and Obstetric Hospital, UCLH, London, United Kingdom
Congenital Lung Disease

Allan L. Coates, MDCM
Professor, Departments of Paediatrics and Physiology, University of Toronto; Division of Respiratory Medicine, Department of Paediatrics, Hospital for Sick Children, Toronto, Ontario, Canada
Drug Administration by Aerosol in Children

Giuseppe N. Colasurdo, MD
Associate Professor and Head, Division of Pediatric Pulmonary and Critical Care Medicine, The University of Texas Health Science Center; Director, Respiratory Science Center, Memorial Hermann Children's Hospital, Houston, Texas
Lung Defenses: Intrinsic, Innate, and Adaptive

Misty Colvin, MD, FAAP
Clinical Lecturer of General Pediatrics, Department of Pediatrics, University of Arizona; Director, Pediatric Urgent Care, Department of Urgent Care, Northwest Hospital, Tuscon, Arizona
Atypical Pneumonias in Children

Dan M. Cooper, MD
Professor, Departments of Pediatrics and Bioengineering; GCRC Satellite Director, University of California, Irvine; Professor, Department of Pediatrics, UCI Medical Center; Professor, Department of Pediatrics, Children's Hospital of Orange County, Orange, California; Professor, Department of Pediatrics, Miller's Children's Hospital, Long Beach, California
Pulmonary Function Assessment in the Laboratory during Exercise

Jonathan Corren, MD
Associate Clinical Professor of Medicine, University of California, Los Angeles; Medical Director, Allergy Research Foundation, Los Angeles, California
The Influence of Upper Airway Disease on the Lower Airway

Robin T. Cotton, MD
Professor, Department of Otolaryngology, University of Cincinnati College of Medicine; Director, Department of Pediatric Oncology–Head and Neck Surgery, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Foreign Body Aspiration

James E. Crowe, Jr., MD
Professor, Departments of Pediatrics and Microbiology and Immunology; Director, Vanderbilt Vaccine Center, Vanderbilt University Medical Center, Nashville, Tennessee
Viral Pneumonia

Garry R. Cutting, MD
Professor of Pediatrics and Medicine, Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland
Genetics and Pathophysiology of Cystic Fibrosis

Cori Daines, MD
Assistant Professor of Pediatrics, University of Cincinnati College of Medicine; Assistant Professor of Pediatrics, Department of Pediatric Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Bronchoscopy and Bronchoalveolar Lavage in Pediatric Patients

Jane C. Davies, MD, MBChB, MRCPCH
Senior Lecturer, Department of Gene Therapy, Imperial College; Honorary Consultant in Paediatric Respiratory Medicine, Royal Brompton Hospital, London, United Kingdom
Acute Infections Producing Upper Airway Obstruction

Jonathan M. Davis, MD
Professor of Pediatrics, Department of Pediatrics, SUNY Stony Brook School of Medicine, Stony Brook, New York; Director of Neonatology; Director, CardioPulmonary Research Institute, Winthrop University Hospital, Mineola, New York
Bronchopulmonary Dysplasia

Pamela B. Davis, MD, PhD
Arline H. and Curtis L. Garvin Research Professor, Department of Pediatrics, Case Western Reserve University School of Medicine; Director, Pediatric Pulmonary Division, Department of Pediatrics, Rainbow Babies and Children's Hospital, Cleveland, Ohio
Pulmonary Disease in Cystic Fibrosis

Robert Dinwiddie, FRCPCH
Honorary Senior Lecturer, Portex Unit, The Institute of Child Health, University of London; Honorary Consultant Paediatrician, Respiratory Unit, Great Ormond Street Hospital for Children, London, United Kingdom
Familial Dysautonomia

Emily L. Dobyns, MD
Associate Professor, Department of Pediatrics, Section of Critical Care Medicine, University of Colorado; Medical Director, PICU, The Children's Hospital/University of Colorado, Denver, Colorado
Acute Respiratory Failure

Michelle Duggan, MB, FFARCSI
Clinical Fellow, Department of Anesthesia, The Hospital for Sick Children, Toronto, Ontario, Canada
Atelectasis

Peter R. Durie, MD, FRCP(C), BSc
Professor, Department of Pediatrics, Faculty of Medicine, University of Toronto; Senior Scientist, Department of Integrative Biology, Research Institute, The Hospital for Sick Children; Staff Physician, Division of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children, Toronto, Ontario, Canada
Nonpulmonary Manifestations of Cystic Fibrosis

Anthony G. Durmowicz, MD
Medical Officer, Division of Pulmonary and Allergy Products, Center for Drug Evaluation and Research, Federal Drug Administration, Silver Spring, Maryland
Acute Respiratory Failure

Joanne Embree, MD, FRCPC
Professor and Head, Department of Medical Microbiology, University of Manitoba; Professor and Section Head, Department of Pediatric Infectious Disease, Children's Hospital/Health Sciences Centre, Winnipeg, Manitoba, Canada
Pneumonia Secondary to Varicella and Measles

Leland L. Fan, MD
Professor of Pediatrics, Pulmonary Section, Department of Pediatrics, Baylor College of Medicine; Texas Children's Hospital, Houston, Texas
Interstitial Lung Disease

Philip M. Farrell, MD, PhD
Dean and Vice Chancellor for Medical Affairs, University of Wisconsin Medical School; Robert Turell Professor in Medical Leadership, Department of Pediatrics, University of Wisconsin Hospital and Clinics, Madison, Wisconsin
Neonatal Screening for Cystic Fibrosis

David Gozal, MD
Children's Foundation Chair of Pediatric Research, Professor of Pediatrics, Pharmacology and Toxicology, Psychology and Brain Sciences, Kosair Children's Hospital Research Institute, Department of Pediatrics, University of Louisville; Director, Sleep Medicine and Apnea Center, Kosair Children's Hospital, Louisville, Kentucky
Disorders of Breathing during Sleep

Cameron Grant, MBChB, FRACP, PhD
Associate Professor, Department of Pediatrics, University of Auckland; Consultant Pediatrician, Department of General Pediatrics, Starship Children's Hospital, Auckland District Health Board, Auckland, New Zealand
Epidemiology of Asthma

Anne Greenough, MD, FRCP, FRCPCH
Professor, Division of Asthma, Allergy, and Lung Biology, King's College; Honorary Consultant Paediatrician, Department of Child Health, King's College Hospital, London, United Kingdom
Respiratory Disorders in the Newborn

Jürg Hammer, MD
Associate Professor of Pediatrics, Division of Intensive Care and Pulmonology, University Children's Hospital Basel, Basel, Switzerland
Near-Drowning and Drowning

Jonny Harcourt, FRCS
Consultant ENT Surgeon, Department of Paediatric ENT, Chelsea and Westminster Hospital; Consultant ENT Surgeon, ENT Department, Royal Brompton Hospital, London, United Kingdom
Congenital Lung Disease

Ulrich Heininger, MD
Professor and Doctor of Medicine, Medical School, University of Basel; Professor and Doctor of Medicine, Department of Pediatric Infectious Diseases and Vaccinology, University Children's Hospital, Basel, Switzerland
Pertussis and Other Bordetella *Infections of the Respiratory Tract*

Marianna M. Henry, MD, MPH
Associate Professor of Pediatrics, Department of Pediatrics, University of North Carolina at Chapel Hill; North Carolina Children's Hospital, University of North Carolina Hospitals, Chapel Hill, North Carolina
Sarcoidosis; Lung Injury Caused by Pharmacologic Agents

Peter W. Heymann, MD
Professor of Pediatrics; Head, Division of Pediatric Respiratory Medicine, Department of Pediatrics, University of Virginia, Charlottesville, Virginia
Immunopathogenesis of Asthma

Ellis K.L. Hon, MBBS, FAAP, FHKCP, FHKAM (Paed)
Associate Professor, Department of Pediatrics, The Chinese University of Hong Kong; Honorary Associate Consultant, Department of Pediatrics, NTEC, Prince of Wales Hospital, Hong Kong
Pediatric Severe Acute Respiratory Syndrome

Alan H. Jobe, MD, PhD
Professor of Pediatrics, University of Cincinnati College of Medicine; Professor of Pediatrics, Department of Neonatology/Pulmonary Biology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
The Surfactant System

Richard B. Johnston, Jr., MD
Professor of Pediatrics and Associate Dean for Research Development, University of Colorado School of Medicine; Executive Vice President for Academic Affairs, National Jewish Medical and Research Center, Denver, Colorado
Chronic Granulomatous Disease of Childhood

Sebastian L. Johnston, MD, PhD, FRCP
Professor of Respiratory Medicine, Department of Respiratory Medicine, National Heart and Lung Institute, Imperial College London; Honorary Consultant Physician, Chest and Allergy Clinic, St. Mary's NHS Trust, London, United Kingdom
Diagnosis of Viral Respiratory Illness: Practical Applications

Meyer Kattan, MD, CM
Professor, Department of Pediatrics, Mount Sinai School of Medicine; Chief, Pediatric Pulmonary and Critical Care, Department of Pediatrics, Mount Sinai Medical Center, New York, New York
Respiratory Disorders in Pediatric HIV Infection

Brian P. Kavanagh, MB, BSc, MRCP(I), FRCP(C)
Associate Professor, Departments of Anesthesia, Medicine, and Physiology, University of Toronto; Dr. Geoffrey Barker Chair in Critical Care Medicine, Staff Physician, and Director of Research, Department of Critical Care Medicine, Scientist, Research Institute, Hospital for Sick Children, Toronto, Ontario, Canada
Atelectasis

James S. Kemp, MD
Associate Professor, Pulmonary Division, Department of Pediatrics, St. Louis University School of Medicine; Medical Director, Respiratory Care and Sleep Clinic, Cardinal Glennon Children's Hospital, St. Louis, Missouri
Sudden Infant Death Syndrome and Acute Life-Threatening Events

Carolyn M. Kercsmar, MD
Professor, Department of Pediatrics, Case Western Reserve Medical School; Director, Asthma Center, Department of Pediatrics, Rainbow Babies and Children's Hospital, Cleveland, Ohio
Wheezing in Older Children: Asthma

Leila Kheirandish, MD
Senior Clinical and Research Post-doctoral Fellow, Division of Pediatric Sleep Medicine, Department of Pediatrics, University of Louisville, Louisville, Kentucky
Disorders of Breathing during Sleep

Jennifer Knight-Madden, MBBS, FRCP(C)
Lecturer, Sickle Cell Unit, Tropical Medicine Research Institute, University of the West Indies; Honorary Consultant, Department of Obstetrics, Gynaecology, and Child Health, University Hospital of the West Indies, Kingston, Jamaica
The Lung in Sickle Cell Disease

Alan P. Knutsen, MD
Professor and Director of Pediatric Allergy and Immunology, Department of Pediatrics, Division of Allergy and Immunology, St. Louis University, St. Louis, Missouri
Hypersensitivity Pneumonitis and Eosinophilic Pulmonary Diseases

Thomas M. Krummel, MD, FACS, FAAP
Emile Holman Professor and Chair, Department of Surgery, Stanford University School of Medicine; Professor of Surgery, Department of Surgery, Stanford Hospital and Clinics; Susan B. Ford Surgeon-in-Chief, Department of Pediatric Surgery, Lucile Packard Children's Hospital, Palo Alto, California
Tumors of the Chest; Disorders of the Respiratory Tract Due to Trauma

Claire Langston, MD
Professor, Departments of Pathology and Pediatrics, Baylor College of Medicine; Department of Pathology, Texas Children's Hospital, Houston, Texas
Interstitial Lung Disease

Ada S. Lee, MD
Assistant Professor of Pediatrics, Department of Pediatrics, Columbia University College of Physicians and Surgeons; Assistant Attending Physician, Department of Pediatrics, The Morgan Stanley Children's Hospital of New York–Presbyterian, New York, New York; Consulting Staff, Pediatric Pulmonology, Department of Pediatrics, Northern Westchester Hospital, Mount Kisco, New York
Lung Injury from Hydrocarbon Aspiration and Smoke Inhalation

Margaret W. Leigh, MD
Professor, Department of Pediatrics, University of North Carolina; Attending Physician, UNC Hospitals, Chapel Hill, North Carolina
Influenza; Primary Ciliary Dyskinesia

Ann Marie LeVine, MD
Associate Professor, Department of Pediatrics, University of Florida, Gainesville, Florida
The Surfactant System

Albert Martin Li, MBBch, MRCP (UK), MRCPCH, FHKCP, FHKAM (Paed)
Associate Professor, Department of Paediatrics, Chinese University of Hong Kong; Honorary Associate Consultant, Department of Paediatrics, Prince of Wales Hospital, Shatin, Hong Kong
Pediatric Severe Acute Respiratory Syndrome

Gerald M. Loughlin, MD
Nancy C. Paduano Professor and Chairman, Department of Pediatrics, Weill Medical College of Cornell University; Pediatrician-in-Chief, Phyllis and David Komansky Center for Child Health, New York–Presbyterian Hospital, New York, New York
Bronchitis

Anna M. Mandalakas, MD
Assistant Professor of Pediatrics and Global Health, Department of Pediatrics, Case Western Reserve University; Assistant Professor, Department of Clinical Epidemiology, Rainbow Babies and Children's Hospital, Cleveland, Ohio
Tuberculosis and Nontuberculous Mycobacterial Disease

Paulo J.C. Marostica, MD
Professor of Pediatrics, Department of Pediatrics, Universidade Federal do Rio Grande do Sul; Professor, Department of Emergency Medicine, Hospital de Clinicas de Porto Alegre, Porto Alegre–Rio Grande do Sul (RS), Brazil
Community-Acquired Bacterial Pneumonia

Robert B. Mellins, MD
Professor of Pediatrics, Columbia University; Morgan Stanley Children's Hospital of New York–Presbyterian, New York, New York
Lung Injury from Hydrocarbon Aspiration and Smoke Inhalation

Mark Montgomery, MD, FRCP(C)
Clinical Associate Professor, Department of Child Health, University of Calgary; Consultant, Division of Pediatric Respiratory Medicine, Alberta Children's Hospital, Calgary, Alberta, Canada
Air and Liquid in the Pleural Space

Samira Mubareka, MD, FRCPC
Fellow in Infectious Diseases and Medical Microbiology, Department of Medical Microbiology and Infectious Diseases, University of Manitoba, Winnipeg, Manitoba, Canada
Pneumonia Secondary to Varicella and Measles

Thomas M. Murphy, MD
Associate Professor and Chief, Division of Pulmonary Medicine, Department of Pediatrics, Duke University School of Medicine; Chief, Division of Pulmonary Medicine, Department of Pediatrics, Duke Children's Hospital and Health Center, Durham, North Carolina
The Lung in Sickle Cell Disease

Joseph J. Nania, MD
Assistant Professor of Pediatrics, Department of Pediatrics, Division of Pediatric Infectious Diseases, Vanderbilt University School of Medicine; Vanderbilt Children's Hospital, Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tennessee
The Mycoses

Christopher J.L. Newth, MB, ChB, FRCPC
Professor of Pediatrics, Departments of Anesthesiology and Critical Care Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California
Acute Respiratory Distress Syndrome in the Pediatric Patient; Near-Drowning and Drowning

Andrew G. Nicholson, DM, FRCPath
Professor of Respiratory Pathology, National Heart and Lung Institute Division, Imperial College School of Medicine; Consultant Histopathologist, Royal Brompton and Harefield NHS Trust, London, United Kingdom
Congenital Lung Disease

Terry L. Noah, MD
Associate Professor, Department of Pediatrics; Investigator, Center for Environmental Medicine, Asthma, and Lung Biology, University of North Carolina at Chapel Hill; University of North Carolina Hospitals, University of North Carolina, Chapel Hill, North Carolina
Sarcoidosis; Lung Injury Caused by Pharmacologic Agents

Lawrence M. Nogee, MD
Associate Professor of Pediatrics, Department of Pediatrics, Johns Hopkins University School of Medicine; Attending Neonatologist, Division of Neonatology, Johns Hopkins Hospital, Baltimore, Maryland
Genetic Causes of Surfactant Deficiency

Blakeslee E. Noyes, MD
Associate Professor of Pediatrics, Department of Pediatrics, St. Louis University School of Medicine; Division of Pulmonary Medicine, Cardinal Glennon Children's Hospital, St. Louis, Missouri
Pediatric Lung Transplantation

Andrew H. Numa, MBBS, FRACP, FJFICM
Senior Lecturer, Department of Pediatrics, University of New South Wales; Senior Consultant, Department of Intensive Care, Sydney Children's Hospital; Senior Consultant, Department of Respiratory Medicine, Sydney Children's Hospital, Sydney, Australia
Acute Respiratory Distress Syndrome in the Pediatric Patient; Near-Drowning and Drowning

Hugh O'Brodovich, MD, FRCP(C)
Professor and Chair of Paediatrics, R.S. McLaughlin Foundation Chair in Paediatrics at The Hospital for Sick Children, Department of Paediatrics, University of Toronto; Paediatrician-in-Chief and Paediatric Pulmonologist, Department of Paediatrics, The Hospital for Sick Children, Toronto, Ontario, Canada
Pulmonary Edema

Christopher O'Callaghan, FRCP, FRCPCH, PhD, DM
Professor of Paediatrics, Department of Infection, Immunity and Inflammation, University of Leicester, Leicester, United Kingdom
Drug Administration by Aerosol in Children

Øystein E. Olsen, PhD
Consultant Radiologist, Department of Radiology, Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom
Diagnostic Imaging of the Respiratory Tract

Catherine M. Owens, BSc, MBBS, MRCP, FRCR
Consultant Paediatric Radiologist and Clinical Director, Department of Radiology, Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom
Diagnostic Imaging of the Respiratory Tract

Nikolaos G. Papadopoulos, MD, PhD
Lecturer in Pediatric Allergy and Head of Research, Allergy Department, Second Pediatric Clinic, University of Athens, Athens, Greece
Diagnosis of Viral Respiratory Illness: Practical Applications

Hans Pasterkamp, MD, FRCPC
Professor, Department of Pediatrics and Child Health, University of Manitoba; Head, Department of Pediatric Respirology, Winnipeg Children's Hospital, Winnipeg, Manitoba, Canada
The History and Physical Examination

Thomas A.E. Platts-Mills, MD, PhD
Professor of Medicine, Division Chief, Asthma and Allergic Diseases, Asthma and Allergic Diseases Center, University of Virginia, Charlottesville, Virginia
Immunopathogenesis of Asthma

Arnold C.G. Platzker, MD
Professor of Pediatrics, Department of Pediatrics, USC/Keck School of Medicine; Director, Cystic Fibrosis Center, Division of Pediatric Pulmonology, Department of Pediatrics, Children's Hospital of Los Angeles; Attending Physician, Department of Pediatrics, UCLA/Matel Children's Hospital; Adjunct Professor, Department of Pediatrics, UCLA/Mattel Children's Hospital, Los Angeles, California
Gastroesophageal Reflux and Aspiration Syndromes; Pulmonary Involvement in Rheumatoid Disorders of Childhood

Jean-Paul Praud, MD, PhD
Professor, Departments of Pediatrics and Physiology, Université de Sherbrooke, Quebec, Canada; Director, Research Institute, Servier, Suresnes, France
Chest Wall Function and Dysfunction

Stelios Psarras, PhD
Allergy Department, University of Athens, Goudi, Athens, Greece
Diagnosis of Viral Respiratory Illness: Practical Applications

Mobeen H. Rathore, MD
Professor and Chief, Department of Pediatric Infectious Diseases and Immunology, University of Florida; Chief, Section of Infectious Diseases and Hospital Epidemiologist, Wolfson Children's Hospital; Chief, Pediatric Infectious Diseases, Shands Jacksonville Medical Center; Director, Rainbow Center for Women, Adolescent Children and Families, University of Florida, Jacksonville, Florida
Toxocariasis, Hydatid Disease of the Lung, Strongyloidiasis, and Pulmonary Paragonimiasis

Gregory J. Redding, MD
Professor of Pediatrics, University of Washington School of Medicine; Chief, Department of Pulmonary Medicine, Children's Hospital and Regional Medical Center, Seattle, Washington
Bronchiectasis

Michael J. Rock, MD
Professor of Pediatrics, Department of Pediatrics, University of Wisconsin; Department of Pediatrics, American Family Children's Hospital, Madison, Wisconsin
Neonatal Screening for Cystic Fibrosis

Erika Berman Rosenzweig, MD
Assistant Professor of Pediatrics (in Medicine), Department of Pediatric Cardiology, Columbia University College of Physicians and Surgeons; Assistant Attending Pediatrician, Department of Pediatric Cardiology, Morgan Stanley Children's Hospital of New York Presbyterian Medical Center; Pulmonary Hypertension Center, New York Presbyterian Medical Center, New York, New York
Childhood Pulmonary Arterial Hypertension

Michael J. Rutter, MD
Associate Professor of Clinical Otolaryngology-Affiliated, Department of Otolaryngology, University of Cincinnati College of Medicine; Associate Professor, Pediatric Otolaryngology, Department of Otolaryngology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Foreign Body Aspiration

L. Barry Seltz, MD
Clinical Associate Professor, Department of Pediatrics, University of Arizona, Tuscon, Arizona
Atypical Pneumonias in Children

Amir H. Shahlaee, MD
Assistant Professor of Pediatrics, Division of Pediatric Hematology and Oncology, University of Florida Health Science Center, Gainesville, Florida
Histiocytic Disorders of the Lung

David Sigalet, MD, PhD, FRCSC, FACS
Professor, Department of Surgery, University of Calgary; Regional Division Head, Division of Pediatric General Surgery, Alberta Children's Hospital, Calgary, Alberta, Canada
Air and Liquid in the Pleural Space

Samatha Sonnappa, MD, DCH, MRCP, FRCPCH
Fellow in Paediatric Respiratory Medicine, Department of Paediatric Respiratory Medicine, Great Ormond Street Hospital, London, United Kingdom
Familial Dysautonomia

Chaim Springer, MD
Associate Professor of Pediatrics, Hadassah Medical School, The Hebrew University; Institute of Pulmonology, Hadassah University Hospital, Ein Kerem, Jerusalem, Israel
Pulmonary Function Assessment in the Laboratory during Exercise

James M. Stark, MD, PhD
Associate Professor, Division of Pediatric Pulmonary and Critical Care Medicine, Department of Pediatrics, University of Texas Health Science Center at Houston; Co-director, Respiratory Sciences Center, Memorial Hermann Children's Hospital, Houston, Texas
Lung Defenses: Intrinsic, Innate, and Adaptive

Jeffrey R. Starke, MD
Professor and Vice Chairman, Department of Pediatrics, Baylor College of Medicine; Chief of Pediatrics, Ben Taub General Hospital, Houston, Texas
Tuberculosis and Nontuberculous Mycobacterial Disease

Renato T. Stein, MD
Professor, Department of Pediatrics, Pontificia Universidade Catolica RGS; Head, Pediatric Pulmonary Section, Hospital São Lucas Purcs, Porto Alegre, RS, Brazil
Community-Acquired Bacterial Pneumonia

Kurt R. Stenmark, MD
Professor and Head of Division of Pediatric Critical Care, Department of Pediatrics, University of Colorado, Denver, Colorado
Acute Respiratory Failure

Janet Stocks, PhD
Professor of Respiratory Physiology, Portex Anaesthesia, Intensive Therapy and Respiratory Unit, Institute of Child Health, University College London, London, United Kingdom
Pulmonary Function Tests in Infants and Preschool Children

Dennis C. Stokes, MD
Professor of Pediatrics, Dartmouth Medical School, Hanover, New Hampshire; Section of Pediatric Pulmonology, Department of Pediatrics, Children's Hospital of Dartmouth, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire
Pulmonary Infections in the Immunocompromised Pediatric Host

James Temprano, MD
Clinical Fellow, Department of Pediatrics, Division of Allergy and Immunology, St. Louis University Health Sciences Center, St. Louis, Missouri
Hypersensitivity Pneumonitis and Eosinophilic Pulmonary Diseases

Bradley T. Thach, MD
Professor of Pediatrics, Newborn Medicine Division, Washington University School of Medicine and St. Louis Children's Hospital, St. Louis, Missouri
Sudden Infant Death Syndrome and Acute Life-Threatening Events

Bruce C. Trapnell, MD
Professor, Departments of Medicine and Pediatrics, University of Cincinnati College of Medicine; Attending Physician, Department of Pediatrics, Cincinnati Children's Hospital Medical Center; Attending Physician, Department of Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio
Rare Childhood Lung Disorders: α_1-Antitrypsin Deficiency, Pulmonary Alveolar Proteinosis, and Pulmonary Alveolar Microlithiasis

Colin Wallis, MD, FRCPCH, DCH
Institute Senior Lecturer, Department of Respiratory Paediatrics, The Institute of Child Health; Consultant Paediatrician, Respiratory Unit, Great Ormond Street Hospital for Children, London, United Kingdom
Diagnosis and Presentation of Cystic Fibrosis

Miles Weinberger, MD
Professor and Director, Pediatric Allergy and Pulmonary Division, Department of Pediatrics, University of Iowa, Iowa City, Iowa
Asthma in the Preschool Child

Susan E. Wert, PhD
Associate Professor, Department of Pediatrics, University of Cincinnati College of Medicine; Associate Professor, Division of Pulmonary Biology, Cincinnati Children's Hospital and Medical Center, Cincinnati, Ohio
Molecular Determinants of Lung Morphogenesis

John B. West, MD, PhD, DSc, FRCP, FRACP
Professor of Medicine and Physiology, Department of Medicine, University of California, San Diego, La Jolla, California
The Functional Basis of Respiratory Disease

Jeffrey A. Whitsett, MD
Professor, Department of Pediatrics, University of Cincinnati College of Medicine; Chief, Divisions of Neonatology, Perinatal and Pulmonary Biology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Molecular Determinants of Lung Morphogenesis

Robert W. Wilmott, BSc (Hons), MD, FRCP (UK)
IMMUNO Professor and Chair, Department of Pediatrics, St. Louis University; Pediatrician-in-Chief, SSM Cardinal Glennon Children's Hospital, St. Louis, Missouri
Hypersensitivity Pneumonitis and Eosinophilic Pulmonary Diseases

Mary Ellen B. Wohl, MD
Professor of Pediatrics, Harvard Medical School; Division Chief Emeritus, Division of Respiratory Diseases, Children's Hospital of Boston, Boston, Massachusetts
Developmental Physiology of the Respiratory System; Bronchiolitis

Robert E. Wood, MD, PhD
Cincinnati Children's Hospital Medical Center, Division of Pulmonary Medicine, Cincinnati, Ohio
Bronchoscopy and Bronchoalveolar Lavage in Pediatric Patients

Peter F. Wright, MD
Professor of Pediatrics, Pathology and Immunology and Microbiology, Department of Pediatrics, Division of Pediatric Infectious Diseases, Vanderbilt University School of Medicine; Vanderbilt Children's Hospital, Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tennessee
The Mycoses

Pamela L. Zeitlin, MD, PhD
Professor of Pediatrics, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland
Genetics and Pathophysiology of Cystic Fibrosis

Preface

Since the publication of the sixth edition in 1998, there have been tremendous changes in the subspecialty of pediatric pulmonology. We continue to be amazed by the pace of change and the accumulation of new knowledge. There are now four editors, who have shared the task of assembling chapters, cajoling authors, and ensuring that the book is up-to-date and comprehensive. The general organization of the book remains the same, but because of the complexity of the topics of asthma and cystic fibrosis, they have now graduated to sections of their own. The seventh edition includes 21 new chapters and more than 80 new authors; we thank them all for their hard work and diligence.

Our objective has expanded from that of the first edition. It is our goal to provide a comprehensive textbook of pediatric respiratory disease for the established pediatric respirologist and intensivist; for those who are in training in these subspecialties; and for pediatric practitioners, residents, and interns. In addition, the book is an important resource for roentgenologists, pediatric allergists, thoracic surgeons, and students in allied specialties with a particular interest in pediatric chest disease. Included are both common and rare childhood disorders of the lungs, as well as basic scientific considerations necessary for an understanding of pulmonary disease processes and their effect on pulmonary function. Edwin Kendig's book has become the bible of pediatric pulmonology, and we have strived to continue his tradition in this edition, which is dedicated to his memory.

Once again, the members of the staff at Elsevier (Saunders) have provided superb support, and we are grateful for their sound advice, patience, and attention to detail. In particular, we thank Kim J. Davis, senior developmental editor, who has been extremely diligent and patient with us, and Todd Hummel, who has provided encouragement and sage advice.

Not least, we acknowledge the tremendous support, tolerance, and forbearance of our partners and families, which have made this volume possible.

Victor Chernick, MD

Thomas F. Boat, MD

Robert W. Wilmott, MD

Andrew Bush, MD

I

General Considerations

1 Molecular Determinants of Lung Morphogenesis

Jeffrey A. Whitsett, MD • Susan E. Wert, PhD

OVERVIEW

The adult human lung consists of a gas exchange area of approximately 100 m^2 that provides oxygen delivery and carbon dioxide excretion required for cellular metabolism. In evolutionary terms, the lung represents a relatively late phylogenetic solution for the efficient gas exchange needed for terrestrial survival of organisms of increasing size, an observation that may account for the similarity of lung structure in vertebrates. The respiratory system consists of mechanical bellows and conducting tubules that bring inhaled gases to a larger gas exchange surface that is highly vascularized. Alveolar epithelial cells come into close apposition to pulmonary capillaries, providing efficient transport of gases from the alveolar space to the pulmonary circulation. The delivery of external gases to pulmonary tissue necessitates a complex organ system that (1) keeps the airway free of pathogens and debris, (2) maintains humidification of alveolar gases and precise hydration of the epithelial cell surface, (3) reduces collapsing forces inherent at air-liquid interfaces within the air spaces of the lung, and (4) supplies and regulates pulmonary blood flow to exchange oxygen and carbon dioxide efficiently. The present chapter will provide a framework for understanding the molecular mechanisms that lead to the formation of the mammalian lung, focusing attention to processes contributing to cell proliferation and differentiation involved in organogenesis and postnatal respiratory adaptation. Where possible, the pathogenesis of congenital or postnatal lung disease will be considered in the context of the molecular determinants of pulmonary morphogenesis and function.

ORGANOGENESIS OF THE LUNG

BODY PLAN

Events critical to organogenesis of the lung begin with formation of anteroposterior and proximodistal axes in the early embryo. The body plan is determined by genes that control cellular proliferation and differentiation and depends on complex interactions among many cell types. The fundamental principles determining embryonic organization are currently and rapidly being elucidated in more simple organisms (e.g., *Drosophila melanogaster* and *Caenorhabditis elegans*) and applied to increasingly complex organisms (e.g., mouse and human) as the genes determining axial segmentation, organ formation, cellular proliferation, and differentiation are identified. Segmentation and organ formation in the embryo are profoundly influenced by sets of master control genes that include various classes of transcription factors. Critical to formation of axial body plan are the homeotic, or Hox, genes.[1–7] Hox genes are arrayed in clearly defined spatial patterns within clusters on several chromosomes. Hox gene expression in the developing embryo is determined in part by the position of the individual genes within these gene clusters, which are aligned along the chromosome in the same order as they are expressed along the anteroposterior axis. Complex organisms have more individual Hox genes within each locus and have more Hox gene loci than in simpler organisms. Hox genes encode nuclear proteins that bind to DNA via a conserved homeodomain motif that modulates the transcription of specific sets of target genes. The temporal and spatial expression of these nuclear transcription factors, in turn, control the expression of other Hox genes and their transcriptional targets during morphogenesis and cytodifferentiation.[8–15] Expression of Hox genes influences many downstream genes, such as transcription factors, growth factors, and cell adhesion molecules (CAMs), which are critical to the formation of the primitive endoderm from which the respiratory epithelium is derived. Specification of endoderm requires the activity of a number of transcription factors, including Foxa2,[16–18] β-catenin,[19,20] Sox-17,[21,22] and GATA-6.[23] These transcription factors are also expressed in respiratory epithelial cells of the lung later in development when they play roles in cell differentiation and organ function.

LUNG MORPHOGENESIS

Lung morphogenesis begins during the embryonic period of fetal development as an outpouching of epithelial cells lining the

laryngotracheal sulcus at the caudal end of the medial pharyngeal groove of the foregut endoderm.[24] In the mouse, the lung bud forms on day 9 of gestation, comparable with 3 to 4 weeks of gestation in the human. The endoderm develops earlier in embryogenesis with formation of the dorsal plate and primitive notochord, which requires the expression of the transcription factor forkhead homologue Foxa2, previously termed hepatocyte nuclear factor-3β (HNF-3β), a protein also involved in differentiation and gene expression in the respiratory epithelium later in development.[16–18,25–31]

Lung morphogenesis can be subdivided into distinct periods on the basis of the morphologic characteristics of the tissue (Table 1-1 and Figs. 1-1 and 1-2). While the timing of the process is highly species specific, the anatomic events underlying lung morphogenesis are shared by all mammalian species. The reader is referred to several reviews that detail anatomic development of the human lung.[32–36]

The Embryonic Period (3–6 Weeks Postconception)

Relatively undifferentiated epithelial cells of the primitive foregut endoderm form tubules that invade the splanchnic mesoderm and undergo branching morphogenesis. This process requires highly controlled cell proliferation and migration to direct dichotomous branching of the tubules to form the main stem, lobar, and segmental bronchi of the primitive lung (see Fig. 1-1*A*; Fig. 1-2*, E10, E11*). The respiratory epithelium remains relatively undifferentiated and is lined predominantly by columnar epithelium in the embryonic period. Experimental removal of mesenchymal tissue from the embryonic endoderm arrests branching morphogenesis, demonstrating the critical role of mesenchyme in formation of the respiratory tract.[37,38] Interactions between epithelial and mesenchymal cells are mediated by a variety of growth factors and associated receptors that regulate gene transcription in differentiating lung cells. Epithelial-mesenchymal interactions involve both autocrine and paracrine signaling, which are critical to lung morphogenesis.[39,40]

Formation of the larger, more proximal conducting airways, including segmental and subsegmental bronchi, is completed by the 6th week postconception; however, both epithelial and mesenchymal cells of the embryonic lung remain relatively undifferentiated. At this stage, tracheobronchial tubules lack underlying cartilage, smooth muscle, or nerves, and the pulmonary and bronchial vessels are not well developed. Vascular connections with the right and left atria are established at the end of the embryonic period (6–7 weeks), creating the primitive pulmonary vascular bed. Developmental anomalies occurring during this period of development may include tracheal, laryngeal, and esophageal atresia, tracheal stenosis, pulmonary agenesis, tracheoesophageal fistulas, and bronchial malformations.

■ **TABLE 1-1.** Morphogenetic periods of human lung development

Period	Age (Weeks)	Structural Events
Embryonic	3–6	Lung buds, trachea, main stem, lobar, and segmental bronchi
Pseudoglandular	6–16	Subsegmental bronchi, terminal bronchioles, acinar tubules, mucous glands, cartilage, smooth muscle
Canicular	16–26	Respiratory bronchioles, acinus formation and vascularization, type I and II cell differentiation
Saccular	26–36	Dilation and subdivision of alveolar saccules, increase of gas-exchange surface area, further growth and alveolarization of lung, maturation of alveolar capillary network
Alveolar	36–maturity	

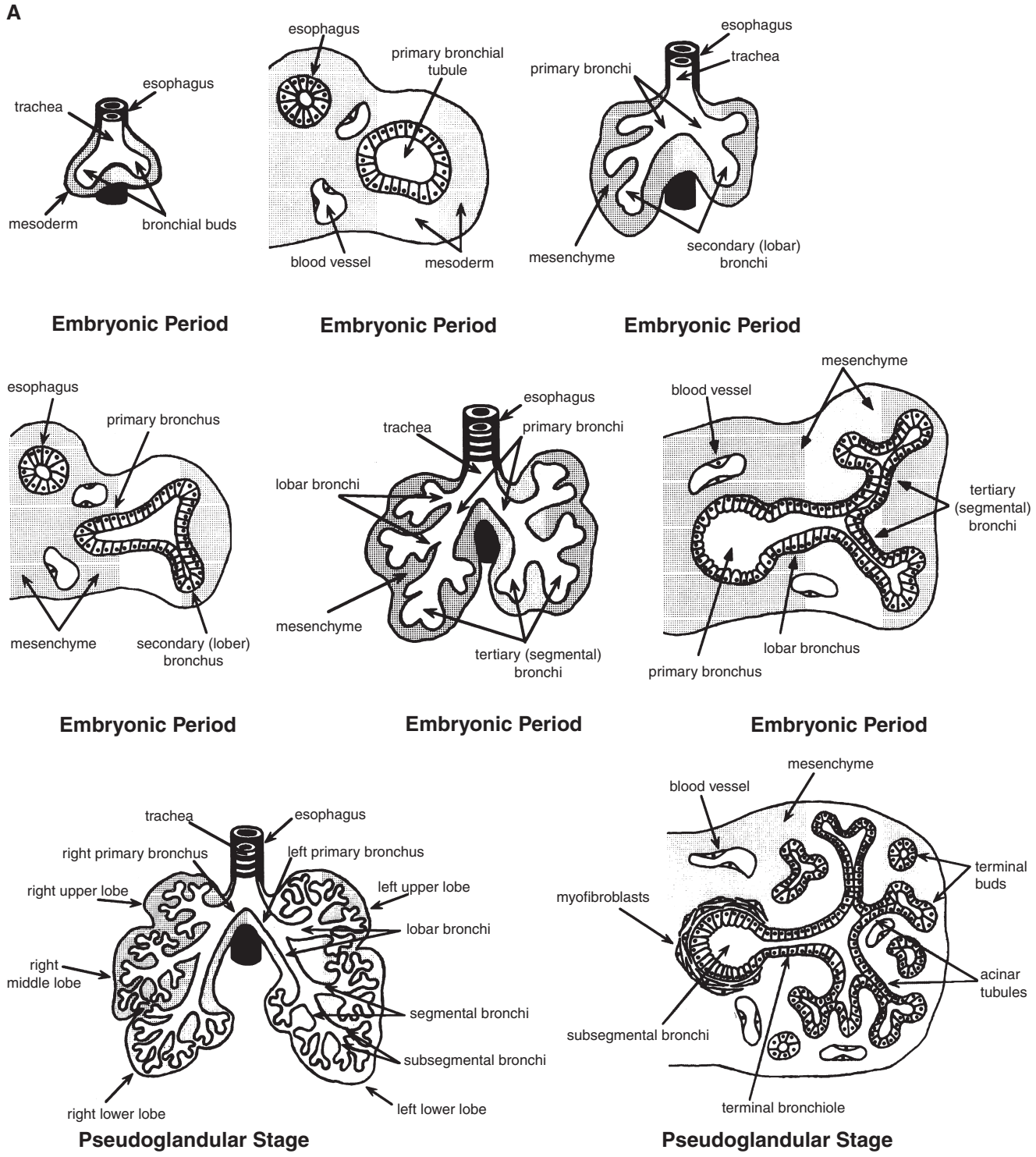
Pseudoglandular Period (6–16 Weeks Postconception)

The pseudoglandular stage is so named because of the distinct glandular appearance of the lung from 6 to 16 weeks of gestation. During this period, the lung consists primarily of epithelial tubules surrounded by a relatively thick mesenchyme. Branching of the airways continues, and formation of the terminal bronchioles and primitive acinar structures is completed by the end of this period (see Fig. 1-1*A*; Fig. 1-2*, E13, E15*). During the pseudoglandular period, epithelial cell differentiation is increasingly apparent; deposition of cellular glycogen and expression of a number of genes expressed selectively in the distal respiratory epithelium is initiated. Surfactant proteins A, B, and C are first detected at 12 to 14 weeks of human gestation.[41,42] Tracheobronchial glands begin to form in the proximal conducting airways. The airway epithelium is increasingly complex, with basal, mucous, ciliated, and nonciliated secretory cells being detected.[32,33] Neuroepithelial cells, often forming clumps of cells termed neuroepithelial bodies and expressing a variety of neuropeptides and transmitters (e.g., bombesin, calcitonin-related peptide, serotonin, and others), are increasingly apparent along the bronchial/bronchiolar epithelium during this stage of development. Smooth muscle and cartilage are now observed adjacent to the conducting airways. The pulmonary vascular system develops in close relationship to the bronchial and bronchiolar tubules between the 9th and 12th weeks of gestation. Bronchial arteries arise from the aorta and form along the epithelial tubules. Smooth muscle actin and myosin are found in the vascular structures during this period of development.[43–45] A variety of congenital defects may arise during the pseudoglandular stage of lung development, including tracheal-bronchiomalacia, pulmonary sequestration, cystadenomatoid malformation, ectopic lobes, cyst formation, and congenital pulmonary lymphangiectasia. The pleuroperitoneal cavity also closes early in the pseudoglandular period. Failure to close the pleural cavity, often accompanied by herniation of the abdominal contents into the chest (congenital diaphragmatic hernia), leads to lung hypoplasia.

Canalicular Period (16–26 Weeks)

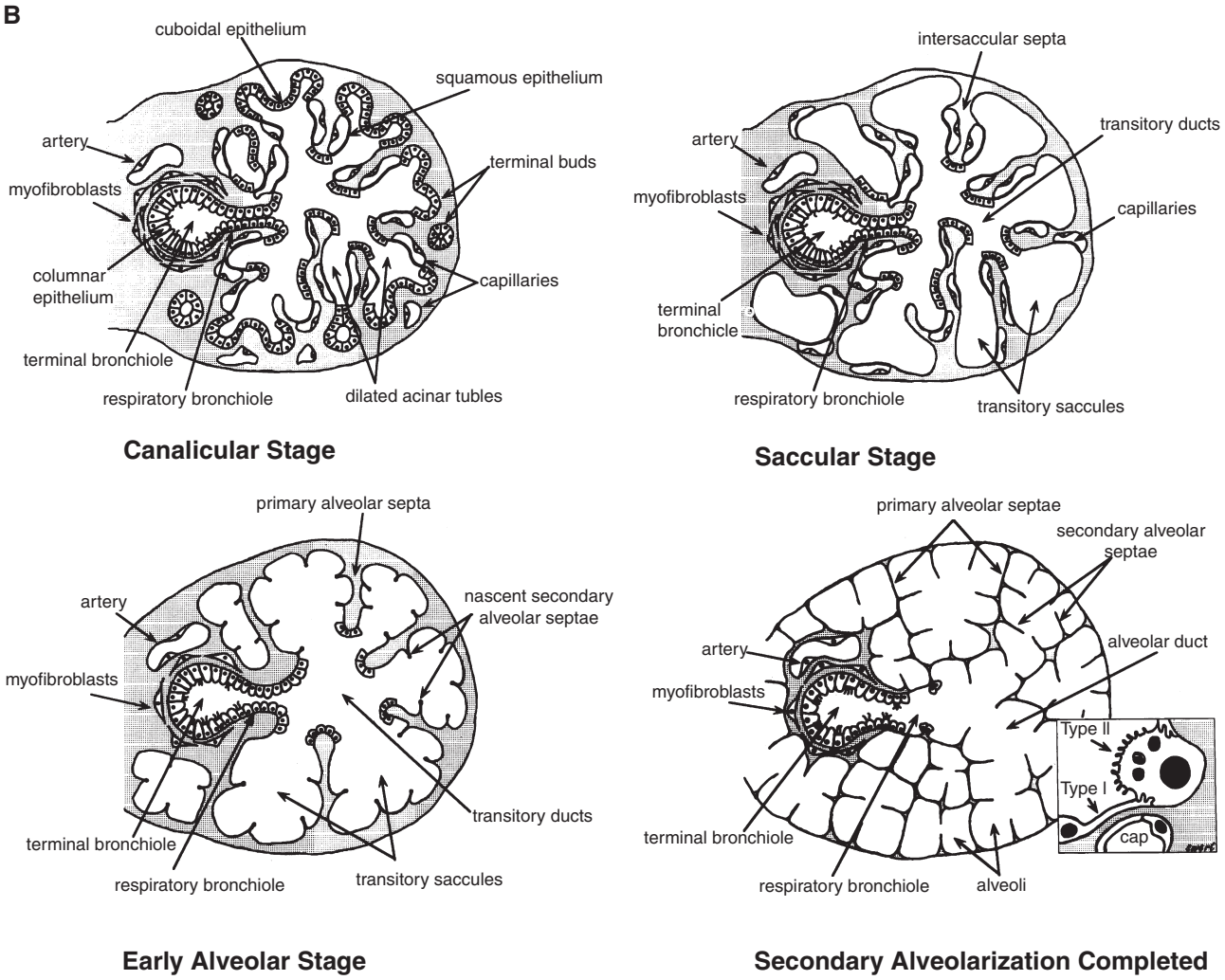
The canalicular period is characterized by luminal expansion, the formation of acinar structures in the distal tubules, thinning of the mesenchyme, and formation of the capillary bed, which comes into close apposition to the dilating acinar tubules (see Fig. 1-1*B*; Fig. 1-2*, E17*). By the end of this period, the terminal bronchioles have divided to form two or more respiratory bronchioles, and each of these have divided into multiple acinar tubules, forming the primitive alveolar ducts and pulmonary acini. Epithelial cell differentiation becomes increasingly complex and is especially apparent in the distal regions of the lung parenchyma. Bronchiolar cells express differentiated features and synthesize Clara cell secretory protein (CCSP).[29,46–48] Cells lining the distal tubules assume cuboidal

shapes and express increasing amounts of surfactant proteins (SP-A, SP-B, and SP-C)[29,41,49–52] and phospholipids.[53] Lamellar bodies, composed of surfactant phospholipids and protein, are seen in association with rich glycogen stores in the cuboidal pre–type II cells lining the distal lung tubules.[49,54–57] Some cells of the acinus become squamous, acquiring features of typical type I alveolar epithelial cells. Thinning of the pulmonary mesenchyme continues; the basal lamina of the epithelium and mesenchyme fuse. Capillaries surround the distal acinar tubules, which together will ultimately form the gas exchange region of the lung. By the end of the canalicular period in the human infant (26–28 weeks), gas exchange can be supported after birth, especially when surfactant is provided by administration of exogenous surfactants. Surfactant synthesis and mesenchymal thinning



■ **FIGURE 1-1.** **A,** Lung morphogenesis is initiated by the evagination of the lung bud into the surrounding splanchnic mesenchyme during the embryonic stage. Bronchi, bronchioles, and acinar tubules are formed by the process of branching morphogenesis during the pseudoglandular stage.

Continued

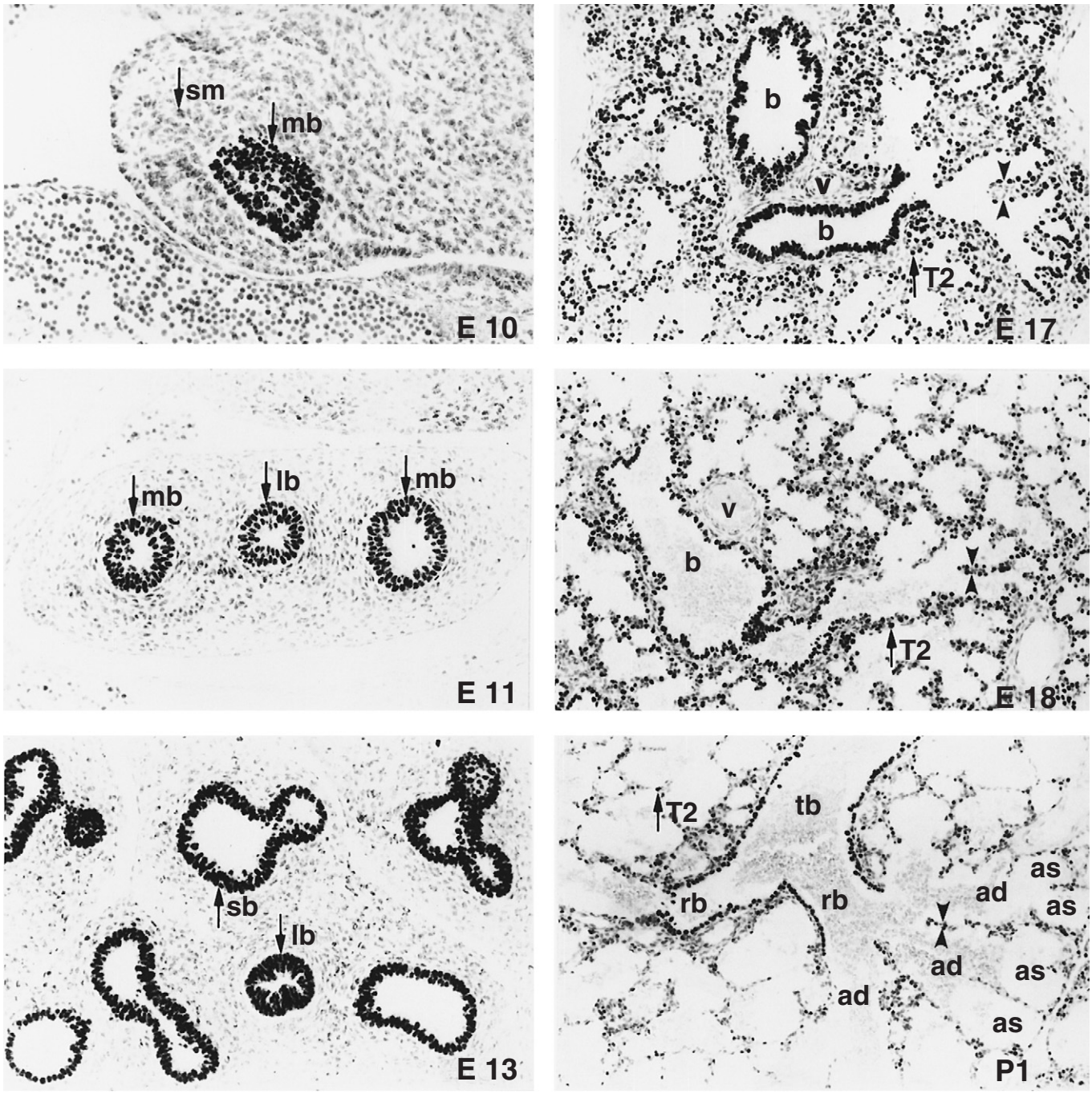


■ **FIGURE 1-1, cont'd.** **B,** Formation of the capillary bed and expansion of acinar structures is initiated during the canalicular stage. Growth and subdivision of terminal saccules and alveoli continue until early adolescence by septation of the distal respiratory structures to form additional alveoli.

are influenced by glucocorticoids,[58–60] which are administered to mothers to prevent respiratory distress syndrome (RDS) after premature birth.[61,62] Abnormalities of lung development occurring during the canalicular period include pulmonary hypoplasia (caused by diaphragmatic hernia or compression by thoracic or abdominal masses and prolonged rupture of membranes causing oligohydramnios) and renal agenesis, in which amniotic fluid production is impaired. While postnatal gas exchange can be supported late in the canalicular stage, infants born during this period generally suffer severe complications related to decreased pulmonary surfactant, which cause RDS and bronchopulmonary dysplasia, a complication secondary to the therapy for RDS.[63]

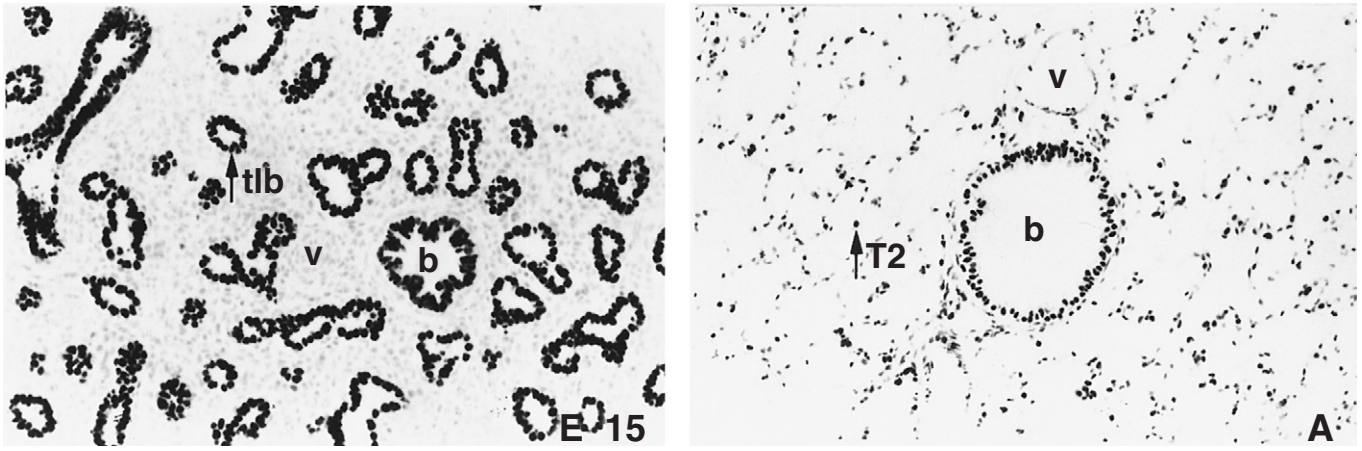
Saccular (26–36 weeks) and Alveolar Periods (36 Weeks through Adolescence)

These periods of lung development are characterized by increased thinning of the respiratory epithelium and pulmonary mesenchyme, further growth of lung acini, and development of the distal capillary network (see Fig. 1-1*B*; Fig. 1-2*, E18, P1, A*). In the periphery of the acinus, maturation of type II epithelial cells occurs in association with increasing numbers of lamellar bodies and increased synthesis of surfactant phospholipids[52,53,64] and SP-A, -B, -C, and -D.[29,41,42,49,50,65] The acinar regions of the lung increase in surface area, and proliferation of type II cells continues.[33] Type I cells, derived from differentiation of type II epithelial cells, line an ever-increasing proportion of the surface area of the distal lung. Capillaries become closely associated with the squamous type I cells, decreasing the diffusion distance between the alveolar gas and pulmonary capillaries. Basal laminae of the epithelium and stroma fuse, and the stroma contains increasing amounts of acellular matrix, including elastin and collagen. The abundance of smooth muscle in the pulmonary vasculature increases prior to birth. In human lung, the alveolar period begins near the time of birth and continues through the first decade of life, during which the lung grows primarily by septation and proliferation of the alveoli,[33,34,66] and by elongation and luminal enlargement of the conducting airways. Pulmonary arteries enlarge and elongate in close relationship to the increased growth of the lung.[35] Pulmonary vascular resistance decreases, and considerable remodeling of the pulmonary vasculature and capillary bed continues during the postnatal period.[34] Lung growth remains active until early adolescence, when the entire complement of more than 200 million alveoli has been formed.



Continued

■ **FIGURE 1-2.** Mouse lung morphogenesis. Lung sections obtained from mice on embryonic days 10 *(E10),* 11 *(E11),* 13 *(E13),* 15 *(E15),* 17 *(E17),* and 18 *(E18),* postnatal day 1 *(P1),* and in adulthood *(A)* were stained for thyroid transcription factor-1, a marker for embryonic respiratory epithelial cells and differentiated type II cells. Mouse lung morphogenesis begins at E9.5 with outgrowth of paired lung buds from the foregut. Epithelium of the main stem bronchus (*E10,* mb) is surrounded by splanchnic mesenchyme (*E10,* sm). During the pseudoglandular stage (E12–E16), two main stem bronchi undergo extensive branching morphogenesis to form the conducting airways, including lobar bronchi (*E11 and E13,* lb), segmental bronchi (*E13,* sb), bronchioles (*E15,* b), and terminal lung buds (*E15,* tlb). Terminal lung buds dilate to form canal-like structures during the canalicular stage *(E17)* and further dilate to form saclike structures during the saccular stage *(E18),* near the end of gestation. After birth, the distal airways expand further and subdivide to form true alveolar structures *(P1, A)*. Terminal bronchiole (tb), respiratory bronchiole (rb), alveolar duct (ad), and alveolar sac (as) are illustrated in *P1*. Distal airway remodeling during the canalicular, saccular, and alveolar stages is accompanied by thinning of the mesenchyme (notice the distance between the two arrowheads in *E17, E18, and P1*), differentiation of type I and type II cells (T2 in *E17, E18, P1, and A*), and evagination of blood vessels. A complicated alveolar network is observed in adult lung *(A)*. Bar = 64 μm. v, vessel. (Courtesy of Dr. Lan Zhou.)

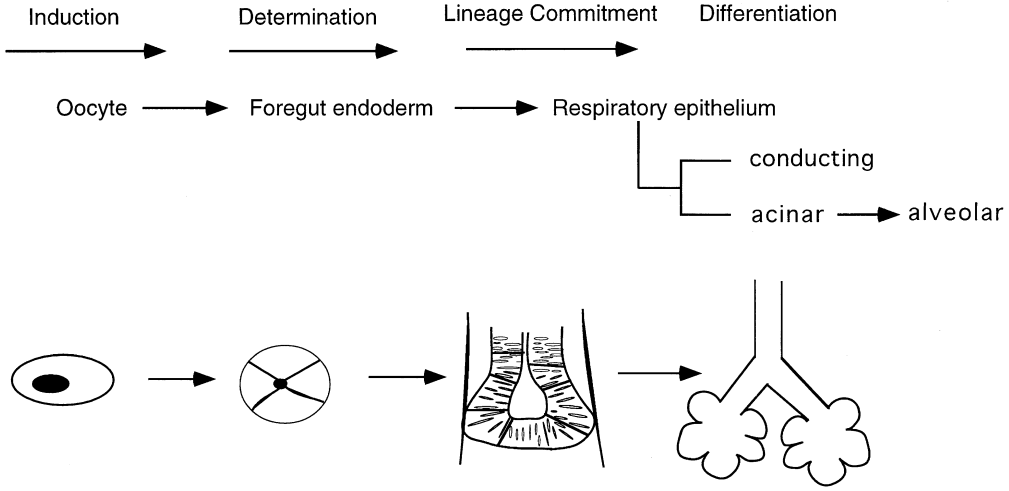


■ **FIGURE 1-2, cont'd**

■ CONTROL OF GENE TRANSCRIPTION DURING LUNG MORPHOGENESIS

Numerous regulatory mechanisms influence cell commitment, proliferation, and terminal differentiation required for formation of the mammalian lung (Fig. 1-3). These events must be precisely controlled in all organs to produce the complex body plan characteristic of higher organisms. In the mature lung, approximately 40 distinct cell types can be distinguished on the basis of morphologic and biochemical criteria.[67] Distinct pulmonary cell types arise primarily from subsets of endodermal and mesodermal progenitor cells (see Fig. 1-3). Pleuripotent or multipotent cells receive precise temporal and spatial signals that commit them to differentiated pathways, which ultimately generate the heterogeneous cell types present in the mature organ. The information directing cell proliferation and differentiation during organogenesis is derived from the genetic code contained within the DNA of each cell in the organism. Unique subsets of messenger RNAs (mRNAs), directing the synthesis of a variety of polypeptides, are expressed in each cell type, ultimately determining cell proliferation, structure, and behavior. Unique features of differentiating cells are controlled by the relative abundance of these mRNAs, which, in turn, determine the relative abundance of proteins synthesized by each cell. Cellular proteins influence morphologic, metabolic, and proliferative behaviors of cells, characteristics that traditionally have been used to assign cell phenotype by using morphologic and cytologic criteria. Gene expression in each cell is also determined by the structure of DNA-protein complexes that comprise the chromatin within the nucleus of each cell. Chromatin structure, in turn, influences the accessibility of individual genes to the transcriptional machinery. Diverse extracellular and intracellular signals also influence gene transcription, mRNA processing, mRNA stability, and translation, processes that determine the relative abundance of proteins produced by each cell.

Only a small fraction of the genetic material present in the nucleus represents regions of DNA that direct the synthesis of mRNAs encoding proteins. There is an increasing awareness that sequences in the noncoding regions of genes influence DNA structure and contain promoter and enhancer elements (usually in flanking and intronic regions of each gene) that determine levels of transcription. The ongoing nucleotide sequencing and identification of expressed complementary DNA (cDNA) sequences encoded within the human genome provide increasing insight into the amount of the genetic code used to synthesize the cellular proteins produced by each organ. At present, nearly all of the expressed cDNAs have been identified and



■ **FIGURE 1-3.** Pulmonary morphogenesis is determined by the genetic code in the oocyte and involves the precise control of cell proliferation, differentiation, or death of subsequent cells that ultimately form a complex organ containing more than 40 diverse cell types.

partially sequenced for most human organs.[68] Analysis of these mRNAs reveals distinct, and often unique, subsets of genes that are expressed in each organ, as well as the relative abundance and types of polypeptides encoded by these mRNAs. Of interest, proteins bearing signaling and transcriptional regulatory information are among the most abundant of various classes of proteins in human cells. Organ complexity in higher organisms is derived, at least in part, by the increasingly complex array of signaling molecules that govern cell behavior. Regulatory mechanisms controlling transcription are listed in Figure 1-4.

TRANSCRIPTIONAL CASCADES/HIERARCHIES

Gene transcription is modulated primarily by the binding of transcriptional factors (or transacting factors), which are nuclear proteins that bind to regulatory motifs consisting of ordered nucleotides (specific nucleotide sequences). The order of these specific nucleotide sequences determines recognition sites within the DNA (*cis*-acting elements) that are bound by these nuclear proteins. The binding of transcriptional factors to the *cis*-acting elements influences the activity of RNA polymerase II, which binds, in turn, to sequences near the transcription start site of target genes, initiating mRNA synthesis. Numerous families of transcription factors have been identified, and their activities are regulated by a variety of mechanisms, including post-translational modification and interactions with other proteins or DNA, as well as by their ability to translocate or remain in the nucleus.[69,70] Transcription factors also activate the transcription of other downstream nuclear factors, which, in turn, influence the expression of additional transacting factors. The number and cell specificity of transcriptional factors have proven to be large and are represented by diverse families of proteins categorized on the basis of structural motifs of their DNA binding or *trans* activating domains.[71–73] These interacting cascades of factors comprise a network with vast capabilities to influence target gene expression. The family of transcription factors (homeodomain, helix-turn-helix-containing family of DNA-binding proteins) represents an example of such a regulatory motif. A series of *HOX* genes are located in arrays containing large numbers of distinct genes arranged 3′ to 5′ in distinct loci within human chromosomes. Hox genes bind to and activate other downstream Hox gene family members that, in turn, bind to and activate the transcription of additional related and unrelated transcription factors, altering the activity of paired-homeodomain-containing genes (Pax), winged helix genes (Fox), zinc finger genes, such as retinoic acid receptors (RARs) or leucine-zipper transcription factors, that may also interact at the transcriptional level. Such cascades are now well characterized in organisms such as in *D. melanogaster*[74] and *C. elegans*.[75–77] Mammalian homologues exist in many of these genes, and their involvement in similar regulatory cascades influences gene expression and organogenesis in more complex organisms.[7,8,10,12,15] In the lung, thyroid transcription factor-1 (TTF-1) and Fox family members are involved in regulatory cascades that determine organogenesis and lung epithelial specific gene expression, and it is highly likely that many other nuclear transcription factors influence lung growth and development. Stat-3, β-catenin, GATA-6, POD-1, Foxa2, nuclear factor-1 (NF-1), Foxf1, Gli family members, Ets family members, N-*myc*, CCAAT/enhancer binding protein (C/EBP) family members, retinoic acid receptors, and glucocorticoid receptors, all nuclear transcription factors, influencing lung growth, cytodifferentiation, and function.[30,39,78,79]

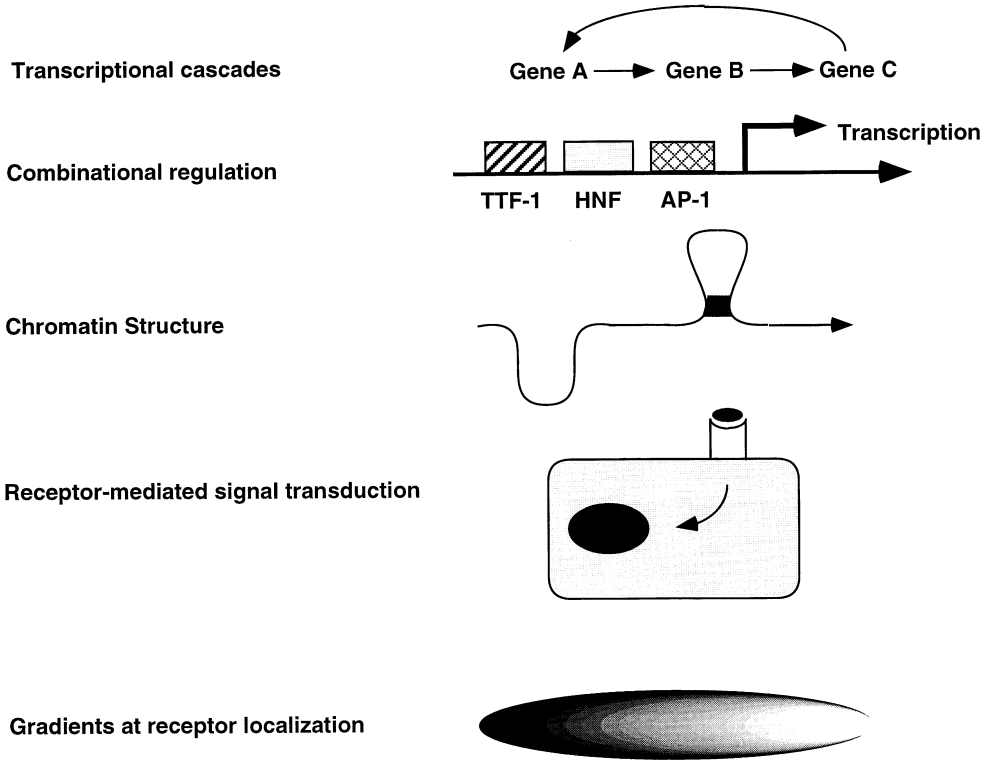


FIGURE 1-4. Diverse cellular mechanisms regulate varying levels of gene transcription that, in turn, control messenger RNA and protein synthesis governing cell differentiation and function during lung development.

COMBINATORIAL REGULATION OF GENE TRANSCRIPTION

The regulatory regions of target genes in eukaryotes are highly complex, usually containing numerous *cis*-acting elements that bind various nuclear transcription proteins. Nuclear proteins may bind DNA as monomers or oligomers, or form homo- or hetero-oligomers with other transcriptional proteins. Furthermore, many transcriptional proteins are modified by posttranslational modifications that are induced by receptor occupancy or phosphorylation/dephosphorylation events. Binding of transcription factors, or groups of transcription factors, may also perturb the structural organization of DNA (chromatin), making sites in the promoter regions more or less accessible to other nuclear proteins. Numerous *cis*-acting elements and their cognate *trans*-acting proteins interact with the basal transcriptional apparatus to regulate mRNA synthesis. The precise stoichiometry and specificity of the occupancy of the various DNA-binding sites influence either positively or negatively the transcription of specific target genes. This mode of regulation is characteristic of most eukaryotic cells, including those of the lung. For example, in pulmonary epithelial cells, a distinct set of transcription factors including TTF-1, activator protein-1 (AP-1), Fox family members, RARs, Stat-3, NF-1, and SP-1 regulate expression of surfactant protein genes that influence postnatal respiratory adaptation.[30]

INFLUENCE OF CHROMATIN STRUCTURE ON GENE EXPRESSION

The structure of chromatin is a critical determinant of the ability of target genes to respond to regulatory information influencing gene transcription. The abundance and organization of histones and other chromatin-associated proteins, including nuclear transcriptional proteins, influence the structure of DNA at genetic loci. The accessibility of regulatory regions within genes or groups of genes for binding and regulation by transcription factors is often dependent on chromatin structure. Changes in chromatin structure are likely determined by the process of cell differentiation during which target genes are made available or unavailable to the regulatory influences of transcription factors. Thus, the activity of a transcription factor at one time in development may be entirely distinct from that at another time. Chemical modification of DNA (e.g., methylation of cytosine) is also known to modify the ability of *cis*-active elements to bind and respond to regulatory influences. cytosine-guanine (CG)– rich islands are found in transcriptionally active genes, and methylation of these regions may vary developmentally or in response to signals that may influence gene transcription.[69] Chromatin structure, in turn, is influenced by post-transcriptional modification of histones and other DNA-associated proteins by acetylation, methylation, and phosphorylation, which is regulated by transcriptional complex and coactivator proteins that interact with the basal transcriptional machinery via polymerase II to alter gene transcription.[69]

RECEPTOR-MEDIATED SIGNAL TRANSDUCTION

Receptor-mediated signaling is well recognized as a fundamental mechanism for transducing extracellular information. Such signals are initiated by the occupancy of membrane-associated receptors capable of initiating additional signals (known as secondary messengers), such as cyclic adenosine monophosphate, calcium, and inositide phosphates, which influence the activity and function of intracellular polypeptides (kinases, phosphatases, proteases, etc.). These polypeptides, in turn, may alter the abundance of transcription factors, the activity of ion channels, or changes in membrane permeability, which subsequently modify cellular behaviors. Receptor-mediated signal transduction, induced by ligand-receptor binding, mediates endocrine, paracrine, and autocrine interactions on which cell differentiation and organogenesis depend. For example, fibroblast growth factor (FGF), Wnt, bone morphogenic protein (BMP), vascular endothelial growth factor (VEGF), ephrins, Notch/Delta, and sonic hedge hog (SHH) signaling have been implicated in organogenesis in many organs, including the lung.[40,80]

GRADIENTS OF SIGNALING MOLECULES AND LOCALIZATION OF RECEPTOR MOLECULES

Chemical gradients within tissues, and their interactions with membrane receptors located at distinct sites within the organ, can provide critical information during organogenesis. Polarized cells have basal, lateral, and apical surfaces with distinct subsets of signaling molecules (receptors) that allow the cell to respond in unique ways to focal concentrations of regulatory molecules. Secreted ligands (e.g., Wnts and SHH) function in gradients that are further influenced by binding of the ligand to basement membranes or proteoglycans. Spatial information is established by gradients of the signaling molecules and the presence and abundance of receptors at specific cellular sites. Such systems provide positional information to the cell that influences its behavior (e.g., shape, movement, proliferation, differentiation, polarized transport, etc.).

NONTRANSCRIPTIONAL MECHANISMS

While regulation of gene transcription is an important factor in organogenesis, numerous regulatory mechanisms, including control of transcriptional RNA expression, mRNA stability, protein translation, and degradation, are also known to provide further refinement in the abundance of mRNAs and proteins synthesized by a specific cell, which ultimately determine its structure and function.[69]

TRANSCRIPTIONAL MECHANISMS CONTROLLING GENE EXPRESSION DURING PULMONARY DEVELOPMENT

While knowledge of the determinants of gene regulation in lung development is rudimentary at present, a number of transcription factors and signaling networks that play critical roles in lung morphogenesis have been identified.[30,39,78,79,81] Lung morphogenesis depends on formation of definitive endoderm, which, in turn, signals from the splanchnic mesenchyme to initiate organogenesis along the foregut, forming thyroid, liver, pancreas, lung, and portions of the gastrointestinal tract.[82] The ventral plate of the endoderm in mammals forms under the direction of Foxa2, a transcription factor that is known to play a critical role in committing progenitor cells of the endoderm to form the primitive foregut.[16,25] Foxa2 is member of a large family of nuclear transcription factors, termed the winged helix family of transcription factors, that are involved in cell commitment, differentiation, and gene transcription in a variety of organs,

such as the central nervous system and derivatives of the foregut endoderm, including the gastrointestinal tract, lung, and liver.[83] Foxa2 plays a critical role in organogenesis of the lung. Foxa2 is required for the formation of foregut endoderm, from which the lung bud is derived by evagination of a subset of endodermal cells into the splanchnic mesenchyme at approximately 3 to 4 weeks of gestation in the human. While Foxa2 plays a critical role in formation and commitment of progenitor cells to form the foregut endoderm, Foxa2 also influences the expression of specific genes in the respiratory epithelium later in development.[29,84–88] Conditional deletion of Foxa2 in respiratory epithelial cells of the developing lung caused respiratory distress at birth, Foxa2 regulating surfactant protein and phospholipid production, as well as morphologic maturation of the lung at birth.[89] Deletion of Foxa2 after birth caused goblet cell metaplasia, airspace enlargement, and inflammation during the postnatal period.[31] Deletion of mouse Foxa2 prior to birth resulted in delayed pulmonary maturation associated with decreased surfactant lipid and protein expression and the development of a respiratory distress–like syndrome.[89] Thus, Foxa2 plays a critical role in specification of foregut endoderm in the early embryo, and is used again in the perinatal and postnatal period to direct alveolarization, postnatal lung function, and homeostasis.

TTF-1 (or Nkx2.1) is a 38-kd nuclear protein, containing a homeodomain DNA-binding motif, that is critical for formation of the lung and for regulation of a number of highly specific gene products produced only in the respiratory epithelium. TTF-1 is also expressed in the thyroid and in specific regions of the developing central nervous system. In the lung, TTF-1 is expressed in the respiratory epithelium of the primitive lung bud[29,90–92] (see Fig. 1-2). Ablation of the mouse *Titf-1* gene impairs lung morphogenesis, resulting in hypoplastic lungs lined by a poorly differentiated respiratory epithelium and lacking gas exchange areas.[90] Substitution of a mutant *Titf-1* gene that lacks phosphorylation sites substantially rescues lung function in the *Titf-1* knockout mouse.[93] Expression of a number of genes, including those regulating surfactant homeostasis, fluid and electrolyte transport, host defense, and vasculogenesis, was regulated by TTF-1 phosphorylation prior to birth. TTF-1 regulates the expression of a number of genes in a highly specific manner in the respiratory epithelium, including surfactant proteins A, B, C, and CCSP.[85,94–98] TTF-1 functions in concert with other transcription factors, including GATA-6, NF-1, Stat-3, nuclear factor of activated T cells (NFAT), Foxa1 and Foxa2, and RARs to regulate lung-specific gene transcription. *Titf-1* gene transcription itself is modulated by the activity of Foxa2, which binds to the promoter enhancer region of the *Titf-1* gene, thus creating a transcriptional network.[88,99] A combinatorial mode of regulation is evidenced by the apposition of clustered TTF-1 *cis*-active elements and Foxa2-binding sites in target genes, such as the *SP-B* and *CCSP* genes.[84–87,100] The stoichiometry, timing, and distinct combinations of transcription factors, as well as posttranscriptional modification of TTF-1 by phosphorylation, are involved in differential, lung epithelial cell, gene expression throughout lung development. TTF-1 and other transcription factors are recruited to complexes at regulatory sites of target genes that influence respiratory epithelial cell differentiation, providing and translating spatial information required for the formation of the highly diverse epithelial cell types lining distinct regions of the respiratory tract. In the mature human lung, more than a dozen distinct epithelial cell types are readily distinguished, yet all are derived from progenitor cells originating in the foregut endoderm.

EPITHELIAL-MESENCHYMAL INTERACTIONS AND LUNG MORPHOGENESIS

In vivo and in vitro experiments support the concept that branching morphogenesis and differentiation of the respiratory tract depends on reciprocal signaling between endodermally derived cells of the lung buds and the pulmonary mesenchyme/stroma. This interdependency depends on autocrine and paracrine interactions that are mediated by the various signaling mechanisms governing cellular behavior[40,80] (Fig. 1-5). Similarly, autocrine/paracrine interactions are known to be involved in cellular responses of the postnatal lung, generating signals that regulate cell proliferation and differentiation necessary for its repair and remodeling following injury. The splanchnic mesenchyme produces a number of growth factors critical for migration and proliferation of cells in the lung buds, including FGF-10, FGF-7, FGF-9, and Wnt family members. In a complementary manner, epithelial cells of the lung tubules produce Wnt7b, Wnt5a, SHH, BMP-4, FGF-9, VEGF, and platelet-derived growth factor (PDGF) that activate receptors on target cells in the mesenchyme.[79,80]

BRANCHING MORPHOGENESIS, VASCULARIZATION, AND SACCULATION

Two distinct processes, branching and sacculation, are critical to morphogenesis of the mammalian lung. The major branches of the conducting airways of the human lung are completed by week 16 by a process of dichotomous branching, initiated by the bifurcation of the main stem bronchi early in the embryonic period of lung development. Epithelial-lined tubules of ever-decreasing diameter are formed from the proximal to distal region of the developing lung. Pulmonary arteries and veins form along

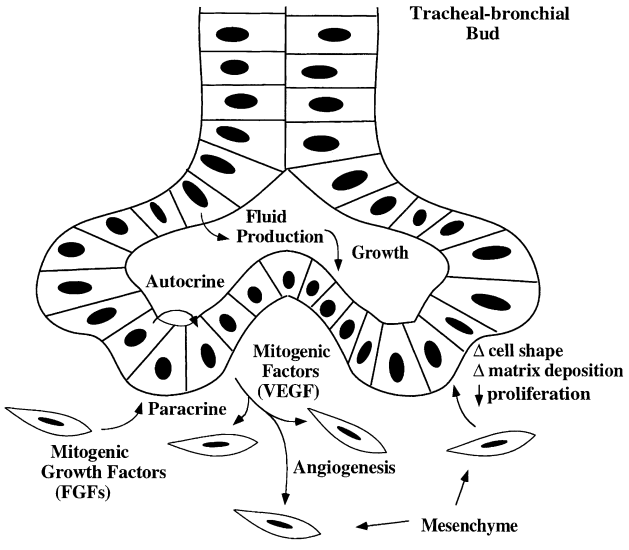


FIGURE 1-5. Branching morphogenesis is initiated by the evagination of the foregut endoderm into the splanchnic mesenchyme. Bronchi and bronchioles are formed by dichotomous branching, which depends on the precise regulation of cell proliferation and differentiation. Autocrine-paracrine interactions among various pulmonary cells are mediated by growth factors and receptors that influence cellular behaviors that are critical to lung formation.

the tubules and ultimately invade the acinar regions, where capillaries form between the arteries and veins, completing the pulmonary circulation. The bronchial vasculature arises from the aorta, providing nutrient supply predominantly to bronchial and bronchiolar regions of the lung. In contrast, the acinus (composed of bronchiolar portal and alveolar regions) is supplied by the pulmonary arterial system. Lymphatics and nerves form along the conducting airways, the latter being prominent in hilar, stromal, and vascular tissues, but lacking in the alveolar regions of the lung. A distinct period of lung sacculation and alveolarization begins in the late canalicular period (16 weeks and thereafter), forming the acinus that ultimately consists of the respiratory bronchiole, alveolar duct, and alveoli. During sacculation, a unique pattern of vascular supply forms the capillary network surrounding each saccule, providing an ever-expanding gas exchange area that is completed in adolescence. Both vasculogenesis and angiogenesis contribute to formation of the pulmonary vascular system.[36] Signaling via SHH, VEGF-A, Foxf1, Notch/Delta, ephrins, and PDGF plays important roles in pulmonary vascular development. VEGF-A is a critical factor in vasculogenesis in many tissues. However, overexpression of the VEGF-A 164 isoform disrupts pulmonary vascular endothelium in newborn conditional transgenic mice, causing pulmonary hemorrhage.[101]

CONTROL OF LUNG PROLIFERATION DURING BRANCHING MORPHOGENESIS

Dissection of the splanchnic mesenchyme from the lung buds arrests cell proliferation, branching, and differentiation of the pulmonary tubules in vitro.[37,38,40] Both in vitro and in vivo experiments strongly support the concept that the mesenchyme produces growth factors critical to the formation of respiratory tubules. In addition, lung growth is influenced by mechanical factors, including the size of the thoracic cavity and by stretch. For example, complete occlusion of the fetal trachea in utero enhances lung growth, while drainage of lung liquid or amniotic fluid causes lung hypoplasia. Regional control of proliferation is required for the process of dichotomous branching: division is enhanced at the lateral edges of the growing bud and inhibited at branch points.[102] Precise positional control of cell division is determined by polypeptides derived from the mesenchyme (e.g., growth factors or matrix molecules) that selectively decrease proliferation at clefts and increase cell proliferation at the edges of the bud (see Fig. 1-5). Proliferation in the respiratory tubule is dependent on a number of growth factors, including the FGF family of polypeptides. In vitro, FGF-1 and FGF-7 (keratinocyte growth factor, KGF) partially replace the requirement of pulmonary mesenchyme for continued epithelial cell proliferation and budding.[103,104] FGF polypeptides are produced by the mesenchyme during lung development and bind to and activate a splice variant of FGF receptor II (FGF-R2) that is present on respiratory epithelial cells, completing a paracrine loop.[105,106] Blockade of FGF-R2 signaling in the epithelium of the developing lung bud in vivo, using a dominant-negative FGF receptor mutant, completely blocked dichotomous branching of all conducting airway segments except the primary bronchi.[107] FGF-10 produced at localized regions of mesenchyme near the tips of the lung buds creates a chemoattractant gradient that activates the FGF-R2IIIb receptor in epithelial cells of the lung buds, which influences cell migration, differentiation, and proliferation required for branching morphogenesis.[108] Deletion of FGF-10 or FGF-R2IIIb blocked lung bud formation, resulting in lung agenesis.[109,110] Increased expression of FGF-10 or FGF-7 in the fetal mouse lung caused severe pulmonary lesions with all of the histologic features of cystadenomatoid malformations.[111,112] FGF-7 is also mitogenic for mature respiratory epithelial cells in vivo, enhancing proliferation of bronchiolar and alveolar cells when administered intratracheally to the lungs of adult rats.[113] Since FGF-7 is produced during lung injury, it is likely that FGF signaling molecules mediate cell proliferation or migration to influence repair.[114] FGF-7 and FGF-1 increase expression of surfactant proteins in vitro and in vivo, suggesting that these factors enhance type II cell differentiation.[111,115,116] Signaling polypeptides known to influence branching morphogenesis and differentiation of the respiratory tract are listed in Box 1-1.

ROLE OF EXTRACELLULAR MATRIX, CELL ADHESION, AND CELL SHAPE

The pulmonary mesenchyme is relatively loosely packed, and there is little evidence that cell type is specified during the early embryonic period of lung development. However, with advancing gestation, increasing abundance of extracellular matrix molecules, including laminin, fibronectin, collagens, elastin, and proteoglycans, is readily detected surrounding the developing epithelial tubules. Variability in the presence and abundance of various matrix molecules surrounding the tubules may influence differentiation and cell interactions.[117–123] Mesenchymal cells differentiate to form distinct vascular elements, endothelium, and smooth muscle and distinct fibroblastic cells that arise from the relatively undifferentiated progenitor cells of the splanchnic mesenchyme. While little is known regarding the factors influencing the differentiation of the pulmonary mesenchyme, the development of pulmonary vasculature is dependent on VEGFs.[124] VEGF-A is expressed by respiratory epithelial cells, stimulating pulmonary vasculogenesis mediated via paracrine signaling to receptors that are expressed by progenitor cells in the mesenchyme.[125–129] PDGF-α chain secreted by the respiratory epithelium influences proliferation and differentiation of myofibroblasts in the developing lung; deletion of PDGF-α causes pulmonary malformation in transgenic mice.[130] The organization of both mesenchyme and epithelium is further

BOX 1-1 Secreted Polypeptides Influencing Lung Morphogenesis and Differentiation

- Transforming growth factor-β (TGF-β)
- Bone morphogenic proteins (BMP-4)
- Fibroblast growth factors (FGF-1, FGF-7, FGF-9, FGF-10)
- Platelet-derived growth factor (PDGF)
- Epidermal/transforming growth factors (EGF/TGF-α)
- Sonic hedge hog (SHH)
- Vascular endothelial growth factor (VEGF-A)
- Hepatocyte growth factor (HGF)
- Insulin-like growth factors (IGFs)
- Granulocyte-macrophage colony-stimulating factor (GM-CSF)
- Wnt family members

modulated by CAMs of various classes, including the cadherins, integrins, and polypeptides, forming tight and gap junctions that contribute to cellular organization and polarity of various tissues during pulmonary organogenesis.[118,120,131] In vitro, inhibitors of collagen, elastin, and glycosaminoglycan (GAG) synthesis, and antibodies to various extracellular and cell attachment molecules, alter cell proliferation and branching morphogenesis of the embryonic lung.[119] Furthermore, the surrounding acellular matrix contains adhesion molecules that interact with attachment sites within cell membranes that in turn influence cell shape. Cell shape is determined, at least in part, by the organization of these cell attachment molecules to the cytoskeleton. Cell shape influences intracellular routing of cellular proteins and secretory products, determining the sites of secretion. Cell shape, polarity, and mobility are further influenced by the cytoskeletal proteins that interact with extracellular matrix, as well as neighboring cells. The organization of cell shape, via the cytoskeleton and its attachments, in turn, modifies cell differentiation in the lung.[132–134] For example, epithelial cells grown on intracellular matrix gels at an air-liquid interface form a highly polarized cuboidal epithelium that maintains cell differentiation and polarity of secretions in vitro. Loss of cell shape is associated with the loss of differentiated features such as surfactant protein and lipid synthesis, demonstrating the profound influence of cell shape on gene expression and cell behavior.

AUTOCRINE-PARACRINE INTERACTIONS IN LUNG INJURY AND REPAIR

As in lung morphogenesis, autocrine-paracrine signaling plays a critical role in the process of repair following lung injury. The repair processes in the postnatal lung, as in lung morphogenesis, require the precise control of cell proliferation and differentiation and, as such, are likely influenced by many of the signaling molecules and transcriptional mechanisms that mediate lung development. Events involved in lung repair may recapitulate events occurring during development in which progenitor cells undergo proliferation and terminal differentiation following lung injury. While many of the mechanisms involved in lung repair and development may be shared, it is also clear that the fetal and postnatal lung respond in distinct ways to autocrine-paracrine signals. Cells of the postnatal lung have undergone distinct phases of differentiation and may have different proliferative potentials or respond in unique ways to the signals evoked by lung injury. For example, after acute or chronic injury, increased production of polypeptide growth factors or cytokines may cause pulmonary fibrosis or pulmonary vascular remodeling in neonatal life, mediated by processes distinct from those occurring during normal lung morphogenesis.[135–140] The role of inflammation and the increasing activity of the immune system that accompanies postnatal development also distinguishes the pathogenesis of disease in the fetal and postnatal lungs.

HOST DEFENSE SYSTEMS

Distinct innate and adaptive defense systems mediate various aspects of host responses in the lung. During the postnatal period, the numbers and types of immune cells present in the lung expand markedly.[141] Alveolar macrophages, dendritic cells, lymphocytes of various subtypes, polymorphonuclear cells, eosinophils, and mast cells each have distinct roles in host defense. Immune cells mediate acute and chronic inflammatory responses accompanying lung injury or infection. Both the respiratory epithelium and inflammatory cells are capable of releasing and responding to a variety of polypeptides that initiate the expression of genes that are involved in (1) cytoprotection (e.g., antioxidants, heat shock proteins); (2) adhesion, influencing the attraction and binding of inflammatory cells to epithelial and endothelial cells of the lung; (3) cell proliferation, apoptosis, and differentiation that occur following injury or infection; and (4) innate host defense. An increasing array of cytokines and chemokines have now been identified that contribute to host defense following injury of the lung.[142–148]

The adaptive immune system includes both antibody and cell-mediated responses to antigenic stimuli. Adaptive immunity depends on the presentation of antigens by macrophages, dendritic cells, or the respiratory epithelium to mononuclear cells, triggering the expansion of immune lymphocytes and initiating antibody production and cytotoxic activity needed to remove infected cells from the lung. The lung contains active lymphocytes (natural killer cells, helper and cytotoxic T cells) that are present within the parenchyma and alveolus. Organized populations of mononuclear cells are also found in the lymphatic system along the conducting airways, termed the bronchiolar-associated lymphocytes (BALT). Cytokines and chemokines (interleukin-1 [IL-1], IL-8, tumor necrosis factor-α, RANTES [regulated on activation, normal T-expressed and secreted], granulocyte-macrophage colony-stimulating factor [GM-CSF], macrophage inflammatory protein-1α [MIP-1α], etc.) are produced by respiratory epithelial and other pulmonary cells, providing proliferative and/or differentiative signals to inflammatory cells that, in turn, amplify these signals by releasing cytokines or other inflammatory mediators within the lung.[149] Receptors for some of these signaling molecules have been identified in pulmonary epithelial cells.[150] For example, GM-CSF plays a critical role in surfactant homeostasis. Genetic ablation of GM-CSF or GM-CSF-IL-3/5β chain receptor causes alveolar proteinosis associated with macrophage dysfunction and surfactant accumulation.[151–155] Pulmonary alveolar proteinosis in adults is associated with high-affinity autoantibodies against GM-CSF that block receptor activation required for surfactant catabolism by alveolar macrophages.[156] However, GM-CSF stimulates both differentiation and proliferation of Type II epithelial cells, as well as activating alveolar macrophages to increase surfactant catabolism. Thus, GM-CSF acts in an autocrine-paracrine fashion as a growth factor for the respiratory epithelium. A number of growth factors, including GM-CSF, FGFs, EGF, TGF-α, PDGF, insulin-like growth factor-1 (IGF-1), TGF-β, and others, are released by lung cells following injury (see Box 1-1). These polypeptide growth factors likely play a critical role in stimulating proliferation of the respiratory epithelial cells required to repair the injured respiratory epithelium.[140,157] For example, intratracheal administration of FGF-7 causes marked proliferation of the adult respiratory epithelium and protects the lung from various injuries.[113]

INNATE DEFENSES

The lung also has innate defense systems that function independently of those provided by the mesodermally derived immune system. The respiratory epithelium and other lung cells secrete a variety of polypeptides that serve defense functions, including bacteriocidal polypeptides (lysozyme and defensins), collectins (surfactant proteins A and D), and other polypeptides

that enhance macrophage activity involved in the clearance of bacteria and other pathogens. SP-A and SP-D, both members of the collectin family of mammalian lectins,[158] are secreted by the respiratory epithelium and bind to and enhance the phagocytosis of pathogenic organisms by alveolar macrophages.[159–170] Polypeptide factors with bacteriocidal activity, such as the defensins, are produced by various cells in response to inflammation within the lung, and are likely to play roles in host defense.[171–177] Thus, the immune system and accompanying production of chemokines and cytokines serve in an autocrine-paracrine fashion to modulate expression of genes mediating innate and immune-dependent defenses, as well as cell growth, critical to the repair of the parenchyma after injury. Uncontrolled proliferation of stromal cells leads to pulmonary fibrosis, just as uncontrolled growth of the respiratory epithelium produces pulmonary adenocarcinoma. Chronic inflammation, whether through inhaled particles, infection, or immune responses, may therefore establish ongoing proliferative cascades that lead to fibrosis and abnormal alveolar remodeling associated with chronic lung disease.[139]

GENE MUTATIONS IN LUNG DEVELOPMENT AND FUNCTION

Knowledge of the role of specific genes in lung development and function is expanding rapidly, extending our understanding of the role of genetic mutations that cause lung malformation and disease. Mutations in the DNA code may alter the abundance and function of encoded polypeptides, causing changes in cell behavior that lead to lung malformation and dysfunction. While poorly understood at present, a congenital malformation, termed acinar dysplasia, is associated with decreased or absent levels of TTF-1, Foxa2, and surfactant proteins; lungs from these infants are severely hypoplastic and lack peripheral airways at birth.[178] Such findings implicate the transcription factors TTF-1 and Foxa2, or their upstream regulators, in acinar dysplasia. Mutations in *TTF-1* cause lung hypoplasia and hypothyroidism.[179] Mutations in *SOX-9* influence the growth of the chest wall and cause lung hypoplasia in campomelic dwarfism.[180–184] Similarly, defects in SHH and FGF receptor signaling have been associated with lung and tracheobronchial malformation in human infants.[185,186] Thus, it is increasingly apparent that mutations in genes influencing transcriptional and signaling networks that control lung morphogenesis cause pulmonary malformations in infants.

Postnatally, mutations in various genes critical to lung function, host defense, and inflammation are associated with genetic disease in humans. Hereditary disorders affecting lung function include cystic fibrosis (cystic fibrosis transmembrane conductance regulator protein [CFTR]), hereditary surfactant protein B deficiency,[187,188] alveolar proteinosis (GM-CSF or receptors),[189] emphysema (α_1-antitrypsin deficiency), pulmonary fibrosis, interstitial lung disease, and respiratory distress (SP-C and ATP-binding cassette transporter 3 [ABCA3]),[190–192] and lymphangiomyomatosis (tuberous sclerosis complex [Tbc]). Mutations in polypeptides controlling neutrophil oxidant production lead to bacterial infections as seen in chronic granulomatous disease. The severity of disease associated with these monogenetic disorders is often strongly influenced by other inherited genes or environmental factors (e.g., smoking) that ameliorate or exacerbate underlying lung disease. The identification of "modifier genes" and the role of gene dosage in disease susceptibility will be critical in understanding the pathogenesis and clinical course of pulmonary disease in the future.

SUMMARY

The molecular and cellular mechanisms controlling lung morphogenesis and function provide a fundamental basis for understanding the pathogenesis and therapy of pulmonary diseases in children and adults. Future advances in pulmonary medicine will depend on the identification of new genes, and their encoded polypeptides, that play critical roles in lung formation and function. Knowledge regarding the complex signaling pathways that govern lung cell behaviors during development and after injury will provide the basis for new diagnostic and therapeutic approaches that will influence clinical outcomes. Diagnosis of pulmonary disease will be facilitated by the identification of new gene mutations that cause abnormalities in lung development and function. Since many of the events underlying lung morphogenesis may also be involved in the pathogenesis of lung disease postnatally, elucidation of molecular pathways governing lung development will provide the knowledge needed to understand the cellular and molecular basis of lung diseases. Advances in recombinant DNA technology and the ability to synthesize bioactive polypeptides and to add or to delete genes via DNA transfer are also likely to influence the therapy of pulmonary disease in the future.

REFERENCES

1. Favier B, Dolle P: Developmental functions of mammalian Hox genes. Mol Hum Reprod 1997;3:115–131.
2. Mark M, Rijli FM, Chambon P: Homeobox genes in embryogenesis and pathogenesis. Pediatr Res 1997;42:421–429.
3. Gellon G, McGinnis W: Shaping animal body plans in development and evolution by modulation of the Hox expression patterns. Bioessays 1998;20:116–125.
4. Veraksa A, del Campo M, McGinnis W: Developmental patterning genes and their conserved functions. From model organisms to humans. Mol Genet Metab 2000;69:85–100.
5. Goodman FR, Scambler PJ: Human HOX gene mutations. Clin Genet 2001;59:1–11.
6. Goodman FR: Congenital abnormalities of body patterning; embryology revisited. Lancet 2003;362:651–662.
7. Hombria JC, Lovegrove B: Beyond homeosis—HOX function in morphogenesis and organogenesis. Differentiation 2003;71:461–476.
8. Botas J: Control of morphogenesis and differentiation by HOM/Hox. Curr Opin Cell Biol 1993;5:1015–1022.
9. Bogue CW, Gross I, Vasavada H, et al: Identification of *Hox* genes in newborn lung and effects of gestational age and retinoic acid on their expression. Am J Physiol 1994;266:L448–L454.
10. Lufkin T: Transcriptional regulation of vertebrate Hox genes during embryogenesis. Crit Rev Eukaryot Gene Expr 1997;7:195–213.
11. Mann RS, Affolter M: Hox proteins meet more partners. Curr Opin Genet Dev 1998;8:423–429.
12. Pradel J, White RA: From selectors to realizators. Int J Dev Biol 1998; 42:417–421.
13. Chariot A, Gielen J, Merville MP, et al: The homeodomain-containing proteins. An update on their interacting partners. Biochem Pharmacol 1999;58:1851–1857.
14. Deschamps J, van den Akker E, Forlani S, et al: Initiation, establishment and maintenance of Hox gene expression patterns in the mouse. Int J Dev Biol 1999;43:635–650.
15. Lohmann I, McGinnis W: Hox genes: It's all a matter of context. Curr Biol 2002;12:R514–R516.
16. Ang SL, Wierda A, Wong D, et al: The formation and maintenance of the definitive endoderm lineage in the mouse. Involvement of HNF3/forkhead proteins. Development 1993;119:1301–1315.
17. Ang SL, Rossant J: HNF-3β is essential for node and notochord formation in mouse development. Cell 1994;78:561–574.

18. Weinstein DC, Ruiz I, Altaba A, et al: The winged-helix transcription factor HNF-3 beta is required for notochord development in the mouse embryo. Cell 1994;78:575–588.
19. Wodarz A, Nusse R: Mechanisms of Wnt signaling in development. Annu Rev Cell Dev Biol 1998;14:59–88.
20. Huelsken J, Behmers J: The Wnt signaling pathway. J Cell Sci 2002; 115:3977–3978.
21. Kanai-Azuma M, Kanai Y, Gad JM, et al: Depletion of definitive gut endoderm in Sox17-null mutant mice. Development 2002;129:2367–2379.
22. Sinner D, Rankin S, Lee M, et al: Sox17 and β-catenin cooperate to regulate the transcription of endodermal genes. Development 2004;131:3069–3080.
23. Morrisey EE, Tang Z, Sigrist K, et al: GATA-6 regulates HNF4 and is required for differentiation of visceral endoderm in the mouse embryo. Genes Dev 1998;12:3579–3590.
24. Moore KL: The respiratory system. In: Moore KL, ed: The Developing Human—Clinically Oriented Embryology, 5th ed. Philadelphia: WB Saunders, 1993, pp 226–236.
25. Monaghan AP, Kaestner KH, Grau E, et al: Postimplantation expression patterns indicate a role for the mouse forkhead/HNF-3 alpha, beta and gamma genes in determination of the definitive endoderm, chordamesoderm and neuroectoderm. Development 1993;119:567–578.
26. Sasaki H, Hogan BL: Differential expression of multiple fork head related genes during gastrulation and axial pattern formation in the mouse embryo. Development 1993;118:47–59.
27. Sasaki H, Hogan BLM: HNF 3β as a regulator of fetal plate development. Cell 1994;70:103–115.
28. Hackett BP, Bingle CD, Gitlin JD: Mechanisms of gene expression and cell fate determination in the developing pulmonary epithelium. Annu Rev Physiol 1996;58:51–71.
29. Zhou L, Lim L, Costa RH, et al: Thyroid transcription factor-1, hepatocyte nuclear factor 3, surfactant protein B, C, and Clara cell secretory protein in developing mouse lung. J Histochem Cytochem 1996;44:1183–1193.
30. Costa RH, Kalinichenko VV, Lim L: Transcription factors in mouse lung development and function. Am J Physiol 2001;280:L823–L838.
31. Wan H, Kaestner KH, Ang S-L, et al: Foxa2 regulates alveolarization and goblet cell hyperplasia. Development 2004;131:953–964.
32. Scarpelli EM: Lung cells from embryo to maturity. In: Scarpelli EM, ed: Pulmonary Physiology. Fetus, Newborn, Child, and Adolescent, 2nd ed. Philadelphia: Lea & Febiger, 1990, pp 42–82.
33. Thurlbeck WM: Pre- and postnatal organ development. In: Chernick V, Mellins RB, eds: Basic Mechanisms of Pediatric Respiratory Disease. Cellular and Integrative. Philadelphia: BC Decker, 1991, pp 23–35.
34. Burri PH: Structural aspects of prenatal and postnatal development and growth of the lung. In: McDonald JA, ed: Lung Growth and Development, 1st ed. New York: Marcel Dekker, 1997, p 1.
35. deMello DE, Reid LM: Pre- and postnatal development of the pulmonary circulation. In: Chernick J, Mellins RB, eds: Basic Mechanisms of Pediatric Respiratory Disease. Cellular and Integrative. Philadelphia: BC Decker, 1991, pp 36–54.
36. deMello DE, Reid LM: Embryonic and early fetal development of human lung vasculature and its functional implications. Pediatr Dev Pathol 2000;3:439–449.
37. Spooner BS, Wessells NK: Mammalian lung development. Interactions in primordium formation and bronchial morphogenesis. J Exp Zool 1970;175:445–454.
38. Masters JRW: Epithelial-mesenchymal interaction during lung development. The effect of mesenchymal mass. Dev Biol 1976;51:98–108.
39. Cardoso WV: Molecular regulation of lung development. Annu Rev Physiol 2001;63:471–494.
40. Shannon JM, Hyatt BA: Epithelial-mesenchymal interactions in the developing lung. Annu Rev Physiol 2004;66:625–645.
41. Khoor A, Gray ME, Hull WM, et al: Developmental expression of SP-A and SP-A mRNA in the proximal and distal respiratory epithelium in the human fetus and newborn. J Histochem Cytochem 1993;41:1311–1319.
42. Khoor A, Stahlman MT, Gray ME, et al: Temporal-spatial distribution of SP-B and SP-C proteins and mRNAs in the developing respiratory epithelium of the human lung. J Histochem Cytochem 1994;42:1187–1199.
43. Leslie KO, Mitchell JJ, Woodcock-Mitchell JL, et al: Alpha smooth muscle actin expression in developing and adult human lung. Differentiation 1990;44:143–149.
44. Woodcock-Mitchell J, White S, Stirewalt W, et al: Myosin isoform expression in developing and remodeling rat lung. Am J Respir Cell Mol Biol 1993;8:617–625.
45. Miano JM, Cserjesi P, Ligon KL, et al: Smooth muscle myosin heavy chain exclusively marks the smooth muscle lineage during mouse embryogenesis. Circ Res 1994;75:803–812.
46. Singh G, Singh J, Katyal SL, et al: Identification, cellular localization, isolation, and characterization of human Clara cell-specific 10 kd protein. J Histochem Cytochem 1988;36:73–80.
47. Strum JM, Singh G, Katyal S, et al: Immunochemical localization of Clara cell protein by light and electron microscopy in conducting airways of fetal and neonatal hamster lung. Anat Rec 1990;227:77–86.
48. Ten Have-Opbroek AAW, DeVries ECP: Clara cell differentiation in the mouse. Ultrastructural morphology and cytochemistry for surfactant protein A and Clara cell 10 kD protein. Microsc Res Tech 1993;26:400–411.
49. Schellhase DE, Emrie PA, Fisher JH, et al: Ontogeny of surfactant proteins in the rat. Pediatr Res 1989;26:167–174.
50. Endo H, Oka T: An immunohistochemical study of bronchial cells producing surfactant protein A in the developing human fetal lung. Early Hum Dev 1991;25:149–156.
51. Otto-Verberne CJM, Ten Have-Opbroek AAW, DeVries ECP: Expression of the major surfactant-associated protein, SP-A, in Type II cells of human lung before 20 weeks of gestation. Eur J Cell Biol 1990;53: 13–19.
52. Weaver TE, Whitsett JA: Function and regulation of expression of pulmonary surfactant-associated proteins. Biochem J 1991;273:249–264.
53. Batenburg JJ, Hallman M: Developmental biochemistry of alveoli. In: Scarpelli EM, ed: Pulmonary Physiology. Fetus, Newborn, Child, and Adolescent. Philadelphia: Lea & Febiger, 1991, pp 106–139.
54. Williams MC, Mason R: Development of the type II cell in the fetal rat lung. Am Rev Respir Dis 1977;115:37–47.
55. Hilfer SR: Development of terminal buds in the fetal mouse lung. Scanning Electron Microsc 1983;111:1378–1401.
56. Chi EY: The ultrastructural study of glycogen and lamellar bodies in the development of fetal monkey lung. Exp Lung Res 1985;8:275–289.
57. Ten Have-Opbroek AAW, Otto-Verberne CJM, Dubbeldam JA: Ultrastructural characteristics of inclusion bodies of type II cells in late embryonic mouse lung. Anat Embryol 1990;181:317–323.
58. Whitsett JA, Weaver TE, Clark JC, et al: Glucocorticoid enhances surfactant proteolipid Phe and pVal synthesis and RNA in fetal lung. J Biol Chem 1987;262:15618–15623.
59. Ballard PL: Hormonal regulation of pulmonary surfactant. Endocr Rev 1989;10:165–181.
60. Mendelson CR, Boggaram V: Hormonal control of the surfactant system in fetal lung. Annu Rev Physiol 1991;53:415–440.
61. Jobe AH, Soll RF: Choice and dose of corticosteroid for antenatal treatments. Am J Obstet Gynecol 2004;190:878–881.
62. Yeomans ER: Prenatal corticosteroid therapy to prevent respiratory distress syndrome. Semin Perinatol 1993;17:253–259.
63. Jobe AH: Antenatal factors and the development of bronchopulmonary dysplasia. Semin Neonatol 2003;8:9–17.
64. Rooney SA, Young SL, Mendelson CR: Molecular and cellular processing of lung surfactant. FASEB J 1994;8:957–967.
65. Crouch E, Rust K, Marienchek W, et al: Developmental expression of pulmonary surfactant protein D (SP-D). Am J Respir Cell Mol Biol 1991; 5:13–18.
66. Langston C, Kida K, Reed M, et al: Human lung growth in late gestation and in the neonate. Am Rev Respir Dis 1984;129:607–613.
67. Gail DB, Lenfant CJM: Cells of the lung. Biology and clinical implications. Am Rev Respir Dis 1983;127:366–387.
68. Adams MD, Kerlavage AR, Fleischman RD, et al: Initial assessment of human gene diversity and expression patterns based upon 83 million nucleotides of cDNA sequence. Nature 1995;377:3–174.
69. Lewin B: Genes VIII. New York: Prentice-Hall, 2003.
70. Latchman DS: Eukaryotic Transcription Factors. San Diego, CA: Academic, 2003.
71. Mitchell DJ, Tjian R: Transcriptional regulation in mammalian cells by sequence specific DNA binding proteins. Science 1989;245:371–378.
72. Pabo CO, Sauer RT: Transcription factors: Structural families and principles of DNA recognition. Ann Rev Biochem 1992;61:1053–1095.
73. Vellanoweth RL, Supakar PC, Arun KR: Transcription factors in development growth and aging. Lab Invest 1994;70:784–799.
74. Davis GK, Patel NH: Short, long, and beyond. Molecular and embryological approaches to insect segmentation. Annu Rev Entomol 2002;47: 669–699.
75. Salser SJ, Kenyon C: Patterning *C. elegans*. Homeotic cluster genes, cell fates and cell migrations. Trends Genet 1994;10:159–164.
76. Kenyon CJ, Austin J, Costa M, et al: The dance of the Hox genes. Patterning the anteroposterior body axis of *Caenorhabditis elegans*. Cold Spring Harb Symp Quant Biol 1997;62:293–305.
77. Aboobaker AA, Blaxter ML: Hox gene loss during dynamic evolution of the nematode cluster. Curr Biol 2003;13:37–40.

78. Cardoso WV: Transcription factors and pattern formation in the developing lung. Am J Physiol 1995;269:L429–L442.
79. Warburton D, Schwarz M, Tefft D, et al: The molecular basis of lung morphogenesis. Mech Dev 2000;92:55–81.
80. Kaplan F: Molecular determinants of fetal lung organogenesis. Mol Genet Metab 2000;71:321–341.
81. Whitsett JA, Korfhagen TR: Regulation of gene transcription in respiratory epithelial cells. Am J Respir Cell Mol Biol 1996;14:118–120.
82. Wells JM, Melton DA: Vertebrate endoderm development. Annu Rev Cell Dev Biol 1999;15:393–410.
83. Clevidence DE, Overdier DG, Tao W, et al: Identification of nine tissue-specific transcription factors of the hepatocyte nuclear factor3/forkhead DNA-binding-domain family. Proc Natl Acad Sci U S A 1993;90: 3948–3952.
84. Sawaya PL, Stripp BR, Whitsett JA, et al: The lung-specific CC10 gene is regulated by transcription factors from the AP-1, octamer, and hepatocyte nuclear factor-3 families. Mol Cel Biol 1993;13:3860–3871.
85. Bohinski RJ, DiLauro R, Whitsett JA: The lung-specific surfactant protein B gene promoter is a target for thyroid transcription factor 1 and hepatocyte nuclear factor 3, indicating common factors for organ-specific gene expression along the foregut axis. Mol Cell Biol 1994;14:5671–5681.
86. Clevidence DE, Overdier DG, Peterson RS, et al: Members of the HNF-3/forkhead family of transcription factors exhibit distinct cellular expression patterns in lung and regulate the surfactant protein B promoter. Dev Biol 1994;166:195–209.
87. Sawaya PL, Luse DS: Two members of the HNF-3 family have opposite effects on a lung transcriptional element; HNF-3α stimulates and HNF-3β inhibits activity of region I from the Clara cell secretory protein (CCSP) promoter. J Biol Chem 1994;269:22211–22216.
88. Ikeda K, Shaw-White JR, Wert SE, et al: Hepatocyte nuclear factor 3 activates transcription of TTF-1 in respiratory epithelial cells. Mol Cell Biol 1996;16:3626–3636.
89. Wan H, Xu Y, Ikegami M, et al: Foxa2 is required for transition to air breathing at birth. Proc Natl Acad Sci U S A 2004;101:14449–14454.
90. Kimura S, Hura Y, Pinlau T, et al: The T/ebp null mouse. Thyroid specific enhancer binding protein is essential for organogenesis of the thyroid, lung ventral forebrain, and pituitary. Genes Dev 1996;10:60–69.
91. Lazzaro D, Price M, de Felice M, et al: The transcription factor TTF-1 is expressed at the onset of thyroid and lung morphogenesis and in restricted regions of the foetal brain. Development 1991;113:1093–1104.
92. Stahlman MT, Gray ME, Whitsett JA: Expression of thyroid transcription factor-1 (TTF-1) in fetal and neonatal human lung. J Histochem Cytochem 1996;44:673–678.
93. DeFelice M, Silberschmidt D, DiLauro R, et al: TTF-1 phosphorylation is required for peripheral lung morphogenesis, perinatal survival, and tissue-specific gene expression. J Biol Chem 2003;278:35574–35583.
94. Bruno MD, Bohinski RJ, Huelsman KM, et al: Lung cell specific expression of the murine surfactant protein A gene is mediated by interactions between the SP-A promoter and thyroid transcription factor-1. J Biol Chem 1995;270:6531–6536.
95. Kelly SE, Bachurski CJ, Burhans MS, et al: Transcription of the lung-specific surfactant protein C gene is mediated by thyroid transcription factor-1. J Biol Chem 1996;271:6881–6888.
96. Yan C, Sever Z, Whitsett JA: Upstream enhancer activity in the human surfactant protein B gene is mediated by thyroid transcription factor 1. J Biol Chem 1995;270:24852–24857.
97. Ray MK, Chen C-Y, Schwartz RJ, et al: Transcriptional regulation of a mouse Clara cell specific protein (mCC10) gene by the NKx transcription factor family member thyroid transcription factor 1 and cardiac muscle-specific homeobox protein (CSx). Mol Cell Biol 1996;16: 2056–2064.
98. Zhang L, Whitsett JA, Stripp BR: Regulation of Clara cell secretory protein gene transcription by thyroid transcription factor-1. Biochim Biophys Acta 1997;1350:359–367.
99. Ikeda K, Clark JC, Shaw-White JR, et al: Gene structure and expression of human thyroid transcription factor-1 in respiratory epithelial cells. J Biol Chem 1995;270:8108–8114.
100. Bingle CD, Gitlin JD: Identification of hepatocyte nuclear factor-3 binding sites in the Clara cell secretory protein gene. Biochem J 1993;295: 227–232.
101. Le Cras TD, Spitzmiller RE, Albertine KH, et al: VEGF causes pulmonary hemorrhage, hemosiderosis, and air space enlargement in neonatal mice. Am J Physiol 2004;287:L134–L142.
102. Kauffman SL: Cell proliferation in the mammalian lung. Int Rev Exp Pathol 1980;22:131–191.
103. Nogawa H, Ito T: Branching morphogenesis of embryonic mouse lung epithelium in mesenchyme-free culture. Development 1995;121: 1015–1022.
104. Deterding, RR, Jacoby CR, Shannon JM: Acidic fibroblast growth factor and keratinocyte growth factor stimulated fetal rat pulmonary epithelial growth. Am J Physiol 1996;271:L495–L505.
105. Han RN, Liu J, Tanswell AK, et al: Expression of basic fibroblast growth factor and receptor—Immunolocalization studies in developing rat fetal lung. Pediatr Res 1992;31:435–440.
106. Peters KG, Werner S, Chen G, et al: Two FGF receptor genes are differentially expressed in epithelial and mesenchymal tissues during limb formation and organogenesis in the mouse. Development 1992;114: 233–243.
107. Peters K, Werner S, Liao X, et al: Targeted expression of a dominant negative FGF receptor blocks branching morphogenesis and epithelial differentiation of the mouse lung. EMBO J 1994;13:3296–3301.
108. Sekine K, Ohuchi H, Fujiwara M, et al: FGF10 is essential for limb and lung formation. Nat Genet 1999;21:138–141.
109. Min H, Danilenko DM, Scully SA, et al: *Fgf-10* is required for both limb and lung development and exhibits striking functional similarity to *Drosophila branchless*. Genes Dev 1998;12:3156–3161.
110. Arman E, Haffner-Krausz R, Chen Y, et al: Targeted disruption of fibroblast growth factor (FGF) receptor 2 suggests a role for FGF signaling in pregastrulation mammalian development. Proc Natl Acad Sci U S A 1998; 95:5082–5087.
111. Tichelaar JW, Lu W, Whitsett JA: Conditional expression of fibroblast growth factor-7 in the developing and mature lung. J Biol Chem 2000;275:11858–11864.
112. Clark JC, Tichelaar JW, Wert SE, et al: FGF-10 disrupts lung morphogenesis and causes pulmonary adenomas in vivo. Am J Physiol 2001;280: L705–L715.
113. Ulich TR, Yi ES, Longmuir K, et al: Keratinocyte growth factor is a growth factor for type II pneumocytes in vivo. J Clin Invest 1994;93: 1298–1306.
114. Charafeddine L, D'Angio CT, Richards JL, et al: Hyperoxia increases keratinocyte growth factor mRNA expression in neonatal rabbit lung. Am J Physiol 1999;276:L105–L113.
115. Sugahara K, Rubin JS, Mason RJ: Keratinocyte growth factor increases mRNAs for SP-A and SP-B in adult rat alveolar type II cells in culture. Am J Physiol 1995;269:L344–L350.
116. Cardoso WV, Itoh A, Nogawa H, et al: FGF-1 and FGF-7 induce distinct patterns of growth and differentiation in embryonic lung epithelium. Dev Dyn 1997;208:398–405.
117. Guzowski DE, Blau H, Bienkowski RS: Extracellular matrix in developing lung. In: Scarpelli EM, ed: Pulmonary Physiology: Fetus, Newborn, Child, and Adolescent. Philadelphia: Lea & Febiger, 1990, pp 83–105.
118. Pilewski JM, Albelda SM: Adhesion molecules in the lung. An overview. Am Rev Respir Dis 1993;148(6; Suppl):31–37.
119. Hilfer SR: Morphogenesis of the lung. Control of embryonic and fetal branching. Annu Rev Physiol 1996;58:93–113.
120. Kampman KA, McDonald JA: Adhesion molecules in lung morphogenesis. In: Ward PA, Fantone JC, eds: Lung Biology in Health and Disease, Vol 89. New York: Marcel Dekker, 1996, pp 99–126.
121. Spurzem JR, Rennard SI, Romberger DJ: Interactions between pulmonary epithelial cells and extracellular matrix. In: Ward PA, Fantone JC, eds: Lung Biology in Health and Disease, Vol 89. New York: Marcel Dekker, 1996, pp 127–146.
122. Crouch E, Mecham RP, Davila RM, et al: Collagen and elastic fiber proteins in lung development. In: McDonald JA, ed: Lung Development, 1st ed. New York: Marcel Dekker, 1997, p 327.
123. Shannon JM, Deterding RR: Epithelial-mesenchymal interactions in lung development. In: McDonald JA, ed: Lung Growth and Development, 1st ed. New York: Marcel Dekker, 1997, p 81.
124. Ferrara N, Houch KA, Jakeman LB, et al: The vascular endothelial growth factor family of polypeptides. J Cell Biochem 1991;47:211–218.
125. Peters KG, DeVries C, Williams LT: Vascular endothelial growth factor receptor expression during embryogenesis and tissue repair suggests a role in endothelial differentiation and blood vessel growth. Proc Natl Acad Sci U S A 1993;90:8915–8919.
126. Monacci WT, Merrill MJ, Oldfield EH: Expression of vascular permeability factor/vascular endothelial growth factor in normal rat tissues. Am J Physiol 1993;264:C995–C1002.
127. Breier G, Albrecht U, Sterrer S, et al: Expression of vascular endothelial growth factor during embryonic angiogenesis and endothelial cell differentiation. Development 1992;114:521–532.

128. Breier G, Clauss M, Risau W: Coordinate expression of vascular endothelial growth factor receptor-1 (flt-1) and its ligand suggests a paracrine regulation of murine vascular development. Dev Dyn 1995;20:228–239.
129. Millauer B, Wizigmann-Voos S, Schnürch H, et al: High affinity VEGF binding and developmental expression suggest flk-1 as a major regulator of vasculogenesis and angiogenesis. Cell 1993;72:835–846.
130. Boström H, Willetts K, Pekny M, et al: PDGF-A signalling is a critical event in lung alveolar myofibroblast development and alveogenesis. Cell 1996;85:863-873.
131. Liley H, Bernfield M: Mechanisms of development and repair of the lung. In: Chernick V, Mellins RB, eds: Basic Mechanisms of Pediatric Respiratory Disease. Cellular and Integrative. Philadelphia: BC Decker, 1991, pp 11–22.
132. Shannon JM, Mason RJ, Jennings SD: Functional differentiation of alveolar type II epithelial cells in vitro. Effects of cell shape, cell-matrix interactions and cell-cell interactions. Biochim Biophys Acta 1987;931: 143–156.
133. Sanchez-Esteban J, Tsai SW, Sang J, et al: Effects of mechanical forces on lung-specific gene expression. Am J Med Sci 1998;316:200–204.
134. Sanchez-Esteban J, Cicchiello LA, Wang Y, et al: Mechanical stretch promotes alveolar epithelial type II cell differentiation. J Appl Physiol 2001;91:589–595.
135. Finkelstein JN, Horowitz S, Sirkin R, Ryan RM: Cellular and molecular responses to lung injury in relation to induction of tissue repair and fibrosis. Clin Perinatol 1992;19:603–620.
136. Valliant P, Menard O, Vignaud JM, et al: The role of cytokines in human lung fibrosis. Monaldi Arch Chest Dis 1996;51:145–152.
137. O'Reilly MA, Stripp BR, Pryhuber GS: Epithelial-mesenchymal interactions in the alteration of gene expression and morphology following lung injury. Microsc Res Tech 1997;38:473–479.
138. DeMayo F, Minoo P, Plopper CG, et al: Mesenchymal-epithelial interactions in lung development and repair. Are modeling and remodeling the same process? Am J Physiol 2002;283:L510–L517.
139. Chapman HA: Disorders of lung matrix remodeling. J Clin Invest 2004; 113:148–157.
140. Warburton D, Bellusci S: The molecular genetics of lung morphogenesis and injury repair. Paediatr Respir Rev 2004;5(Suppl A):283–287.
141. Kamani NR, Bonagura VR: Developmental immunology of the lung. In: Scarpelli EM, ed: Pulmonary Physiology. Fetus, Newborn, Child, and Adolescent, 2nd ed. Philadelphia: Lea & Febiger, 1990, pp 140–160.
142. Elias JA, Freundlich B, Kern JA, et al: Cytokine networks in the regulation of inflammation and fibrosis in the lung. Chest 1990;97:1439–1445.
143. Kelley J: Cytokines of the Lung. New York: Marcel Dekker, 1992.
144. Lukas NW, Ward PA: Inflammatory mediators, cytokines, and adhesion molecules in pulmonary inflammation and injury. Advan Immunol 1996; 62:257–304.
145. Standiford TJ: Cytokines and pulmonary host defenses. Curr Opin Pulm Med 1997;3:81–88.
146. Zhang P, Summer WR, Bagby GJ, et al: Innate immunity and pulmonary host defense. Immunol Rev 2000;173:39–51.
147. Strieter RM, Belperio JA, Keane MP: Cytokines in innate host defense in the lung. J Clin Invest 2002;109:699–705.
148. Strieter RM, Belperio JA, Keane MP: Host innate defenses in the lung. The role of cytokines. Curr Opin Infect Dis 2003;16:193–198.
149. Adler KB, Fischer BM, Wright DT, et al: Interactions between respiratory epithelial cells and cytokines. Relationships to lung inflammation. Ann NY Acad Sci 1994;725:120–145.
150. Sheperd VL: Cytokine receptors of the lung. Am J Respir Cell Mol Biol 1991;5:403–410.
151. Dranoff G, Crawford AD, Sadelain M, et al: Involvement of granulocyte-macrophage colony stimulating factor in pulmonary homeostasis. Science 1994;264:713–716.
152. Lieschke GJ, Stanley E, Grail D, et al: Mice lacking both macrophage- and granulocyte-macrophage colony-stimulating factor have macrophages and coexistent osteoporosis and severe lung disease. Blood 1994;84:27–35.
153. Stanley E, Lieshke GJ, Grail D, et al: Granulocyte/macrophage colony stimulating factor-deficient mice show no major perturbation of hematopoiesis but develop a characteristic pulmonary pathology. Proc Natl Acad Sci U S A 1994;91:5592–5594.
154. Huffman JA, Hull WM, Dranoff G, et al: Pulmonary epithelial cell expression of GM-CSF corrects the alveolar proteinosis in GM-CSF-deficient mice. J Clin Invest 1996;97:649–655.
155. Ikegami M, Ueda T, Hull W, et al: Surfactant metabolism in transgenic mice after granulocyte macrophage-colony stimulating factor ablation. Am J Physiol 1996;270:L650–L658.
156. Trapnell BC, Whitsett JA: GM-CSF regulates pulmonary surfactant homeostasis and alveolar macrophage-mediated innate host defense. Annu Rev Physiol 2002;64:775–802.
157. Perkett EA: Role of growth factors in lung repair and diseases. Curr Opin Pediatr 1995;7:242–249.
158. Sastry K, Ezekowitz RA: Collectins. Pattern recognition molecules involved in first line host defense. Curr Opin Immunol 1993;5:59–66.
159. Van Iwaarden JF, Pikaar JC, Storm J, et al: Binding of surfactant protein A to the lipid A moiety of bacterial lipopolysaccharides. Biochem J 1994; 303:407–411.
160. McNeely TB, Coonrod JD: Aggregation and opsonization of type A but not type B *Hemophilus influenzae* by surfactant protein A. Am J Respir Cell Mol Biol 1994;11:114–122.
161. Limper AH, Crouch EC, O'Riordan DM, et al: Surfactant protein-D modulates interaction of *Pneumocystis carinii* with alveolar macrophages. J Lab Clin Med 1995;126:416–422.
162. Geertsma MF, Nibbering PH, Haagsman HP, et al: Binding of surfactant protein A to C1q receptors mediates phagocytosis of *Staphylococcus aureus* by monocytes. Am J Physiol 1994;267:L578–L584.
163. Downing JF, Pasula R, Wright JR, et al: Surfactant protein A promotes attachment of *Mycobacterium tuberculosis* to alveolar macrophages during infection with human immunodeficiency virus. Proc Natl Acad Sci U S A 1995;92:4848–4852.
164. Benne CA, Kraaijeveld CA, van Strijp JAG, et al: Interactions of surfactant protein A with influenza A viruses. Binding and neutralization. J Infect Dis 1995;171:335–341.
165. Wright JR: Immunomodulatory functions of surfactant. Semin Respir Crit Care Med 1995;16:61–68.
166. Tino MJ, Wright JR: Surfactant protein A stimulates phagocytosis of specific pulmonary pathogens by alveolar macrophages. Am J Physiol 1996;270:L677–L688.
167. Williams MD, Wright JR, March KL, et al: Human surfactant protein A enhances attachment of *Pneumocystis carinii* to rat alveolar macrophages. Am J Respir Cell Mol Biol 1996;14:232–238.
168. LeVine AM, Whitsett JA: Pulmonary collectins and innate host defense of the lung. Microbes Infect 2001;3:161–166.
169. Crouch E, Wright JR: Surfactant proteins A and D and pulmonary host defense. Annu Rev Physiol 2001;63:521–554.
170. McCormack FX, Whitsett JA: The pulmonary collectins, SP-A and SP-D, orchestrate innate immunity in the lung. J Clin Invest 2002;109: 707–712.
171. Bevins CL: Antimicrobial peptides as agents of mucosal immunity. Ciba Found Symp 1994;186:250–260.
172. Ganz T: Biosynthesis of defensins and other microbial peptides. Ciba Found Symp 1994;186:62–71.
173. Ganz T, Lehrer RI: Defensins. Curr Opin Immunol 1994;6:584–589.
174. Kagan BL, Ganz T, Lehrer RI: Defensins. A family of antimicrobial and cytotoxic peptides. Toxicology 1994;87:131–149.
175. van Wetering S, Sterk PJ, Rabe KF, et al: Defensins. Key players or bystanders in infection, injury, and repair in the lung? J Allergy Clin Immunol 1999;104:1131–1138.
176. Cole AM, Waring AJ: The role of defensins in lung biology and therapy. Am J Respir Med 2002;1:249–259.
177. Schutte BC, McCray PB Jr: β-Defensins in lung host defense. Ann Rev Physiol 2002;64:709–748.
178. Wert SE, Profitt SA, Kirwin KL, et al: Acinar dysplasia is associated with the absence of TTF-1 and HNF-3β expression during human lung development. Pediatr Res 1996;39:355A.
179. Devriendt K, Vanhole C, Matthijs G, et al: Deletion of thyroid transcription factor-1 gene in an infant with neonatal thyroid dysfunction and respiratory failure. N Engl J Med 1998;338:1317–1318.
180. Houston CS, Opitz JM, Spranger JW, et al: The campomelic syndrome. Review, 17 cases, and follow up on the currently 17-year-old boy first reported by Maroteaux et al in 1971. Am J Med Genet 1983;15: 3–28.
181. Foster JW, Dominguez-Steglich MA, Guioli S, et al: Campomelic dysplasia and autosomal sex reversal caused by mutations in an SRY-related gene. Nature 1994;372:525–530.
182. Wagner T, Wirth J, Meyer J, et al: Autosomal sex reversal and campomelic dysplasia are caused by mutations in and around the SRY-related gene SOX9. Cell 1994;79:1111–1120.
183. Mansour S, Hall CM, Pembrey ME, et al: A clinical and genetic study of campomelic dysplasia. J Med Genet 1995;32:415–420.
184. Mansour S, Offiah AC, McDowall S, et al: The phenotype of survivors of campomelic dysplasia. J Med Genet 2002;39:597–602.

185. Pepicelli CV, Lewis PM, McMahon AP: Sonic hedgehog regulates branching morphogenesis in the mammalian lung. Curr Biol 1998;8: 1083–1086.
186. Kan SH, Elanko N, Johnson D, et al: Genomic screening of fibroblast growth-factor receptor 2 reveals a wide spectrum of mutations in patients with syndromic craniosynostosis. Am J Hum Genet 2002;70:472–486.
187. Nogee LM: Alterations in SP-B and SP-C expression in neonatal lung disease. Annu Rev Physiol 2004;66:601–623.
188. Nogee LM: Genetic mechanisms of surfactant deficiency. Biol Neonate 2004;85:314–318.
189. Trapnell BC, Whitsett JA, Nakata K: Pulmonary alveolar proteinosis. N Engl J Med 2003;349:2527–2539.
190. Nogee LM, Dunbar AE 3rd, Wert SE, et al: A mutation in the surfactant protein C gene associated with familial interstitial lung disease. N Engl J Med 2001;344:573–579.
191. Nogee LM: Abnormal expression of surfactant protein C and lung disease. Am J Respir Cell Mol Biol 2002;26:641–644.
192. Shulenin S, Nogee LM, Annilo T, et al: ABCA3 gene mutations in newborns with fatal surfactant deficiency. N Engl J Med 2004;350: 1296–1303.

2 The Surfactant System

Ann Marie LeVine, MD • Alan H. Jobe, MD

Pulmonary surfactant is a complex substance with multiple functions in the microenvironments of the alveoli and small airways. The traditional functions of surfactant are the biophysical activities to keep the lungs open, to decrease the work of breathing, and to prevent alveolar flooding. More recently, most of the components of surfactant were found to contribute to innate host defenses and injury responses in the lung. Surfactant deficiency states occur with prematurity and with severe lung injury syndromes. Recent studies in humans and in mice are defining an expanding number of genetic and metabolic abnormalities that disrupt surfactant and cause lung diseases that range from lethal respiratory failure at birth to chronic interstitial lung disease in later life. Our goal is to summarize those aspects of surfactant biology that are relevant to children.

SURFACTANT COMPOSITION AND METABOLISM

COMPOSITION

Surfactant recovered from lungs by bronchoalveolar lavage contains about 80% phospholipids, about 8% protein, and about 8% neutral lipids, primarily cholesterol (Fig. 2-1). The phosphatidylcholine species of the phospholipids contribute about 70% by weight to surfactant. The phospholipids in surfactant are unique relative to the lipid composition of lung tissue or other organs. About 50% of the phosphatidylcholine species have two palmitic acids or other saturated fatty acids esterified to the glycerol-phosphorylcholine backbone, resulting in "saturated" phosphatidylcholine, which is the principal surface-active component of surfactant. About 8% of surfactant is the acidic phospholipid phosphatidylglycerol. Surfactant from the immature fetus contains relatively large amounts of phosphatidylinositol, which then decreases as phosphatidylglycerol appears with lung maturity.

Four surfactant-specific proteins have been identified and their functions in part elucidated.[1,2] Surfactant protein A (SP-A) is a water-soluble collectin coded on human chromosome 10. The 24-kd protein is heavily glycosylated in the carboxy-terminal region to yield a reduced protein of about 36 kd. SP-A forms a collagen-like triple helix that then aggregates to form a multimeric protein with a molecular size of 650 kd. SP-A contributes to the biophysical properties of surfactant primarily by decreasing protein-mediated inhibition of surfactant function. The major functions of SP-A are an innate host defense protein and as a regulator of inflammation in the lung.[1] SP-A levels are low in surfactant from preterm lungs and increase with corticosteroid exposure. SP-A is not a component of surfactants used for treatment of respiratory distress syndrome (RDS).

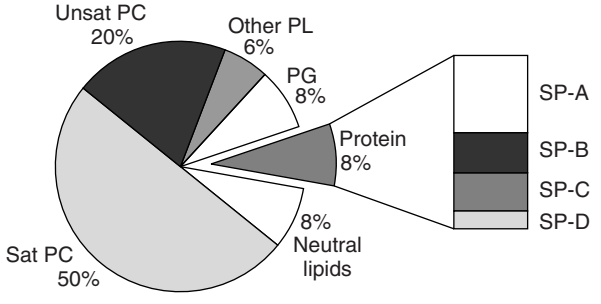


FIGURE 2-1. Composition of surfactant. Saturated phosphatidylcholines are the major components of alveolar surfactant. The proteins contribute about 8% to the weight of surfactant.

SP-B is a small hydrophobic protein that contributes about 2% to the surfactant mass.[2] The SP-B gene is on human chromosome 2, and the primary translation product is 40 kd. The protein is clipped in the type II cell to become an 8-kd protein prior to associating with phospholipids to form lamellar bodies. SP-B facilitates surface absorption of lipids and the development of low surface tensions on surface area compression. A genetic lack of SP-B causes a loss of normal lamellar bodies in type II cells, a lack of mature SP-C, and the appearance of incompletely processed SP-C in the airspaces.[3]

The SP-C gene is on chromosome 8, and its primary translation product is a 22-kd protein that is processed to an extremely hydrophobic 4-kd protein that is associated with lipids in lamellar bodies.[4] The messenger RNA (mRNA) for SP-C appears in cells lining the developing airways from early gestation. With advancing lung maturation, the mRNA for SP-C becomes localized only to type II cells. The sequence and cellular localization of SP-C have been remarkably conserved across species. SP-B and SP-C function cooperatively to optimize rapid adsorption and spreading of phospholipids on a surface and to facilitate the development of low surface tensions on surface area compression. Surfactants prepared by organic solvent extraction of natural surfactants or from lung tissue contain SP-B and SP-C. Such surfactants are similar to natural surfactants when evaluated for in vitro surface properties or for function in vivo.

SP-D is a 43-kd hydrophilic collectin with structural similarities to SP-A with a collagen-like domain and a glycosylated head group that gives it lectin-like functions.[5] SP-D is synthesized by type II cells and by Clara cells, as well as in other epithelial sites. Like the other SPs, its expression is developmentally regulated and induced by glucocorticoids and inflammation. SP-D is soluble and not associated with the surfactant lipids or other surfactant proteins.

SURFACTANT METABOLISM AND SECRETION

The synthesis and secretion of surfactant by the type II cell is a complex sequence of biochemical events that results in the release by exocytosis of lamellar bodies to the alveolus.[6] Enzymes within the endoplasmic reticulum use glucose, phosphate,

and fatty acids as substrates for phospholipid synthesis. The details of how the surfactant components condense with SP-B and SP-C to form the surfactant lipoprotein complex within lamellar bodies remain obscure. Ultrastructural abnormalities of type II cells with SP-B deficiency and ABCA3 deficiency in full-term infants indicate that these gene products are essential for lamellar body formation.[4,7] A basal rate of surfactant secretion occurs continuously, and surfactant secretion can be stimulated by a number of mechanisms. Type II cells increase surfactant secretion in response to β agonists and purines. Surfactant secretion also is stimulated by mechanical stretch such as with lung distention and hyperventilation.

The alveolar pool size of saturated phosphatidylcholine of about 2 μmol/kg in the adult human is equivalent to about 4 mg/kg surfactant.[8] The lung tissue of the adult human contains about 28 μmol/kg. Thus, about 7% of the lung saturated phosphatidylcholine is in the secreted pool. The surfactant pool size per kilogram probably changes little with age after the newborn period. While no estimates exist for the full-term human, full-term animals have alveolar pool sizes of about 100 mg/kg, and this large pool decreases to adult values by 1 week of age in rabbits, for example. The alveolar surfactant pool size in the adult (and presumably young child) is small relative to other mammalian species (e.g., about 30 mg/kg in adult sheep), which may make the human lung more susceptible to surfactant deficiency with lung injury. Infants with RDS have alveolar surfactant pool sizes of less than 5 mg/kg.

The metabolic activity of surfactant was measured in animals using radioisotopes to pulse label surfactant components, which then were tracked from synthesis to secretion and catabolism or recycling.[9] Surfactant components are synthesized rapidly from precursors and then packaged in lamellar bodies for storage and secretion. The time from synthesis to peak alveolar secretion of the newly synthesized surfactant is about 6 hours in adult rabbits. The turnover time for surfactant lipids is about 5 hours, with about 50% of the lipids being recycled from the airspaces back into lamellar bodies for resecretion. No measurements of surfactant metabolism have been reported in older children or adult humans. The few measurements in large juvenile or adult animals indicate that surfactant is dynamically metabolized by efficient recycling from secretion to uptake for resecretion. The surfactant proteins also are recycled to variable extents.

More extensive measurements of surfactant metabolism have been made in developing animals and in preterm and full-term infants. In general, alveolar pool sizes are larger per kilogram body weight, secretion rates may be lower, and turnover times longer at full term. Recycling is very efficient in the newborn. Stable isotopically labeled precursors of surfactant lipids were used for studies in newborn humans.[10] These studies will be extended to children and adults in the near future.

ALVEOLAR LIFE CYCLE OF SURFACTANT

After secretion, surfactant goes through a series of form transitions in the airspace (Fig. 2-2). The lamellar bodies unravel to form the elegant structure called tubular myelin. This lipoprotein array has SP-A at the corners of the lattice and requires at least SP-A, SP-B, and the phospholipids for its unique structure.[11] Tubular myelin and other large surfactant lipoprotein structures are the reservoir in the fluid hypophase for the formation of the surface film within the alveolus and small airways. The hypophase is a very thin fluid layer covering the distal epithelium with a volume of about 0.5 mL/kg body weight that has a surfactant concentration of perhaps 10 mg/mL. New surfactant enters the surface film, and "used" surfactant leaves in the form of small vesicles. The surface-active tubular myelin forms contain SP-A, SP-B, and SP-C while the biophysically inactive small vesicular forms that are recycled and catabolized contain very little protein. The total surfactant pool size is less than the amount of active surfactant because 30% to 50% of the alveolar phospholipids are in catabolic forms in the normal lung.

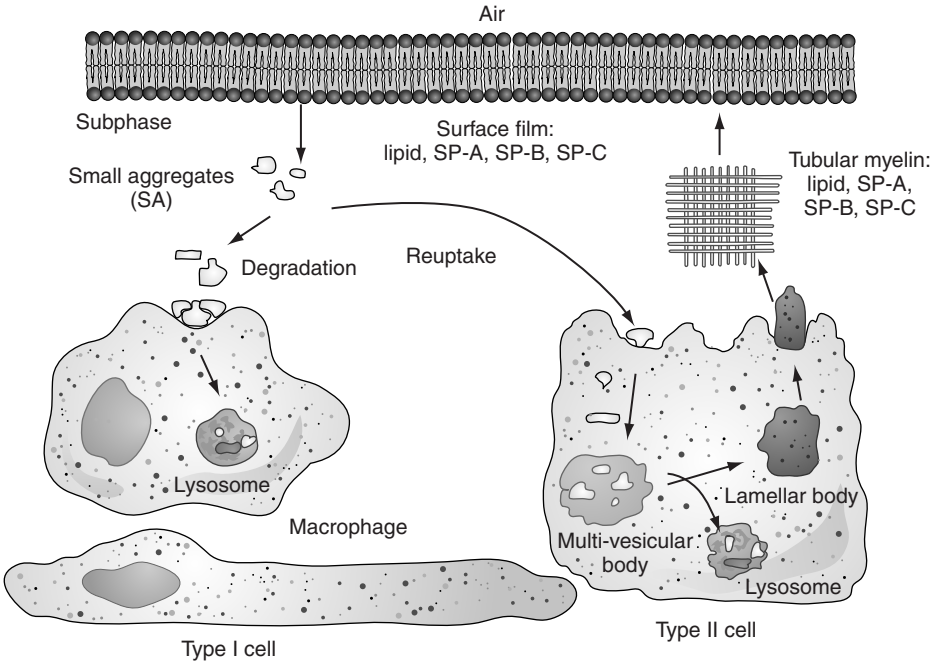


FIGURE 2-2. Alveolar life cycle of surfactant. Surfactant is secreted from lamellar bodies in type II cells. In the alveolar fluid lining layer, the surfactant transforms into tubular myelin and other surfactant protein–rich forms that facilitate surface adsorption. The lipids are catabolized as small vesicular forms by macrophages and type II cells and recycled by type II cells.

In the preterm infant, conversion from surface active to inactive forms occurs more rapidly, probably because less surfactant proteins are present. Pulmonary edema and products of lung injury can accelerate form conversion and cause a depletion of the surface active fraction of surfactant despite normal or high total surfactant pool sizes.[12]

Surfactant is catabolized primarily by type II cells and alveolar macrophages. Granulocyte-macrophage colony-stimulating factor deficiency prevents alveolar macrophages from catabolizing surfactant and results in the clinical syndrome of alveolar proteinosis. The important concept is that the alveolar pool of functional surfactant is maintained by dynamic metabolic processes that include secretion, reuptake, and resecretion balanced by catabolism.

SURFACTANT FUNCTION

ALVEOLAR STABILITY

Alveoli are polygonal with flat surfaces and curvatures where the walls of adjacent alveoli intersect. Alveoli are interdependent in that their structure is determined by the shape and elasticity of neighboring alveolar walls. The forces acting on the pulmonary microstructure are chest wall elasticity, lung tissue elasticity, and surface tensions of the air-fluid interfaces of the small airways and alveoli. Although the surface tension of surfactant decreases with surface area compression and increases with surface area expansion, the surface area of an alveolus changes little with tidal breathing. The low surface tensions resulting from surfactant help to prevent alveolar collapse and keep interstitial fluid from flooding the alveoli. Surfactant also keeps small airways from filling with fluid and thus prevents the potentially ensuing luminal obstruction.[13] If alveoli collapse or fill with fluid, the shape of adjacent alveoli will change, which can result in distortion, overdistention, or collapse. When positive pressure is applied to a surfactant-deficient lung, the more normal alveoli will tend to overexpand and the alveoli with inadequate surfactant will collapse, generating a nonhomogeneously inflated lung.

PRESSURE-VOLUME CURVES

The static effects of surfactant on a surfactant-deficient lung are evident from the pressure-volume curve of the preterm lung (Fig. 2-3). Preterm surfactant-deficient rabbit lungs do not begin to inflate until pressures exceed 20 cm H_2O.[14] The pressure needed to open a lung unit is related to the radius of curvature and surface tension of the meniscus of fluid in the airspace leading to the lung unit. The units with larger radii and lower surface tensions will "pop" open first because, with partial expansion, the radius increases and the forces needed to finish opening the unit decrease. Surfactant decreases the opening pressure from greater than 20 to 15 cm H_2O in this example with preterm rabbit lungs. Because surfactant does not alter airway diameter, the decreased opening pressure results from surface adsorption of the surfactant to the fluid in the airways. The inflation is more uniform as more units open at lower pressures, resulting in less overdistention of the open units.

A particularly important effect of surfactant on the surfactant-deficient lung is the increase in maximal volume at maximal pressure. In this example, maximal volume at 30 cm H_2O is increased over two times with surfactant treatment. Surfactant also stabilizes the lung on deflation. The surfactant-deficient lung collapses at low transpulmonary pressures, whereas the surfactant-treated lung retains about 30% of the lung volume on deflation. This retained volume is similar to the total volume of the surfactant-deficient lung at 30 cm H_2O and demonstrates how surfactant treatments increase the functional residual capacity of the lung.

HOST DEFENSE FUNCTIONS OF SURFACTANT

SP-A enhances microbial phagocytosis by macrophages because it acts as opsonin, can directly stimulate macrophage activity, and is chemotactic for alveolar macrophages and peritoneal macrophages.[15] SP-A binds a variety of microorganisms, including bacteria, viruses, and fungi, and stimulates the release of oxygen radicals from alveolar macrophages. SP-A also regulates cytokine production by macrophages, granulocytes,

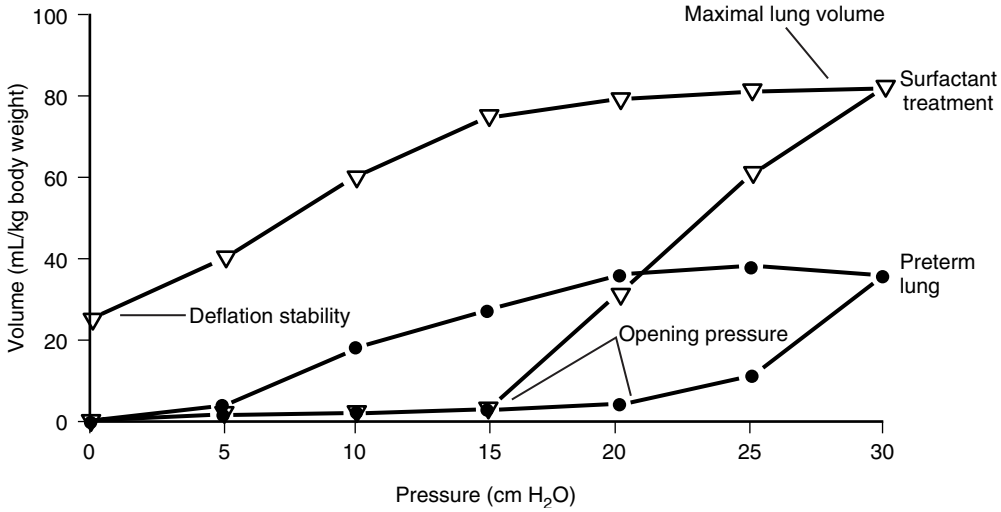


FIGURE 2-3. Effect of surfactant treatment on surfactant deficient lungs. These idealized pressure-volume curves illustrate the effect of surfactant treatment with natural sheep surfactant on the opening pressure, the maximal lung volume, and the deflation stability of lungs from preterm rabbits. (Curves based on data from Rider ED, Jobe AH, Ikegami M, Sun B: Different ventilation strategies alter surfactant responses in preterm rabbits. J Appl Physiol 1992;73:2089–2096.)

and lymphocytes. SP-A has multiple roles in regulating innate immune and inflammatory responses in the lung during acute lung injury.[16] SP-A also may contribute to adaptive immune responses. SP-A inhibits the maturation of dendritic cells in response to potent T-cell stimulators and enhances the endocytic ability of dendritic cells. In addition, SP-A down-regulates lymphocyte activity and proliferation. Thus, SP-A may have a complex role in adaptive immune responses.[17]

The hydrophobic surfactant proteins SP-B and SP-C may also have host defense functions. Although SP-B can inhibit bacterial growth in vitro, overexpression of SP-B or reduced expression of SP-B in the lungs of mice did not alter bacterial clearance, suggesting that the SP-B is not involved in innate host defense.[18] However, elevated levels of SP-B in the lungs of endotoxin-exposed mice decreased pulmonary inflammation.[19] Thus, SP-B may contribute to modulation of inflammation in the injured lung. SP-C binds lipopolysaccharide and blocks the production of tumor necrosis factor-α by macrophages.[20] However, possible roles for SP-C in bacterial clearance or lung inflammation in vivo have not been evaluated.

SP-D increases phagocytosis of gram-negative and gram-positive bacteria, viruses, fungi, and parasites by alveolar macrophages in a calcium-dependent manner.[1] SP-D also enhances calcium-dependent uptake of *Escherichia coli*, *Streptococcus pneumoniae,* and *Staphylococcus aureus* by neutrophils. In addition to binding microorganisms, SP-D is more chemotactic than SP-A for monocytes and neutrophils. Both SP-A and SP-D increase the production of oxygen radicals by alveolar macrophages, down-regulate lymphocyte activity and proliferation, and inhibit allergen-induced proliferation of lymphocytes.[16,17] SP-D has an important role in regulating innate and adaptive immune responses in the lung.

SURFACTANT DEFICIENCY

THE PRETERM INFANT WITH RESPIRATORY DISTRESS SYNDROME

RDS in preterm infants is a surfactant deficiency that initially does not include lung injury. The surfactant system normally is mature by about 35 weeks' gestation, but early appearance of surfactant and lung maturation is frequent for infants delivered prematurely. Early maturation is thought to occur in response to fetal stress resulting in increased fetal cortisol levels, or by exposure of the fetal lung to inflammation as a result of chorioamnionitis. Maternal treatments with corticosteroids to decrease the risk of RDS are routinely given if preterm delivery before 32 to 34 weeks' gestation is anticipated.[21] Induced lung maturation includes not only an induction of surfactant but also thinning of the mesenchyme, which increases lung gas volumes. Unless preterm infants have early lung maturation, they develop progressive respiratory distress from birth characterized by tachypnea, grunting, an increased work of breathing, and cyanosis. Infants who have died of RDS have alveolar pool sizes of surfactant of less than 5 mg/kg. Although this amount is similar in amount to the surfactant recovered from healthy adult humans, surfactant from the preterm infant has decreased function, probably because it contains less of the surfactant proteins that are critical for biophysical function.[22] The surfactant from the preterm infant also is more susceptible to inactivation by edema fluid, and the preterm lung is easily injured if a stable functional residual capacity (FRC) is not maintained or if the lung is overstretched.

THE INJURED MATURE LUNG

Acute respiratory distress syndrome (ARDS) describes an overwhelming inflammatory reaction within the pulmonary parenchyma leading to global lung dysfunction. ARDS is defined by acute onset, an oxygenation index less than 200 mm Hg, bilateral infiltrates on chest x-ray, and a pulmonary capillary wedge pressure of less than 18 mm Hg or absence of clinical evidence for left-sided heart failure. The etiology of ARDS is multifactorial and can occur in association with lung injury secondary to trauma, sepsis, aspiration, pneumonia, massive blood transfusions, or near drowning to name some associations. It is a common disease, affecting roughly 15% to 20% of all patients ventilated in the adult intensive care unit (ICU) and 1% to 4.5% of patients in the pediatric ICU. ARDS has a high mortality rate of 40% to 50%.

Impairment of surfactant with ARDS can result from inhibition, degradation, or decreased production.[12] The proteinaceous pulmonary edema characteristic of ARDS can inactivate surfactant by dilution and by competition for the interface. Plasma proteins known to inhibit surfactant function include serum albumin, globulin, fibrinogen, and C-reactive protein. In addition to proteins, phospholipases A2 and C, along with their products, fatty acids, and dipalmitin inhibit surface activity. Epithelial cell injury by inflammatory mediators can decrease surfactant production and contribute to surfactant deficiency.

Surfactant is present in the alveoli as tubular myelin and lipoprotein aggregates that are biophysically active and as small vesicles that are not bioactive. Normally in the lung, about 50% of surfactant is present in the bioactive form that has a high SP-B and SP-C content. In ARDS, small vesicular forms increase and deplete the pool of active surfactant.

The composition of surfactant is altered in ARDS. In bronchoalveolar lavage fluid (BALF) from patients with ARDS, there is a reduced phospholipid content and abnormal phospholipid composition.[23] SP-A, SP-B, and SP-C also are decreased in BALF from patients with ARDS. The surfactant protein levels can remain low for at least 14 days after the onset of ARDS. Changes in surfactant composition including phospholipids, fatty acids, and proteins likely represent alveolar type II cell injury with altered metabolism, secretion, or recycling of components. SP-A and SP-B concentrations are also reduced in the lungs of patients at risk for ARDS, even before the onset of lung injury clinically. In contrast, SP-D levels in BALF remain normal, except in a subgroup of patients who later died. Decreased SP-D levels in BALF were 85.7% sensitive and 74% specific in predicting death with ARDS.[24]

GENETIC DEFICIENCIES OF SURFACTANT IN MICE AND HUMANS

SP-A-deficient mice have normal survival without changes in surfactant composition, function, secretion, and reuptake; however, there is no tubular myelin.[25] SP-A-deficient mice are highly susceptible to various bacterial (group B *Streptococcus, Haemophilus influenza, Pseudomonas aeruginosa*) and viral (respiratory syncytial virus [RSV], influenza A virus) pathogens in vivo.[16] There are currently no documented genetic deficiencies of SP-A

in humans. However, polymorphisms in the human genes for SP-A affecting their function have been identified, and humans with these polymorphisms have increased susceptibility to infections with respiratory syncytial virus and *Mycobacterium tuberculosis*.[26]

Gene-targeted mice lacking SP-B and infants with hereditary SP-B deficiency demonstrate the critical role of SP-B in surfactant function, homeostasis, and lung function.[27] Targeted disruption of the mouse SP-B gene caused respiratory failure at birth. Despite normal lung structure, the mice failed to inflate their lungs postnatally. Type II cells of SP-B-deficient mice had large multivesicular bodies but did not have lamellar bodies, and the proteolytic processing of pro-SP-C (the preprocessed form of SP-C) was disrupted.[2] Infants with SP-B deficiency die from respiratory distress in the early neonatal period with the same anatomic findings.[28] Mutations leading to partial SP-B function have been associated with chronic lung disease in infants. Mice and infants without the adenosine triphosphate–binding cassette transporter A3 (ABCA3) have type II cells without lamellar bodies and the same lethal respiratory failure phenotype.[7]

SP-C-deficient mice survive and have normal surfactant composition and amounts. However, surfactant isolated from the SP-C-deficient mice forms less stable bubbles, demonstrating a role for SP-C in developing and maintaining lipid films.[29] SP-C mutations recently were identified in families with familial interstitial lung disease that can present in childhood or in adulthood.[30] These individuals have lungs with a thickened interstitium, infiltration with inflammatory cells and macrophages, fibrosis, and abnormalities of the respiratory epithelium.

SP-D-deficient mice develop increased surfactant lipid pools in the lung, indicating that SP-D plays a critical role in the regulation of surfactant homeostasis. SP-D also regulates alveolar macrophage function because SP-D-deficient mice accumulate foamy activated macrophages in the lung and develop emphysema due to increased oxidant and metalloproteinase expression by these macrophages.[1] SP-D-deficient mice are also highly susceptible to infection by influenza A virus and RSV.[16] SP-D deficiency has not been described in humans.

SURFACTANT TREATMENT OF SURFACTANT DEFICIENCY

RESPIRATORY DISTRESS SYNDROME

The respiratory morbidities of preterm infants with RDS have decreased strikingly in recent years because of the combined effects of antenatal corticosteroid treatments and more gentle approaches to mechanical ventilation. The original randomized trials of surfactant for RDS evaluated treatments given after the disease was established, generally after 6 hours of age. Other trials evaluated treatment of all high-risk infants soon after birth to prevent RDS. Subsequent trials demonstrated that treatments of the highest-risk infants (generally infants with birth weights less than 1 kg) as soon after birth as convenient and before significant mechanical ventilation will minimize lung injury. However, many very low birth weight infants can be transitioned to air breathing successfully using continuous positive airway pressure (CPAP), and the decision to treat with surfactant can be made after the initial stabilization at birth. An advantage of allowing the infant to breathe spontaneously with CPAP used to recruit and maintain FRC is that hyperventilation and overdistention of the delicate preterm lung can be avoided. Larger infants who develop RDS generally are treated with oxygen and nasal CPAP until the oxygen concentration approaches 40%. They then are treated with surfactant. Preterm infants will respond to surfactant treatments even if the treatment is delayed for several days.

Full-term infants with severe meconium aspiration or pneumonia also will respond to surfactant treatments with improved oxygenation. Surfactant also can improve lung function in infants with the group B streptococcal sepsis/pneumonia syndrome. Current practice is to treat most any infant with severe respiratory failure with surfactant because there seems to be no contraindications.

The surfactants that are commercially available for clinical use in infants are made from organic solvent extracts of animal lungs or alveolar lavages of animal lungs. While there are differences in composition, the clinical results do not demonstrate any compelling differences in clinical responses. All of the commercial surfactants lack SP-A, contain SP-C, and have variable amounts of SP-B. Surfactants that contain synthetic peptides or surfactant proteins are being developed for clinical use.

ACUTE RESPIRATORY DISTRESS SYNDROME

ARDS is a significant therapeutic challenge for intensivists despite recent advances in understanding pathophysiology and new treatment modalities. Surfactant content and composition are altered in ARDS, resulting in decreased surface activity, atelectasis, and decreased lung compliance.[12] Surfactant treatment for ARDS can improve gas exchange, but to a lesser degree than that seen with RDS. ARDS results in primarily surfactant inactivation rather than deficiency, and surfactant inhibitors such as plasma proteins and inflammatory mediators decrease the efficacy of treatment. Several recent pilot studies in adults and children have examined surfactant therapy in ARDS.

Adults with ARDS treated with a natural bovine surfactant had significant improvements in gas exchange and a trend toward decreased mortality.[31] Walmrath and colleagues examined the efficacy of bronchoscopic administration of a bovine surfactant preparation in adult patients with ARDS. Patients demonstrated improved gas exchange, recruitment of collapsed alveoli, and improved ventilation-perfusion mismatch.[32] A phase II study in Europe recently evaluated the efficacy of intratracheal administration of a recombinant SP-C in ARDS patients.[33] Patients were randomized to receive either standard therapy alone or standard therapy plus recombinant SP-C surfactant, given as either 200 mg/kg in four doses or 500 mg/kg in four doses. The lower-dose group had significant improvement in oxygenation index, and patients were weaned more rapidly from the ventilator compared with the standard therapy group. Results in the high-dose group were not different from those of the standard therapy group.

In a large trial, full-term infants with severe respiratory failure treated with surfactant had improved oxygenation and required less extracorporeal membrane oxygenation (ECMO) than did controls.[34] Children with ARDS or acute lung injury (ALI) have been treated with a number of different surfactants in small trials. No large or definitive trials of surfactant for respiratory failure in children have been performed. Representative responses have improved oxygenation and decreased ventilator days,[35] results that are consistent with the larger trials in adults with ARDS.

There is strong experimental evidence that alterations in the pulmonary surfactant system play an important role in the pathophysiology of ARDS.[36] While it is still unclear whether mortality and morbidity from ARDS will be reduced, surfactant treatments can improve oxygenation, improve lung compliance, and decrease the need for ventilatory support.

REFERENCES

1. McCormack FX, Whitsett JA: The pulmonary collectins, SP-A and SP-D, orchestrate innate immunity in the lung. J Clin Invest 2002;109:707–712.
2. Whitsett JA, Weaver TE: Hydrophobic surfactant proteins in lung function and disease. N Engl J Med 2002;347:2141–2148.
3. Nogee LM: Genetics of the hydrophobic surfactant proteins. Biochim Biophys Acta 1998;1408:323–333.
4. Weaver TE, Conkright JJ: Function of surfactant proteins B and C. Annu Rev Physiol 2001;63:555–578.
5. Crouch E, Wright JR: Surfactant proteins a and d and pulmonary host defense. Annu Rev Physiol 2001;63:521–554.
6. Mason RJ, Voelker DR: Regulatory mechanisms of surfactant secretion. Biochim Biophys Acta 1998;1408:226–240.
7. Shulenin S, Nogee LM, Annilo T, et al: ABCA3 gene mutations in newborns with fatal surfactant deficiency. N Engl J Med 2004;350: 1296–1303.
8. Rebello CM, Jobe AH, Eisele JW, Ikegami M: Alveolar and tissue surfactant pool sizes in humans. Am J Respir Crit Care Med 1996;154:625–628.
9. Jobe AH, Rider ED: Catabolism and recycling of surfactant. In: Robertson B, van Golde LMG, Batenburg JJ, eds: Pulmonary surfactant. From molecular biology to clinical practice. Amsterdam: Elsevier, 1992.
10. Torresin M, Zimmermann LJ, Cogo PE, et al: Exogenous surfactant kinetics in infant respiratory distress syndrome. A novel method with stable isotopes. Am J Respir Crit Care Med 2000;161:1584–1589.
11. Schurch S, Green FHY, Bachofen H: Formation and structure of surface films. Captive bubble surfactometry. Biochim Biophys Acta 1998;1408: 180–202.
12. Lewis JF, Jobe AH: Surfactant and the adult respiratory distress syndrome. Am Rev Respir Dis 1993;147:218–233.
13. Enhorning G, Duffy LC, Welliver RC: Pulmonary surfactant maintains patency of conducting airways in the rat. Am J Respir Crit Care Med 1995; 151:554–556.
14. Rider ED, Jobe AH, Ikegami M, Sun B: Different ventilation strategies alter surfactant responses in preterm rabbits. J Appl Physiol 1992;73: 2089–2096.
15. Wright JR, Youmans DC: Pulmonary surfactant protein A stimulates chemotaxis of alveolar macrophage. Am J Physiol 1993;264:L338–L344.
16. LeVine AM, Whitsett JA: Pulmonary collectins and innate host defense of the lung. Microbes Infect 2001;3:161–166.
17. Hohlfeld JM, Erpenbeck VJ, Krug N: Surfactant proteins SP-A and SP-D as modulators of the allergic inflammation in asthma. Pathobiology 2002; 70:287–292.
18. Akinbi HT, Bhatt H, Hull WM, Weaver TE: Altered surfactant protein B levels in transgenic mice do not affect clearance of bacteria from the lungs. Pediatr Res 1999;46:530–534.
19. Epaud R, Ikegami M, Whitsett JA, et al: Surfactant protein B inhibits endotoxin-induced lung inflammation. Am J Respir Cell Mol Biol 2003;28:373–378.
20. Augusto LA, Synguelakis M, Johansson J, et al: Interaction of pulmonary surfactant protein C with CD14 and lipopolysaccharide. Infect Immun 2003;71:61–67.
21. Crowley P: Prophylactic Corticosteroids for Preterm Birth. The Cochrane Library, Issue 2. Oxford, UK: Update Software, 2001.
22. Ueda T, Ikegami M, Jobe AH: Developmental changes of sheep surfactant: In vivo function and in vitro subtype conversion. J Appl Physiol 1994;76: 2701–2706.
23. Gunther A, Siebert C, Schmidt R, et al: Surfactant alterations in severe pneumonia acute respiratory distress syndrome, and cardiogenic lung edema. Am J Respir Crit Care Med 1996;153:176–184.
24. Greene KE, Wright JR, Steinberg KP: Serial changes in surfactant-associated proteins in lung and serum before and after onset of ARDS. Am J Respir Crit Care Med 1999;160:1843–1850.
25. Ikegami M, Korfhagen TR, Bruno MD, et al: Surfactant metabolism in surfactant protein A-deficient mice. Am J Physiol 1997;272: L479–L485.
26. Lofgren J, Ramet M, Renko M, et al: Association between surfactant protein A gene locus and severe respiratory syncytial virus infection in infants. J Infect Dis 2002;185:283–289.
27. Clark JC, Wert SE, Bachurski CJ, et al: Targeted disruption of the surfactant protein B gene disrupts surfactant homeostasis, causing respiratory failure in newborn mice. Proc Natl Acad Sci U S A 1995;92: 7794–7798.
28. Nogee LM, Wert SE, Profitt SA, et al: Allelic heterogeneity in hereditary SP-B deficiency. Am J Respir Crit Care Med 2000;161:973–981.
29. Glasser SW, Burhans MS, Korfhagen TR, et al: Altered stability of pulmonary surfactant in SP-C deficient mice. Proc Natl Acad Sci U S A 2001;98:6366–6371.
30. Thomas AQ, Lane K, Phillips J III, et al: Heterozygosity for a surfactant protein C gene mutation associated with usual interstitial pneumonitis and cellular nonspecific interstitial pneumonitis in one kindred. Am J Respir Crit Care Med 2002;165:1322–1328.
31. Gregory TJ, Steinberg KP, Spragg R, et al: Bovine surfactant therapy for patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 1997;155:1309–1315.
32. Walmrath D, Gunter A, Ghofrani HA, et al: Bronchoscopic surfactant administration in patients with severe ARDS and sepsis. Am J Respir Crit Care Med 1996;154:57–62.
33. Spragg RG, Lewis JF, Wurst W, et al: Treatment of acute respiratory distress syndrome with recombinant surfactant protein C surfactant. Am J Respir Crit Care Med 2003;167:1562–1566.
34. Lotze A, Mitchell BR, Bulas DI, et al: Multicenter study of surfactant (beractant) use in the treatment of term infants with severe respiratory failure. Survanta in Term Infants Study Group. J Pediatr 1998; 132:40–47.
35. Moller JC, Schaible T, Roll C, et al: Treatment with bovine surfactant in severe acute respiratory distress syndrome in children. A randomized multicenter study. Intens Care Med 2003;29:437–446.
36. Poynter SE, Levine AM: Surfactant biology and clinical application. Crit Care Clin 2003;19:459–472.

3 Developmental Physiology of the Respiratory System

Mary Ellen B. Wohl, MD

Respiratory diseases are among the four leading causes of death in the United States.[1] Immaturity of the lung has been a major contributing factor to infant mortality, although in recent years this has been reduced by the antenatal administration of corticosteroids and the postnatal administration of surfactants. However, respiratory distress of the newborn still ranks fifth as a contributor to infant mortality. After infancy, mortality rates related to respiratory causes are low but are still included in the 10 most frequent causes of death. Respiratory morbidity rates, on the other hand, are high, and respiratory diseases continue to be one of the most common causes of hospital admissions and absence from school.

AGE SPECIFICITY OF RESPIRATORY PATHOGENS

Certain respiratory pathogens are age specific: they produce disease of consequence at certain ages and not at other ages. Some respiratory infections, such as cytomegalovirus pneumonia, depend on exposure in utero. With the exception of infections in the immunocompromised host, cytomegalovirus rarely causes disease beyond the perinatal period. Other infectious agents, such as chlamydia and group B streptococci, cause pneumonia after exposure of the host during birth. Respiratory syncytial virus produces bronchiolitis in infants but usually only upper respiratory symptoms in school-aged children and adults. Parainfluenza virus causes croup in the child between 2 and 3 years old. Acute epiglottitis, rarely seen since *Hemophilus influenzae* B vaccination became commonplace, is usually, but not always, seen in children 2 to 7 years of age. *Mycoplasma* rarely produces disease in preschool children but is a common cause of bronchopneumonia in school-aged children and young adults.

Part of the age specificity of respiratory pathogens is related to development of the immune system, of defenses within the lung itself,[2,3] and to age-related exposure. The influence of age on respiratory structure and function, however, may contribute to this age specificity and is the subject of this chapter.

AGE AND RESPIRATORY STRUCTURE

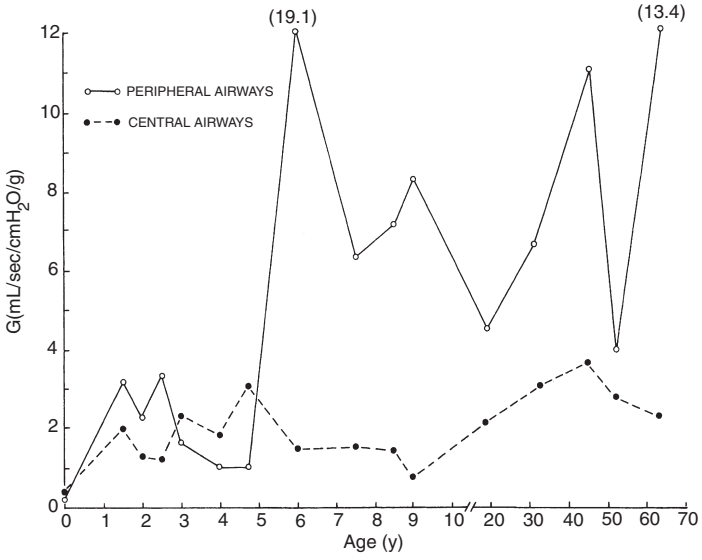
The respiratory system continues to develop from birth to young adulthood. Some of the steps in the development of the lung have a strong influence on lung function during childhood and on the pattern of respiratory disease. There have been a number of reviews of lung development in recent years elucidating the mechanisms underlying morphogenesis, molecular regulation, maturation, and vascular development.[4–7] This chapter considers the structural factors of lung development.

AIRWAYS

The airways are derived from an outpouching of the ventral groove of the embryo. During the embryonal period of lung development, the proximal branches are formed. Further branching of the airways, which is more or less dichotomous, occurs during the pseudoglandular period, so named because of the appearance of the lung on microscopic section. By the 17th week of gestation, the full number of generations of conducting airways has been established.[7,8] Thereafter, no new conducting airways develop, but there is continuing growth (increase in length and diameter) of the existing airways, remodeling of the peripheral airways,[9] and thinning of the respiratory epithelium.

The airway wall and the respiratory epithelium change during gestation and postnatal life. During fetal life, the thick, columnar, glycogen-rich epithelium develops cilia and thins, particularly in the periphery of the airway. The thinning of the epithelium continues postnatally in the human. Although the epithelium of the infant's airway, like the adult's, is a ciliated pseudostratified columnar type in the trachea and gradually thins to a columnar type in the bronchioles, there are substantial differences. The infant's airway epithelium contains a higher ratio of mucous glands than the adult's, and the constituents of the secretions may change throughout childhood.[10] The respiratory epithelium is substantially thicker, approaching (at a given generation of airways) the thickness found in asthmatics.[11] The rate of tracheal mucociliary clearance, studied in animals, is greater in the young adult than in the infant.[12] Smooth muscle is present in the airways of the fetus early in development and extends from the trachea to the alveolar ducts in both newborns and adults.[13] Between 5 and 17 weeks of gestation airway wall cells differentiate to form cartilage, submucosal glands, smooth muscle, and types of epithelial cells. In the rabbit, the amount of smooth muscle is increased and the amount of cartilage is decreased in the immature compared with the mature animal.[14] In contrast to the work of James,[11] airway wall thickness is similar in both mature and immature rabbits.[14] The amount of cartilage increase in the first years of life, contributing to the stiffening of the airways observed in the first months of an infant's postnatal life.[15]

Postnatal growth of the airway has been investigated by only a limited number of anatomic studies in humans, and the data are conflicting.[16,17] Hislop and associates[16] show the infant's airway to be a miniature of the adult's. The limited anatomic and more extensive physiologic studies on excised human lung performed by Hogg and co-workers[17] suggest that peripheral airways, those distal to the 10th or 12th generation, increase in size relative to the central airways until age 5 years (Fig. 3-1).

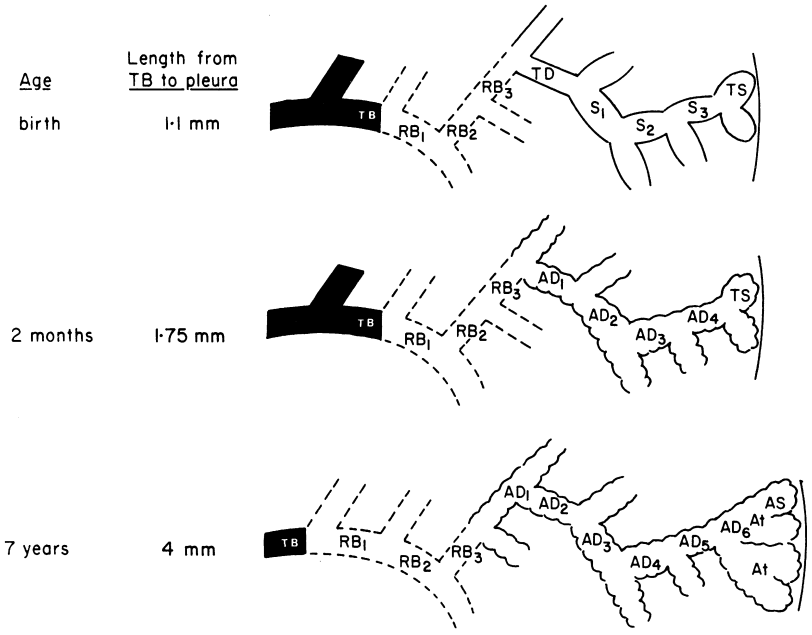


■ **FIGURE 3-1.** Comparison of peripheral and central airway conductance as a function of age in normal human lungs. The data are corrected for size by expressing the conductance as mL/sec/g of lung and for lung inflation by expressing all data at a transpulmonary pressure of 5 cm H_2O. (Replotted from Hogg JC, Williams J, Richardson JB, et al: Age as a factor in the distribution of lower-airway conductance and in the pathologic anatomy of obstructive lung disease. N Engl J Med 1970;282:1283.)

■ ALVEOLI AND LUNG PARENCHYMA

Whereas the airways are established in early gestational life and grow by enlargement, the alveoli develop in late gestational life and early childhood by forming new structures (i.e., alveolar ducts and alveoli). Only later do they grow by enlargement[9] (Fig. 3-2). The development of alveoli is preceded by the formation of saccules at the end of the budding airway. These structures—larger, thicker walled, and more irregular than alveoli—are probably capable of sustaining gas exchange. From 28 to 32 weeks of gestation, some of the subdivisions of the saccules have the cupped shape and single capillary layer characteristic of alveoli, but infants born at less than 28 weeks have virtually no alveoli.

Approximately 150 million alveoli are present at birth in the full-term infant. The number is likely to be extremely variable. Pulmonary hypoplasia is diagnosed when a baby has an associated abnormality (i.e., a congenital renal abnormality or a diaphragmatic hernia), and may be considered when a newborn develops a spontaneous pneumothorax. In all likelihood, considerable variability in lung size as expressed by the number of terminal units may go undetected by the pediatrician but may influence the child's respiratory reserve. Dunhill[18] carried out morphometric studies on lungs obtained at autopsy. His data suggest that most of the 300 million alveoli present in the adult lung are formed by the age of 2 years. Current data suggest that this is an underestimation of the number or alveoli present in the adult lung[19] and that mean data have a wide range. The variability in the number of alveoli present at a given age[20] makes the age at which the increase in alveolar number ceases less certain. Nonetheless, a substantial fraction of the total number of alveoli is formed in the first few months and years of life. Thereafter, growth of alveoli takes place for the most part by enlargement.



■ **FIGURE 3-2.** Diagram showing that the lung grows initially by increasing the number of alveoli by the ingrowth of septa and formation of the alveolar ducts. AD, alveolar duct; RB, respiratory bronchiole; TB, terminal bronchiole. (Modified from Hislop A, Reid L: Development of the acinus in the human lung. Thorax 1974;29:90.)

It seems reasonable to assume that factors that influence growth of the fetus during the last trimester and during the first year of life would be of particular importance to lung development. Some of these factors are under active investigation. Nutrition,[21] vitamin A,[22] administration of corticosteroids,[23] hyperoxia,[24] and maternal smoking[25] play important roles in lung development. Although both collagen and elastin are important in airway morphogenesis and branching, the interstitium of the lung contains little collagen and elastin during late gestation and at birth. This near absence of collagen and elastin may contribute to the relative ease of rupture of air spaces in the premature lung. Elastin, which appears to be closely related to the development of alveoli, increases during early postnatal life. Lung collagen also increases during postnatal life. The formation and changing ratio of elastin and collagen probably contribute to the change in volume-pressure relationships of the lung and to the increased stiffness of the lung with increasing age until young adulthood.

PULMONARY VESSELS

The pulmonary arterial system develops by vasculogenesis, the production of vessels from endothelial cells differentiating from mesenchymal precursors, and angiogenesis, the sprouting of new vessels from preexisting vessels. It appears that until about 17 weeks of gestation new vessels are produced by vasculogenesis and the airway acts as a template. Postnatally there is a marked increase in the number of arteries in the acinus that seem to be formed by angiogenesis.[7] To some extent, the postnatal development of acinar arteries and capillaries parallels the postnatal development of alveoli. The pulmonary veins originate as proliferating endothelial cells that migrate away from the artery, are surrounded by lymphatic channels, and never develop any smooth muscle.

The origins of smooth muscle cells include cells that migrate from the airway into the vessel wall at the penultimate generation of the airway and form the innermost layer of the vessel wall. Later, fibroblasts differentiate and express both alpha and gamma actin. Finally, endothelial cells, later in development, express alpha actin and form smooth muscle cells.[7] Muscular arteries extend only to the level of the terminal bronchioles in the fetus and young child, and during childhood, muscle extends out to the alveolar duct, and in the adult out to the alveoli. A number of studies of the pulmonary vascular system relating structure to function have been carried out, and these reveal differences between infants and adults. The extension of muscle out into the acinus and the rise in the ratio of arteries to alveoli that occurs during childhood is consistent with an increasing responsiveness to acute hypoxia with increasing age. However, the development of the fetal and infant lung is strongly influenced by chronic hypoxia with decreased airway, vascular, and alveolar development.

Although structural features of the infant's pulmonary vasculature may influence the infant's response to a variety of vasoconstrictors and vasodilators, there may be substantial differences in response governed at the cellular level between infants and adults. This is an active area of investigation and beyond the scope of this chapter.

OTHER STRUCTURES

In the adult, collateral ventilation—the movement of gas from one acinus to another—occurs through holes in the alveoli (the pores of Kohn) and epithelium-lined channels between terminal bronchioles and adjacent alveoli (the canals of Lambert). These structures may be present in the infant lung, but they are probably not of sufficient size to allow for air drift. Although collateral pathways in the adult are probably not of great significance for ventilation, they do help to prevent absorption of gas in regions distal to airway obstruction. The relative absence of functional collateral pathways probably contributes to the patchy atelectasis so common in airway disease of infants and young children.

CHEST WALL

Considerable structural changes occur in the chest wall, particularly during early postnatal life. In infancy the ribs are oriented in a horizontal plane. As growth occurs, they slant in a progressively caudal direction. By 10 years of age they have the downward slope of adults.[26] Ossification of the rib cage sternum and vertebrae begins in utero and continues until about age 25. Calcification of costal cartilage can continue into old age. Muscle mass develops progressively throughout childhood and adolescence and in some into adulthood.

In adults, lung volume at end-expiration or functional residual capacity (FRC) is mainly set passively by the balance between the inward recoil of the lung and outward recoil of the chest wall. Newborns have compliant chest walls that would allow nearly complete collapse of lungs if it were not for the activity of muscles. Expiratory braking occurs by active glottic narrowing and by the interruption of expiration by the onset of inspiration, or by both mechanisms. Indeed, the major function of the active Hering-Breuer reflex in infants may be to terminate expirations before lung volume gets too small. This response may disappear once the chest wall has become stiff enough to prevent collapse. End-expiratory lung volume is actively maintained by infants until about 6 to 12 months of age, when the passive characteristics of the lung and chest wall appear to determine resting end-expiratory lung volume.[27]

The easy collapsibility of the rib cage is probably advantageous during birth, when it allows for deformation of the chest as it passes through the birth canal and for easier expulsion of liquid from the lungs before the first breath. Thereafter the collapsibility is probably disadvantageous but affordable in a healthy infant because of relatively small metabolic demands. The parenchyma of the lungs develops during the postnatal period, and the rib cage may be thought of as doing the same. The infant rib cage "caves in" during obstructed inspiration, whereas the adult rib cage does not.

AGE AND RESPIRATORY FUNCTION

Respiratory structures change remarkably during growth. What are the functional implications of such changes? Lung volume and volume-pressure relationships (e.g., pulmonary compliance) should reflect parenchymal (alveolar) development, and airflows and pressure-flow relationships (resistances and conductances) should reflect airway development. But the relationships are not as direct as they might seem.

Pulmonary compliance depends on the number of air spaces expanded, the size and geometry of the air spaces, the characteristics of their surface lining layer, and the properties of the lung parenchyma that change with growth and maturation.

Changes in the shape, magnitude, or curvilinearity of volume-pressure curves do point to maturational changes in growing lungs.

The lung volume at which airways close is higher in younger children (7 years) and in elderly adults than in older children and young adults.[28] Airway closure in infants is graphically illustrated by the atelectasis observed in dependent portions of the lung in computed tomography scans. Lung recoil is reduced in younger lungs[29–31] and increases as the lungs mature in early adulthood to decline again in the elderly[32] (Fig. 3-3).

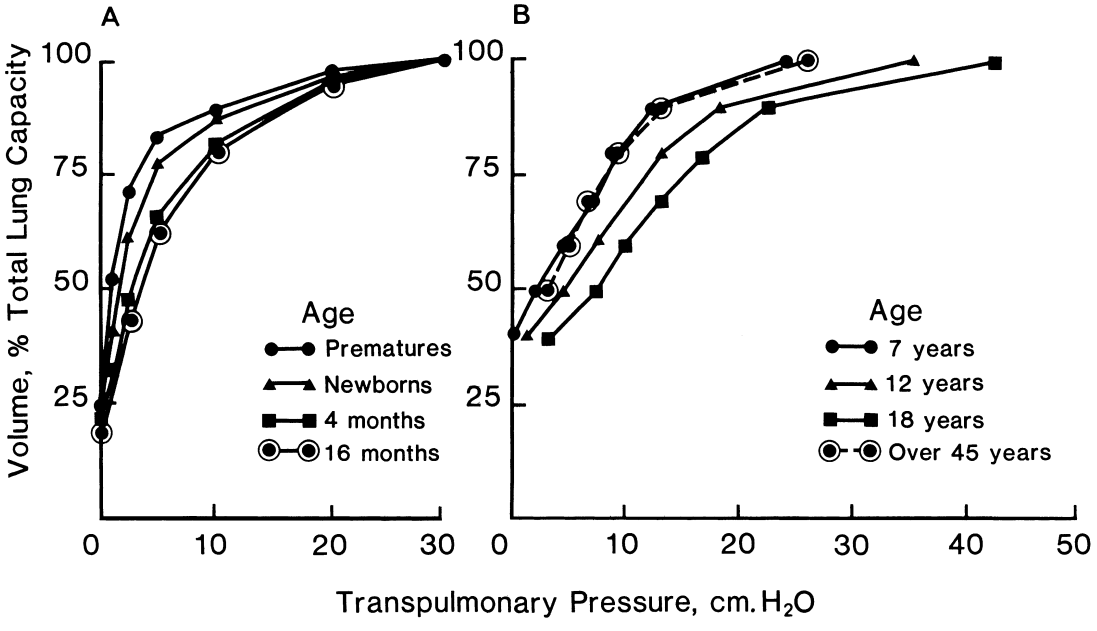
Measurements of chest wall compliance in the tidal range in children younger than 4 years[33] further confirm the marked stiffening of the chest wall in early childhood suggested by the measurements of Thorsteinsson and co-workers[34] and the earlier measurements of Sharp and co-workers.[35] Chest wall compliance corrected for body and therefore lung size was about 50% greater in infants younger than 1 year compared to children older than 1 year. Furthermore, the relationship between chest wall and lung compliance changes. In infants chest wall compliance is threefold greater than lung compliance, but in children and adults these values are virtually equal. These marked physiologic changes in mechanical properties of both the lung and the chest wall parallel the remarkable growth of these structures.

Pressure-volume curves of the total respiratory system[34] mimic those of the lung in young children in that they are more curvilinear and at a given pressure the respiratory system is at a higher fraction of its total volume. However, for individuals 2 to 16 months of age, curves are very similar, probably reflecting increasing inward recoil of the lung balanced by increasing outward recoil of the chest wall. Overall, the total respiratory system becomes increasingly stiff with increasing age, and these changes are particularly remarkable in the child younger than 5.

Changes in airways and pulmonary and total respiratory system resistance with age are difficult to interpret, since they involve a substantial and often variable contribution from the upper airway, notably the glottis. This upper airway resistance can comprise more than 50% of measured resistance, making measurements of resistance less useful for inferring growth patterns in normal subjects or changes associated with diseased lungs. The available measurements of resistance, despite the limitations noted above, suggest that resistance declines through infancy and compliance increases, but the increase in compliance is greater than the reduction in resistance during the first years of life.[36] These observations and the observation that specific conductance in infant lungs is greater than in older lungs is entirely consistent with the sequence of airway and parenchymal development.[37] The airways in the newborn lung are large compared with the relatively scanty parenchyma they serve.

Maximal expiratory flow (MEF) does not depend on any manipulation of the glottis and reflects only the intrathoracic properties of the lung and airway. It is another measure of airway properties, depending on the physical properties of the gas, the physical properties of the airway wall, the elastic recoil of the lung, the degree of lung inflation, and the resistive pressure losses along the airway. Nevertheless, MEF-volume curves can be interpreted in terms of the relative size of airways and parenchyma. The average slope of a flow-volume curve (i.e., the best straight line fit to the descending portion of the curve) expresses the mean maximum rate of emptying. This rate depends on the relative sizes of the airways and lung parenchyma. The smaller the lung, the more rapidly it empties through an airway of a given size and resistance. Similarly, the greater the size of the airways, and hence the lower their resistance, the more rapidly a lung of a given size empties. Estimates of rates of lung emptying can be made for infants, children, and adults. The lung of the infant empties four times faster than the lung of an adult, with rate constants of 7.8 compared to 1.7 (rate constant is flow/volume, which is 1/time, i.e., rate).[38] Data collected in children 3 weeks to 15 years of age supports the relative greater increase in lung parenchyma growth relative to airway growth throughout childhood.[36]

The available measurements from infancy to adolescence reflect and parallel structural changes in the lungs. Compliance in



■ **FIGURE 3-3.** Deflation volume-pressure curves of the lung. **A,** Data plotted from curves on excised lungs obtained by Fagan.[29,30] The lung volume at a transpulmonary pressure of 30 cm H_2O is taken as 100% of total lung capacity. **B,** Data taken from the work of Zapletal and co-workers[31] are plotted in solid lines. Age is estimated from height. For comparison, the curve for subjects older than 45 years is shown with dashed lines.[32] With increasing age up to young adulthood the curves become straighter, and at a given lung volume elastic recoil is greater. The curve from elderly subjects (*dashed line*) resembles that from a 7-year-old.

absolute terms increases as new alveoli develop, but the changes in shape of the volume-pressure curve suggest that to some extent maturation makes the lung relatively stiffer. As the volume of the lung parenchyma enlarges relative to airway volume, specific conductance and indices of rates of emptying fall. However, these broad developmental changes may not be as important to the occurrence of lung disease as individual variability. In adults, considerable variability in indices of airway and lung size exists. Some individuals apparently have relatively large airways and small lungs, and vice versa. Some data indicate substantial tracking of lung volumes and of indices of airway size that have been documented from age 6 years through adolescence.[39] These observations suggest that this dysanapsis between airway and lung parenchyma growth begins in early life and presumably is genetically determined. Whether it bears on disease susceptibility remains to be seen, but there is increasing epidemiologic evidence that disease in childhood, at least the occurrence of wheezing with lower respiratory infections, is linked to physiologic indicators of lung and airway size established during early infancy.[40–42]

AGE, STRUCTURE, FUNCTION, AND AIRWAY REACTIVITY

Data from a number of investigators suggest that infants' and children's airways are more reactive to methylcholine and histamine than are the airways of adults.[42] Under static conditions the amount, location, and length-tension relationship determine the contractile response of smooth muscle. However, airway reactivity may be modulated by cyclic changes in tidal volume and cyclic changes in force applied to the smooth muscle.[43,44] This force may be altered by the number of attachments to the airway wall, elastic recoil of the lung, airway wall thickness both inside and outside the airway, and presence of fluid within the airway.[45] A number of these factors, for example, the thickness of the airway wall and the number of parenchymal attachments, are altered by growth of the lung.

Edema of the outer airway wall, which occurs in viral illnesses, pulmonary overcirculation, and inflammation of the airway wall, uncouples the attachments of the parenchyma to the airway wall. This results in increased airway reactivity to inhaled bronchoconstrictors.

To evaluate airway reactivity, usually increasing concentrations of a bronchoconstrictor, methacholine or histamine, are nebulized and inhaled. The dose required to produce a decrease in a measured parameter of some fixed percentage of baseline value is used as the expression of reactivity, for example, a 20% decline in forced expiratory volume in 1 second (FEV_1).

Infants and young children have lower inspiratory flow rates than do adults and will entrain less air to dilute the nebulizer output. Normal children 6 months to 1 year of age have inspiratory flow rates that approximate nebulizer output and will deliver a higher dose of the bronchoconstricting agent to the airways.[46] On the other hand, adjusting the concentration of the bronchoconstrictor on a mg/kg basis results in very little drug or bronchoconstrictor delivered to the child, since the dose is further "size corrected" by the lower minute ventilation of smaller subjects. In studies where "dose" appears to be adequately controlled, younger human subjects appear to be more reactive than older ones.

The younger lung thus has many of the features of the asthmatic lung. These structural features may be important determinants of the frequency of wheezing in young children and the increased response to bronchoconstricting agents. It does not require a greater inflammatory response, cytokine release, or smooth muscle response, although these may or may not be present.

AGE STRUCTURE, FUNCTION, AND MANIFESTATION OF DISEASE

When the structure and mechanical behavior of the young infant's and child's respiratory system are compared to those of the mature adult (but not the elderly), important differences emerge that are likely to influence the pattern of disease. Some of these differences, such as the reduced lung recoil, are shared by the elderly and likely influence the pattern of respiratory disease in that population as well.

1. The young lung lacks elastic recoil; as a result, airways are less well supported. This will be particularly true if there are fewer parenchymal attachments.[16] Greater airway closure favors inhomogeneity of gas exchange and the development of patchy atelectasis frequently observed in the child under school age.
2. Airway walls of young lungs may be thicker.[10,16] This, combined with reduced elastic recoil, favors greater airway narrowing for any degree of smooth muscle contraction.
3. The chest wall is relatively more compliant in the young child and stiffens with increasing age. As a result, the infant can develop paradoxical respiration. Respiratory muscle activation during inspiration can produce inward displacement of the rib cage, contributing to increased respiratory work for a given level of ventilation, particularly during rapid eye movement (REM) sleep. The apparent fatigue resistance of the infant's respiratory muscles may offset the increased demand for respiratory work. The deformability of the chest wall influences findings on physical examination. Chest wall–abdominal paradox may be normal in the premature infant during REM sleep but not in the older child or adult.
4. Finally, infants and children have frequent respiratory tract infections, particularly if they attend daycare, school, or come from large families. It may be that the profuse secretions are aspirated and with a shorter path length to peripheral airways, the epithelium lining these structures becomes infected. Airway cell sloughing, loss of ciliated epithelial cells, injury to epithelial cells with cytokine release, and possible increased bronchovascular permeability contribute to airway wall thickening, edema of the airway wall, and attenuation of the tethering effects of parenchymal–airway wall attachments. The effects of any degree of airway smooth muscle contraction will be exaggerated and contribute to the uneven ventilation and perfusion and modest hypoxemia observed in so many children with respiratory tract infections.

REFERENCES

1. Arias E, Smith BL: Deaths. Preliminary data for 2001. Natl Vital Stat Rep 2003;51:1.
2. Whitsett JA: Intrinsic and innate defenses in the lung. Intersection of pathways regulating lung morphogenesis, host defense, and repair. J Clin Invest 2002;109:565.

3. McCormack FX, Whitsett JA: The pulmonary collectins, SP-A and SP-D, orchestrate innate immunity in the lung. J Clin Invest 2002;109:707.
4. Hilfer SR: Morphogenesis of the lung. Control of embryonic and fetal branching. Ann Rev Physiol 1996;58:93.
5. Cardoso WV: Molecular regulation of lung development. Annu Rev Physiol 2001;63:471.
6. McMurtry IF: Introduction. Pre- and postnatal lung development, maturation, and plasticity. Am J Physiol Lung Cell Mol Physiol 2002;282:L341.
7. Hislop AA: Airway and blood vessel interaction during lung development. J Anat 2002;201:325.
8. Bucher U, Reid L: Development of the intrasegmental bronchial tree. The pattern of branching and development of cartilage at various stages of intra-uterine life. Thorax 1961;16:207.
9. Hislop A, Reid L: Development of the acinus in the human lung. Thorax 1974;29:90.
10. Matsuba K, Thurlbeck WM: A morphometric study of bronchial and bronchiolar walls in children. Am Rev Respir Dis 1972;105:908.
11. James A, Christmas T: Mechanisms of bronchial hyperresponsiveness in infants. Am Rev Respir Dis 1989;139:A106.
12. Wanner A, Salathé M, O'Riordan TG: Mucociliary clearance in the airways. Am J Respir Crit Care Med 1996;154:1868.
13. Leslie K, Mitchell J, Woodcock-Mitchell J, Low R: Alpha smooth muscle actin expression in developing and adult human lung. Differentiation 1990; 44:143.
14. McCray P, Nakamura K: Development of airway smooth muscle. Lung Growth and Development. New York: Marcel Dekker, 1997.
15. Croteau JR, Cook CD: Volume-pressure and length-tension measurements in human tracheal and bronchial segments. J Appl Physiol 1961;16:170.
16. Hislop A, Muir DCF, Jacobsen M, et al: Postnatal growth and function of the pre-acinar airways. Thorax 1972;27:265.
17. Hogg JC, Williams J, Richardson JB, et al: Age as a factor in the distribution of lower-airway conductance and in the pathologic anatomy of obstructive lung disease. N Engl J Med 1970;282:1283.
18. Dunhill MS: Postnatal growth of the lung. Thorax 1962;17:329.
19. Ochs M, Nyengaard JR, Jung A, et al: The number of alveoli in the human lung. Am J Respir Crit Care Med 2004;169:120.
20. Brody JS, Thurlbeck WM: Development, growth, and aging of the lung. In: Fishman AP, ed: Handbook of Physiology. Vol III. Mechanics of Breathing. Part 1. The Respiratory System. Bethesda, Md: American Physiological Society, 1986, p 355.
21. Sosenko IRS, Frank L: Nutritional influences on lung development and protection against chronic lung disease. Semin Perinatol 1991;15:462.
22. Massaro D, Massaro GDC: Retinoids, alveolus formation, and alveolar deficiency. Clinical implications. Am J Respir Cell Mol Biol 2003;28:271.
23. Tschanz SA, Makanya AN, Haenni B, Burri PH: Effects of neonatal high-dose short-term glucocorticoid treatment on the lung. A morphologic and morphometric study in the rat. Pediatr Res 2003;53:72.
24. Haworth SG, Hislop AA: Lung development—The effects of chronic hypoxia. Semin Neonatol 2003;8:1.
25. Hanrahan JP, Tager IB, Segal MR, et al: The effect of maternal smoking during pregnancy on early infant lung function. Am Rev Respir Dis 1992; 145:1129.
26. Openshaw P, Edwards S, Helms P: Changes in rib cage geometry during childhood. Thorax 1984;39:624.
27. Colin AA, Wohl MEB, Mead J, et al: Transition from dynamically maintained to relaxed end-expiratory volume in human infants. J Appl Physiol 1989; 67:2107.
28. Mansell AL, Bryan C, Levison H: Airway closure in children. J Appl Physiol 1972;33:711.
29. Fagan DG: Post-mortem studies of the semistatic volume-pressure characteristics of infants' lungs. Thorax 1976;31:534.
30. Fagan DG: Shape changes in static V-P loops from children's lungs related to growth. Thorax 1977;32:198.
31. Zapletal A, Paul T, Samanek M: Pulmonary elasticity in children and adolescents. J Appl Physiol 1976;40:953.
32. Turner JM, Mead J, Wohl MEB: Elasticity of human lungs in relation to age. J Appl Physiol 1968;25:664.
33. Papastamelos C, Panitch HB, England SE, Allen JL: Developmental changes in chest wall compliance in infancy and early childhood. J Appl Physiol 1995;78:179.
34. Thorsteinsson A, Larsson A, Jonmarker C, Werner O: Pressure-volume relations of the respiratory system in healthy children. Am J Respir Crit Care Med 1994;150:421.
35. Sharp JT, Druz WS, Balagot RC, et al: Total respiratory compliance in infants and children. J Appl Physiol 1970;29:775.
36. Lanteri CJ, Sly PD: Changes in respiratory mechanics with age. J Appl Physiol 1993;74:369.
37. Stocks J, Godfrey S: Specific airway conductance in relation to postconceptional age during infancy. J Appl Physiol 1977;43:144.
38. Bryan AC, Wohl MEB: Respiratory mechanics in children. In: Fishman AP, ed: Handbook of Physiology. Vol. III, Part 1. Mechanics of Breathing. The Respiratory System. Bethesda, Md: American Physiological Society, 1986, p 179.
39. Martin TR, Feldman HA, Fredberg JJ, et al: The relationship between maximal expiratory flows and lung volumes in growing humans. J Appl Physiol 1988;65:822.
40. Martinez F, Morgan W, Wright A, et al: Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. N Engl J Med 1988;319:1112.
41. Martinez F, Morgan W, Wright A, et al: Initial airway function is a risk factor for recurrent wheezing respiratory illnesses during the first three years of life. Am Rev Respir Dis 1991;143:312.
42. Martinez FD, Wright AL, Taussig LM, et al: Asthma and wheezing in the first six years of life. N Engl J Med 1995;332:133.
43. Fredberg JJ: Frozen objects. Small airways, big breaths, and asthma. J Allergy Clin Immunol 2000;106:615.
44. Seow CY, Fredberg JJ: Historical perspective on airway smooth muscle. The saga of a frustrated cell. J Appl Physiol 2001;91:938.
45. Moreno R, Hogg J, Paré PD: Mechanics of airway narrowing. Am Rev Respir Dis 1986;133:1171.
46. Le Souëf PN: Validity of methods used to test airway responsiveness in children. Lancet 1992;339:1282.

4 The Functional Basis of Respiratory Disease

Victor Chernick, MD • John B. West, MD

Knowledge of the normal development and physiologic function of the lungs is required to understand the pathophysiology that is seen in disease. Historically, our understanding of lung function was derived solely from clinical observation and postmortem histologic examination. The development of invasive and noninvasive techniques that were capable of assessing lung function in living subjects greatly improved our understanding of lung physiology on an "organ basis." There has been an explosion of knowledge in cellular and molecular biology, which are covered in detail in other chapters in this section. This chapter will concentrate on organ physiology.

NORMAL LUNG ANATOMY AND CELL FUNCTION

A knowledge of normal lung anatomy is one of the basic requirements for understanding lung function in health and disease. Because detailed descriptions of lung anatomy are available elsewhere, this section will focus on selected aspects of gross and microscopic anatomy to enable the reader to understand the physiologic changes that occur in congenital and acquired lung disease.

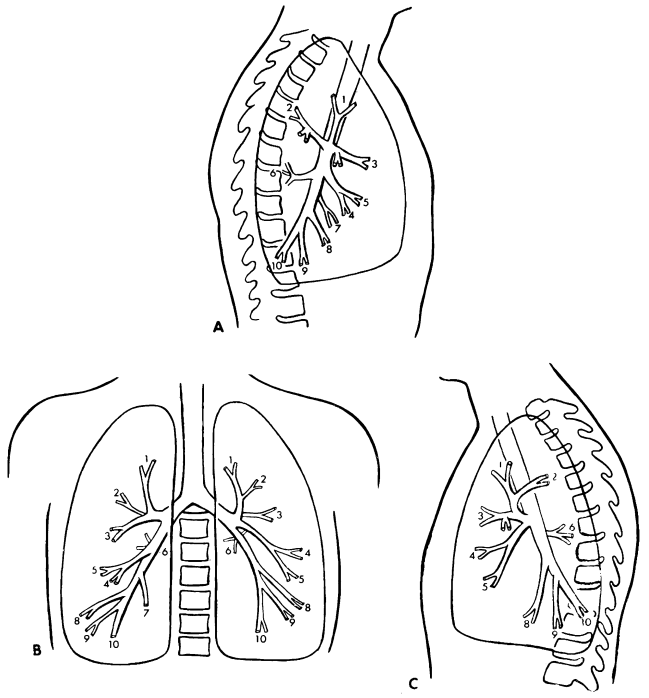
AIRWAYS

The basic structure of the airways is already present at birth, and thus neonates and adults share a common bronchopulmonary anatomy (Fig. 4-1). When airways divide, they do so by dichotomous branching, but the number of times that branching occurs varies. For example, there may be anywhere from 10 (hilar region) to 25 (basal region) airway divisions before the gas-exchanging units are reached. This airway variability has physiologic implications; different pathways will have different resistances to airflow, and a heterogeneous distribution of gases or inhaled particles may occur. As the bronchi branch and decrease in size, they lose their cartilage and become bronchioles. Ultimately, a terminal bronchiole opens up into the gas-exchanging area of the lung (Fig. 4-2).

The airways are lined with an epithelial membrane that gradually changes from ciliated pseudostratified columnar epithelium in the bronchi to a ciliated cuboidal epithelium near the gas-exchanging units. Ciliated cells predominate throughout this epithelium and are responsible for propelling mucus from the peripheral airways to the pharynx. This mucociliary transport system is an important defense mechanism of the lungs. The mucous layer has two parts, a superficial gel layer and a deeper sol layer. The cilia form a dense, long carpet on top of the epithelial cells, and their coordinated to-and-fro action propels the gel mucous layer toward the oropharynx. Cilia are a derivative of the centrioles, and there are approximately 200 of them on the apex of each ciliated cell. The cilia are anchored within the cell with a basal body that is oriented in the direction of mucous movement. The shaft of the cilium has a central pair of single tubules that are connected via radial spokes to nine peripheral pairs of tubules. The tip of the cilium has tiny hooklets that probably help grab the gel component of the mucous layer and propel it forward. The cilium has a beat frequency of 12 ± 1 SD Hz and is coordinated both with other cilia on that cell and concurrently with the cilia on adjacent cells to yield a synchronized wave flowing up the airway. Primary ciliary dyskinesia (PCD) is a group of disorders that includes Kartagener's syndrome and the erroneously named immotile cilia syndrome. In PCD there are defects within the tubules, in their inner or outer dynein arms, or in the radial arms that result in a disorganized movement of the cilia that precludes normal mucociliary transport and results in chronic bronchitis and repeated pneumonias (see Chapter 63).

Mucous glands, which are present in large and small bronchi, are the chief source of airway secretions, and contain both serous and mucus-producing cells. Goblet cells are seen in the trachea and bronchi. They produce mucin within their rough endoplasmic reticulum and Golgi apparatus. Mucin is a viscous mixture of acid glycoproteins that contributes to the mucous layer. Mucous glands and goblet cells can increase in number in disorders such as chronic bronchitis, the result being mucous hypersecretion and increased sputum production. There are several other cell types found within the airways; however, their functional significance is less well understood. The basis cell, commonly seen within the pseudostratified columnar epithelium, is undifferentiated and may be a precursor of ciliated or secretory cells. The brush cell has a dense tuft of broad, short microvilli and is only rarely seen within the conducting airways and alveolar space. Clara cells are seen exclusively within the bronchiolar region of the lung. Their physiologic role has been uncertain, but data suggest that they may play two important roles. First, because they contain but do not synthesize surfactant apoproteins, they may recycle surfactant within the distal lung unit. Second, they are capable of actively transporting sodium from their apical to their basal side and thus may be involved in the reabsorption of fluid from the distal lung unit.

There are curious cells found within the airways that are believed to possess neuroendocrine properties. They are known under a variety of names, including Feyrter or Kulchitsky cells. Histochemical staining indicates that they contain a variety of vasoactive peptides, including serotonin and kinins, so these cells may belong to the class of amine precursor uptake and decarboxylation (APUD) cells. These neuroendocrine cells are innervated and are found more frequently, and in groups (neuroepithelial bodies), within the fetal airways or in pediatric disorders characterized by chronic hypoxemia (e.g., bronchopulmonary dysplasia).



■ **FIGURE 4-1.** The nomenclature of bronchopulmonary anatomy, from a report by the Thoracic Society in 1950. **A,** Right lateral view. **B,** Anterior view. **C,** Left lateral view. (Adapted from Negus V: The Biology of Respiration. Baltimore: Williams & Wilkins, 1955.)

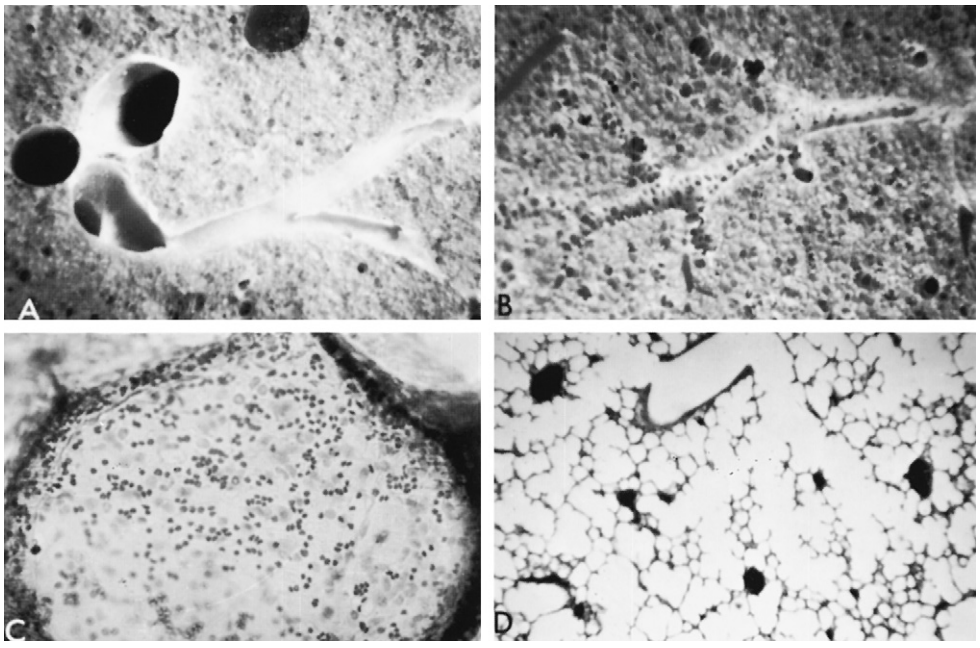
Histologically, the remainder of the airway consists of the submucosa, with its network of blood vessels and nerves, and a variable amount of smooth muscle and cartilage. Within the submucosa are found mast cells containing vasoactive peptides and amines, cells of the immune system (plasma cells, lymphocytes, and phagocytes), and mucous glands. In the main stem bronchi, cartilage is present in C-shaped rings. However, as further branching occurs, progressively less cartilage is present, so that bronchi 2 mm in diameter have cartilage only at the origins of the bronchioles. Cartilage adds structural rigidity to the airway and thus plays an important role in maintaining airway patency, especially during expiration. Congenital deficiency of airway cartilage and hence airway instability has been associated with bronchiectasis (Williams-Campbell syndrome) and congenital lobar emphysema.

The smooth muscle content of the airway also varies with its anatomic location. In the largest airways a muscle bundle connects the two ends of the C-shaped cartilage. As the amount of cartilage decreases, the smooth muscle assumes a helical orientation and gradually becomes thinner, ultimately reaching the alveolar ducts. Muscle contraction increases airway rigidity in all airways and terminal respiratory units.

Although it has been widely assumed that the airway muscles of newborn infants are inadequate for bronchoconstriction, this assumption is not correct. Even premature infants have smooth muscle, and although the amount may be statistically less than that seen in adults, it is likely enough to constrict the infant's much more compliant airways. Indeed, pulmonary function test results have demonstrated that airway resistance can be altered with bronchodilating drugs. The belief that infants have little or no smooth muscle in their airways is even less tenable in such disorders as bronchopulmonary dysplasia and left-to-right congenital heart disease, in which hypertrophy of the airway smooth muscle has been demonstrated by morphometric measurement. Congenital deficiency of large-airway smooth muscle and elastic fibers is associated with marked dilatation of the trachea and bronchi, which promotes retention of airway secretions and ultimately leads to recurrent pulmonary sepsis (Mounier-Kuhn syndrome).

■ TERMINAL RESPIRATORY UNIT

The terminal respiratory (gas-exchanging) unit consists of the structures distal to the terminal bronchiole: the respiratory bronchioles (bronchioles with alveoli budding from their walls), alveolar ducts, and alveoli. This unit is also known as an acinus

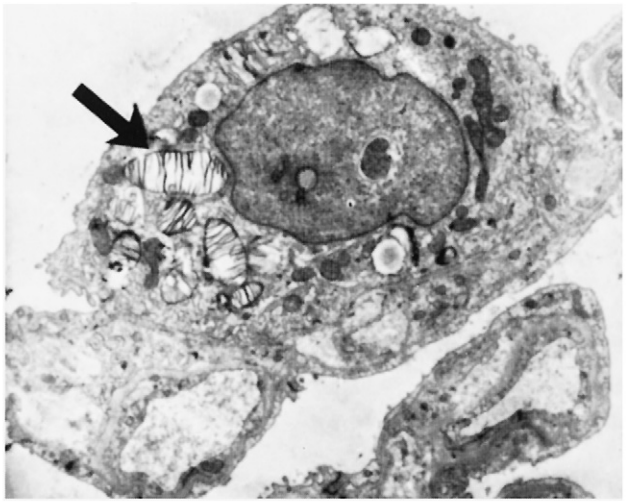


■ **FIGURE 4-2.** The architecture of the lung. **A,** Fresh frozen cat lung. Segmental cartilaginous bronchus and branches. The pulmonary artery is close to the airway; the pulmonary vein is in a more peripheral location (original magnification ×4). **B,** Fresh frozen cat lung (original magnification ×4). Terminal bronchiole with many alveolar ducts arising from it. **C,** Thick section of cat lung. A single alveolar wall is in the plane of focus. Individual red blood cells in alveolar capillaries are clearly seen (original magnification ×100). **D,** Guinea pig, fixed thin section. The terminal respiratory unit, with alveoli shown as outpouchings of the alveolar duct, arises from the terminal bronchiole at the top of the picture. Note that three vessels, probably pulmonary veins, mark the distal boundaries of the unit (original magnification ×15). (From Dr. Norman Staub [All but **A** appeared in color in]: The interdependence of pulmonary structure and function. Anesthesiology 1963;24:831–834.)

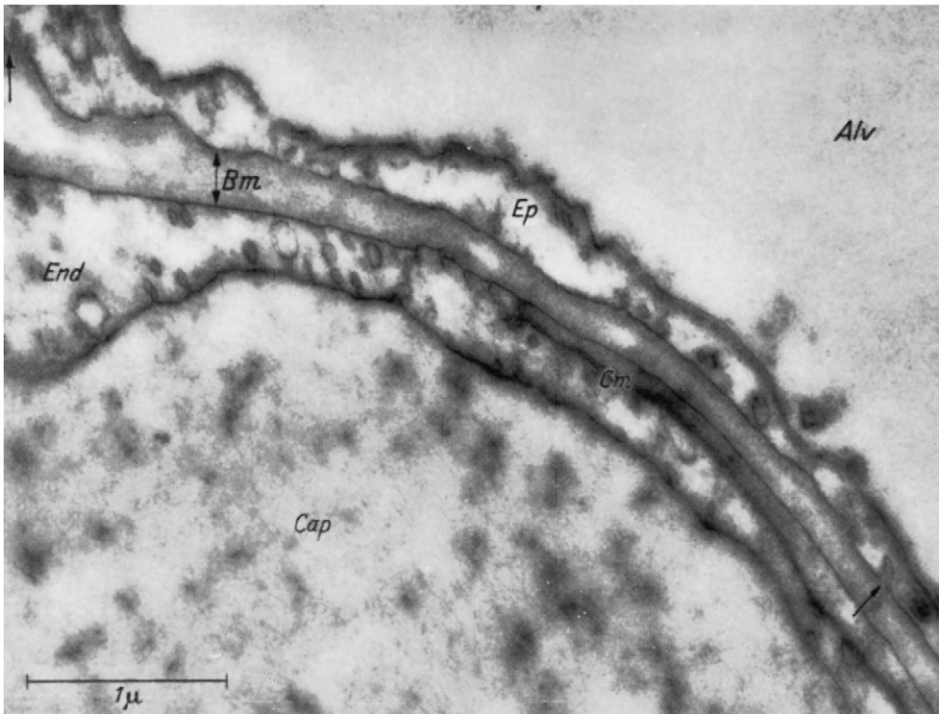
and may be considered the basic functional unit of the lung. Terminal respiratory units are well suited for gas exchange. In the adult lung these units have a total gas volume of 2500 mL and a surface area of about 80 m^2, yet all alveoli are within 5 mm of the closest terminal bronchiole. True alveoli are not spherical but more closely resemble hexagons with flat, sheet-like surfaces. The average alveolar diameter ranges from 250 to 300 μm. Within the terminal respiratory units, two types of intercommunicating channels provide collateral ventilation for the gas-exchanging units. The alveolar pores of Kohn are holes in the alveolar wall 3 to 13 μm in diameter that perhaps provide channels for gas movement between contiguous alveoli. These pores are not present in newborn lungs. The canals of Lambert are accessory channels that connect a small airway to an airspace normally supplied by a different airway.

The alveoli are lined by two types of epithelial cells (Fig. 4-3). The type I epithelial cell is an extremely broad, thin (0.1 to 0.5 μm) cell that covers 95% of the alveolar surface. It is a markedly differentiated cell possessing few organelles. The type II epithelial cells are more numerous than type I cells, but owing to their cuboidal shape, type II cells occupy only 5% of the alveolar surface area (Table 4-1). They are characterized histologically by microvilli and osmophilic inclusion bodies.

The type II epithelial cell maintains homeostasis within the alveolar space in several ways. First, it is the source of pulmonary surfactant and as such indicates maturity of the lung; it decreases the surface tension at the alveolar air-liquid interface. Second, this cell is likely the precursor of the alveolar type I cell and thus plays a key role in the repair process following lung injury. Third, it is capable of actively transporting ions against an electrochemical gradient and likely is involved in both fetal lung liquid secretion and, postnatally, the reabsorption of fluid from the airspace following the development of alveolar pulmonary edema (see the later section on Fetal Lung Liquid Secretion).



A



B

■ **FIGURE 4-3.** **A,** Electron micrograph of a type II epithelial cell. This particular cell is from a dog's lung but is similar to those found in all mammalian lungs. The airspace is in the upper portion of the figure. The *arrow* points to the osmophilic inclusions that are thought to be associated with the alveolar lining substance. The cell rests on a basement membrane that separates it from the capillary endothelium in the lower part of the picture. **B,** Normal human lung showing the attenuated alveolar cytoplasm of a type I epithelial cell. Alv, alveolus; Bm, basement membrane; Cap, capillary; Cm, erythrocyte cell membrane; End, capillary endothelium; Ep, cytoplasmic layer of an epithelial cell. (**A,** Courtesy of E.S. Boatman and H.B. Martin. **B,** From Schultz H: The Submicroscopic Anatomy and Pathology of the Lung. Berlin: Springer-Verlag, 1959.)

■ **TABLE 4-1.** Cellular characteristics of the human lung

Cell Type	Total Cells (%)	Apical Surface Area (μm²)
Epithelium		
Alveolar type I	8.3	5098
Alveolar type II	15.9	183
Endothelium	30.2	1353
Interstitial	36.1	
Alveolar macrophages	9.4	

Data from Crapo JD, Barry BE, Gehr P, et al: Cell number and cell characteristics of the normal human lung. Am Rev Respir Dis 1982;125:740–745.

Two pediatric disorders associated with the type II epithelial cell are (1) its lack of maturity and surfactant secretion in respiratory distress syndrome and (2) its excessive and disordered secretion of surfactant in alveolar proteinosis.

The cell junctions (zonulae occludentes) between alveolar type I and type II epithelial cells are very tight and restrict the movement of both macromolecules and small ions such as sodium and chloride. This tightness is an essential characteristic of the cells lining the alveolar space; it enables the active transport of ions. Also these tight junctions provide a margin of safety for patients susceptible to pulmonary edema: significant interstitial pulmonary edema can be present without alveolar flooding occurring, thus preserving gas exchange.

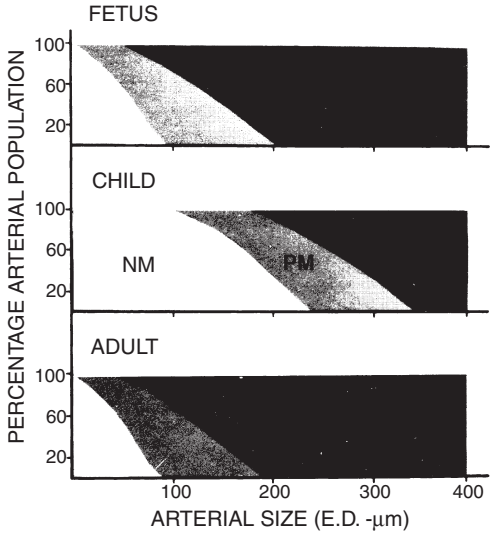
There is a thick side and a thin side to the alveolar capillary membrane. Gas exchange is thought to occur predominantly on the thin side, where there are only the alveolar epithelial cell, fused basement membranes, and capillary endothelial cell (see Fig. 4-3). Capillaries undergo considerable stress (e.g., during exercise or lung hyperinflation) and must have great tensile strength. This strength is mainly imparted by type IV collagen located in the basement membrane. The thick side of the barrier consists of connective tissue, amorphous ground substance, and scattered fibroblasts. The thick side, in addition to providing structural support, acts as a site of fluid and solute exchange.

■ PULMONARY VASCULAR SYSTEM

The lung receives blood from both ventricles. The entire right ventricular output enters the lung via the pulmonary arteries, and blood ultimately reaches the gas-exchanging units by one of the pulmonary arterial branching systems. Conventional arteries accompany the bronchial tree and divide with it, each branch accompanying the appropriate bronchial division. Supernumerary arteries do not travel with the airways but directly supply the gas-exchanging units. These extra arteries actually outnumber the conventional ones and supply approximately one third of the pulmonary capillary bed. Their specific physiologic role is unclear. The pulmonary capillary bed is the largest vascular bed in the body and covers a surface area of 70 to 80 m^2. The network of capillaries is so dense that it may be thought of as a sheet of blood interrupted by small vertical supporting posts. The pulmonary veins return blood to the left atrium via conventional and supernumerary branches. By virtue of their larger numbers and thinner walls, the pulmonary veins provide a large reservoir for blood and help maintain a constant left ventricular output in the face of a variable pulmonary arterial flow.

The bronchial arteries, usually three in number, provide a source of well-oxygenated systemic blood to the lungs. This blood supply nourishes the walls of the bronchi, bronchioles, blood vessels, and nerves in addition to perfusing the lymph nodes and most of the visceral pleura. There are numerous communications between the bronchial arterial system and the remainder of the pulmonary vascular bed: a portion of the blood returns to the right atrium via bronchial veins, and a portion drains into the left atrium via pulmonary veins. Although normally the bronchial arteries receive only 1% to 2% of the cardiac output, they hypertrophy in chronically infected lungs, and blood flow may easily increase by more than 10-fold. This is clinically important because virtually all hemoptysis originates from the bronchial vessels in such disorders as cystic fibrosis or bronchiectasis.

Histologically, the pulmonary arteries can be classified as elastic, muscular, partially muscular, or nonmuscular. The elastic pulmonary arteries are characterized by elastic fibers embedded in their muscular coat, whereas the smaller muscular arteries have a circular layer of smooth muscle bounded by internal and external elastic laminae. As arteries decrease further in size, only a spiral of muscle remains (partially muscular arteries), which ultimately disappears so that vessels still larger than capillaries have no muscle in their walls (nonmuscular arteries). In the adult lung, elastic arteries are greater than 1000 μm in diameter, and muscular arteries range from 150 to 100 μm. In the pediatric age group, histologic structure is not as easily determined from vessel size. Reid and co-workers have demonstrated that during growth of the lung a remodeling of the pulmonary vasculature occurs. Muscularization of the arteries lags behind multiplication of alveoli and appearance of new arteries. Therefore, the patient's age must be considered before histologic structure can be assumed from vessel size within the pulmonary acinus (Fig. 4-4). Notably, in the fetus and newborn the amount of pulmonary arterial smooth muscle is increased and regresses after birth. This is functionally important since a high pulmonary arterial resistance is a feature of the fetal circulation in association with a large right to left shunt via the ductus arteriosus.



■ **FIGURE 4-4.** The populations of the three arterial types: muscular (M), partially muscular (PM), and nonmuscular (NM), in fetus, child, and adult. The distribution of structure in size is similar in fetus and adult, whereas during childhood NM and PM structures are found in much larger arteries. E.D., external diameter. (From Reid LM: The pulmonary circulation. Remodelling in growth and disease. Am Rev Respir Dis 1979;119:531.)

The endothelium of the pulmonary vascular system is continuous and nonfenestrated. It is an intensely active cell layer and is not just serving a passive barrier function. The endothelial cell produces a glycocalyx that interacts with blood-borne substances and blood cellular elements, thereby influencing such homeostatic functions as hemostasis. The endothelium produces von Willebrand factor, which is part of the factor VIII complex and is necessary for normal platelet function. Similarly, there are enzymes located on the surface and within the cell itself that are capable of synthesizing, altering, or degrading blood-borne vasoactive products. The individual cells are separated by gaps of approximately 35 Å in radius, which allow the free movement of water and small ions but restrict the movement of proteins. The cells and the basement membrane on which they sit carry different net surface charges, which affect the movement of anionic macromolecules such as proteins and thus affect lung water and solute exchange (see Chapter 43). The capacity of the pulmonary endothelium and its basement membrane to restrict fluid and protein movement is impressive. It has been estimated that the amount of lung lymph flow is only 10 to 20 mL/hr despite a total blood flow of 300,000 mL/hr.

LYMPHATIC SYSTEM

There is an extensive interconnecting network of lymphatic vessels throughout the lung. The major function of this network is to collect the protein and water that has moved out of the pulmonary vascular space and to return it to the circulation, thus maintaining the lung at an appropriate degree of hydration. The lymphatic vessels travel alongside the blood vessels in the loose connective tissue of the pleura and bronchovascular spaces. It is likely that there are no lymphatics within the alveolar wall itself and that juxta-alveolar lymphatics represent the beginning of the pulmonary lymphatic system. Histologically, the lymphatic capillaries consist of thin, irregular endothelial cells lacking a basement membrane. Occasionally, there are large gaps between endothelial cells that allow direct communication with the interstitial space. Larger lymphatic vessels contain smooth muscle in their walls that undergoes rhythmic contraction. This muscular contraction plus the presence of funnel-shaped, monocuspid valves ensures an efficient unidirectional flow of lymph. In addition to helping maintain lung water balance, the lymphatic system is one of the pulmonary defense mechanisms. It aids in removal of particulate matter from the lung, and aggregates of lymph tissue near major airways contribute to the host's immune response.

INNERVATION OF THE LUNG

The lung is innervated by both components of the autonomic nervous system. Parasympathetic nerves arise from the vagus nerve, and sympathetic nerves are derived from the upper thoracic sympathetic ganglia. These branches congregate around the hila of the lung to form the pulmonary plexus. Myelinated and nonmyelinated fibers then enter the lung tissues and travel along with and innervate the airways and blood vessels. Although the anatomic location of pulmonary nerves has been elucidated, their physiologic role in health and disease is incompletely understood. In general, the airways constrict in response to vagal stimulation and dilate in response to adrenergic stimulation. The pulmonary vasculature appears to be maximally dilated under normal conditions, and it is difficult to demonstrate any significant physiologic effect of either parasympathetic or sympathetic stimulation. The vascular response, however, is influenced by age and initial vascular tone. For example, in fetal lungs where there is an abundance of pulmonary vascular smooth muscle, vagal stimulation results in significant vasodilatation, and sympathetic stimulation results in marked vasoconstriction.

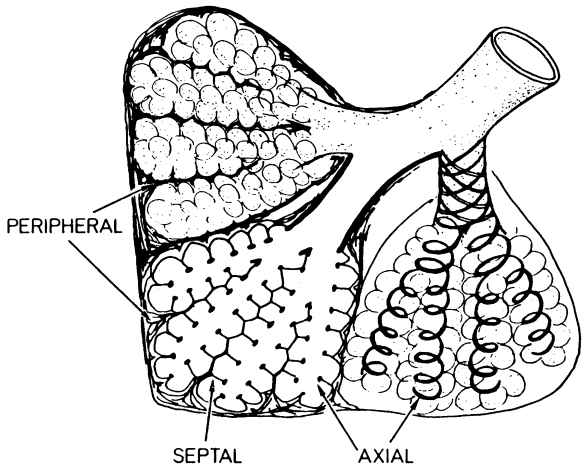
Sensory nerves from the lungs are vagal in origin and arise from slowly and rapidly adapting receptors and from C-fiber receptors. The slowly adapting (stretch) receptors, located in the smooth muscle of the airway, are stimulated by an increase in lung volume or transpulmonary pressure. They induce several physiologic responses including inhibition of inspiration (Hering-Breuer reflex), bronchodilatation, increased heart rate, and decreased systemic vascular resistance. The rapidly adapting vagal (irritant) receptors are activated by a wide variety of noxious stimuli, ranging from mechanical stimulation of the airways to anaphylactic reactions within the lung parenchyma. The rapidly adapting receptors induce hyperpnea, cough, and constriction of the airways and larynx. C-fiber receptors are the terminus of nonmyelinated vagal afferents. They include the J receptors that are located near the pulmonary capillaries and are stimulated by pulmonary congestion and edema; they evoke a sensation of dyspnea and induce rapid shallow breathing along with laryngeal constriction during expiration.

In addition to the sympathetic and parasympathetic nervous systems, humans and several other species have a third nervous system within their lungs. The noncommittal name *nonadrenergic noncholinergic nervous system* has been chosen because its function and properties are not understood. Purines, substance P, and vasoactive intestinal polypeptide have been suggested as possible neurotransmitters for this system.

INTERSTITIUM

The interstitium plays several roles in lung function in addition to providing a structural framework that consists of insoluble proteins. The ground substance influences cell growth and differentiation and lung water and solute movement. The cells contained within the interstitial region of the lung not only play individual roles that result from their contractile or synthetic properties but they also interact with other cells, such as the endothelium and epithelium, to alter the basic structure and function of the lung.

Most of the interstitial matrix of the lung is composed of type I collagen. Type I collagen, along with the less common types II, III, IV, and V, forms a structural, fibrous framework within the lung. The three principal components of this framework, which include the axial, peripheral, and septal fiber systems, are illustrated in Figure 4-5. Elastin, a contractile insoluble protein, provides elasticity and support to the structures. Both elastin and collagen turn over very slowly under normal conditions. However, rapid remodeling with changes in these proteins sometimes occurs. In diseases such as α_1-antitrypsin deficiency (affecting elastin) and pulmonary fibrosis (affecting collagen), there are marked qualitative and quantitative changes in these proteins. The remainder of the matrix is made up of proteoglycans and glycosaminoglycans. These carbohydrate-protein complexes can affect cell proliferation and differentiation in addition to their known effect on cell adhesion and attachment (e.g., laminin) and ability to diminish fluid movement (glycosaminoglycans).



■ **FIGURE 4-5.** Schematic diagram of the fibrous support of the lung. See text for detail. (From Weibel ER, Bachofen H: How to stabilize the alveoli. Surfactant or fibers. News Physiol Sci 1987;2:72–75.)

Fibroblasts are capable of synthesizing collagen, elastin, and glycosaminoglycans and hence contribute significantly to the composition of the lung's interstitial space. They can be found within all of the interstitial regions of the lung, although their apparent structure may change. For example, because "myofibroblasts" contain obvious contractile elements, they may represent fibroblasts that are capable of contraction, or they may be cells that are intermediate between fibroblasts that are capable of contraction, or they may be cells that are intermediate between fibroblasts and smooth muscle cells. Similarly, it is likely that morphologically similar fibroblasts are not similar in terms of proliferative capacity and ability to synthesize various types of collagen. Data suggest that fibrotic lung diseases are characterized by the loss of the normal heterogeneous fibroblast population and that there may be a selection for certain clones that promote inappropriate collagen deposition within the lung parenchyma.

Smooth muscle cells are contractile interstitial cells that influence the bronchomotor and vasomotor tone within the conducting airways and blood vessels. They are also seen within the free edge of the alveolar septa, and they form an alveolar entrance ring that is capable of constricting or dilating. The smooth muscle cells form bundles connected by nexus or gap junctions that enable electrical coupling and synchronous contraction. The pericyte is another interstitial cell that is found between the basement membrane and the endothelium. It is believed to be a precursor cell that can differentiate into a mature vascular smooth muscle cell.

There are a variety of interstitial cells that are concerned with immune and nonimmune defense of the lung. The interstitial macrophage and the alveolar macrophage are predominantly responsible for nonimmune defense, which they manage by ingesting particulate matter and removing it from the lung. These macrophages are capable of secreting many compounds, including proteases and cytokines (substances capable of modulating the growth and function of other cells). B and T lymphocytes are present in the lung and especially within the bronchus-associated lymphoid tissue, where they contribute to the humoral and cellular-mediated immune response.

Although not within the interstitium per se, there are large numbers of intravascular granulocytes that adhere to the pulmonary endothelium. Indeed, next to the bone marrow and spleen, there are more granulocytes within the lung than in any other organ. These granulocytes can be released into the systemic circulation during such stimuli as exercise or the infusion of adrenalin, and this demargination is responsible for the concomitant blood leukocytosis. These leukocytes are also in a prime location for movement into the lung should an infection or inflammatory stimulus occur. There is much evidence to suggest that the pulmonary granulocyte contributes to the pulmonary dysfunction seen in acute lung injury or acute respiratory distress syndrome. Leukocytes also contain proteases that are thought to play a role in the development of emphysema and in the lung destruction that occurs in cystic fibrosis.

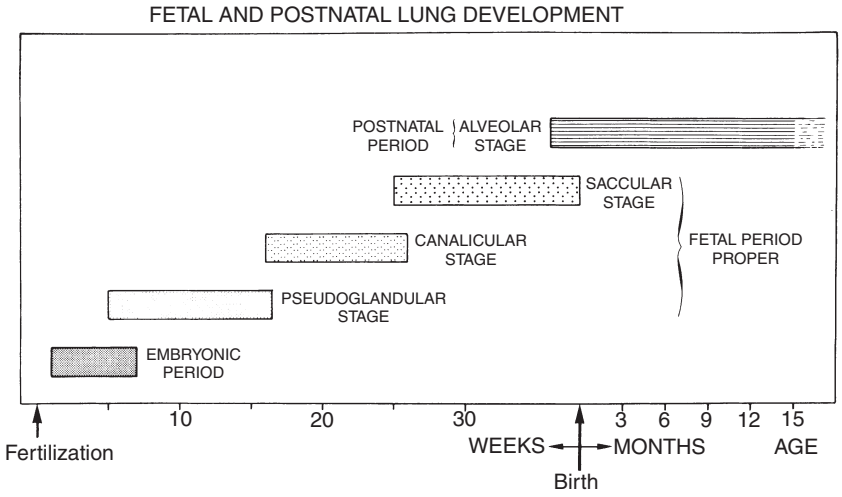
■ GROWTH AND DEVELOPMENT OF THE LUNG

■ PRENATAL LUNG GROWTH

Intrauterine growth and development of the lung have been divided into various stages with names that reflect the respective histologic appearance of the lung, the region of the lung that is most obviously developing, or both. Obviously, all the regions of the lung are developing during the various stages; in addition, there are variations in growth rates among individual fetuses. Thus, there is no exact differentiation between the various stages. However, the major reason for identifying these stages of development is to improve our understanding of how and why specific congenital lesions occur. Obviously, the child with unilateral lung agenesis must have had defective lung development much earlier than another child with a peripheral congenital lung cyst.

The five stages of lung development are (1) embryonic (days 26 to 52), (2) pseudoglandular (day 52 to week 16), (3) canalicular (weeks 16 to 28), (4) saccular (weeks 28 to 36), and (5) alveolar (week 36 to term). This classification recognizes that there are true alveoli present in the human lung before birth, with the first being seen at 29 to 32 weeks of gestation. This example illustrates the inexact nature of staging lung development, since the alveolar period does not "begin" until 36 weeks (Fig. 4-6).

The lung first appears in the embryonic period as a ventral outpouching of the primitive gut. The primary bronchi elongate into the mesenchyme and divide into the two main bronchi. In the pseudoglandular period, the branching continues by means of a higher mitotic rate in the epithelium relative to the mesenchyme. The mesenchyme differentiates into cartilage, smooth muscle, and connective tissue around the epithelial tubes. By the end of the pseudoglandular period (16 weeks) all the major conducting airways, including the terminal bronchioles, have formed. The canalicular period is characterized by the development of respiratory bronchioles, each of which ends in two or three thin-walled dilatations called terminal sacs or primitive alveoli. Vascularization of the lung interstitium intensifies, and the glandular appearance is lost as there is a decrease in the relative amount of connective tissue. Further differentiation of the respiratory portion of the lung takes place during the saccular period. During this period, there is for the first time close contact between the airspace and the bloodstream, as the pulmonary capillaries rapidly proliferate and the epithelium thins. Gas exchange is now possible, although obviously it is not optimal. Elastic fibers, which will be important in



■ **FIGURE 4-6.** Various stages of lung development. The actual separation of individual stages is not discrete, and it overlaps. Note that the alveolar stage commences before birth. (From Burri PH: Fetal and postnatal development of the lung. Annu Rev Physiol 1984;46:617–628. © 1984 by Annual Reviews, Inc.)

subsequent true alveolar development, are beginning to be laid down. At this time, cuboidal (type II) and thin (type I) epithelial cells line the airspace. During the alveolar period, further refinement takes place as tiny secondary septa form on the walls of the larger saccules. These outpouchings grow into the lumen and form the walls of true alveoli, thus further increasing the surface area available for gas exchange.

The development of the pulmonary vasculature coincides with the development of the airways. During the embryonic period, the main pulmonary artery arises from the sixth branchial arch and nourishes the developing lung bud. Throughout the pseudoglandular period, arteries are evident alongside the conducting airways. In addition to the conventional arteries that branch and travel with the airways, supernumerary arteries are evident by 12 weeks of gestation. By 16 weeks of gestation, all preacinar arterial branches have formed; although these will increase in size and length, no new preacinar branches will appear. During the canalicular period, the lung develops a rich vascular supply that is closely associated with the respiratory bronchioles. As saccules begin to develop during the saccular period, capillaries can be found within the walls of the airspaces in close contact with the epithelium. Gas exchange can now occur.

The maturation of surfactant production has been studied intensively since the discovery that prematurely born infants with hyaline membrane disease had abnormal surface tension at the air-liquid interface. It is now known that the source of pulmonary surfactant is the mature type II epithelial cell. When the type II epithelial cell first appears within the lung during the saccular stage, however, it is immature and contains much intracellular glycogen. Many drugs and hormones, including steroids and thyroid and peptide hormones, can influence surfactant biosynthesis and accelerate lung maturation. The surfactant system is discussed in detail in Chapter 2.

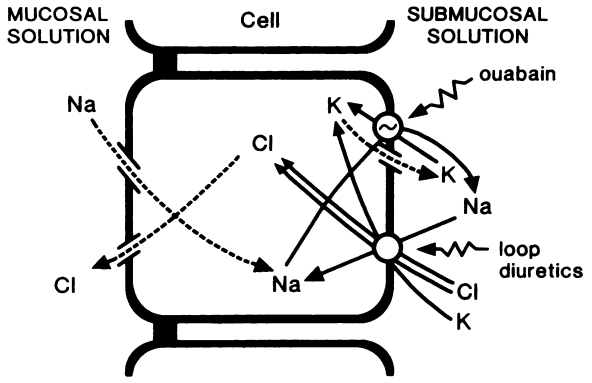
The control of lung development is complex and is now known to be strongly influenced by interactions between the pulmonary epithelium and mesenchyme. A family of about 28 fibroblast growth factors are important in regulating cell proliferation, migration, and differentiation during lung development. Epithelium isolated in vitro does not undergo morphogenesis; when it is recombined with pulmonary mesenchyme, development resumes. In a similar manner, it has been demonstrated that the mesenchymal signals can be organ specific. For example, submandibular mesenchyme can induce mammary gland epithelium to express submandibular epithelium gene products. Thus, defects in lung epithelial development could conceivably result from abnormalities within the mesenchymal rather than the epithelial structures.

The mesenchyme's influence on lung development can be classified as instructive (directive) or permissive. The former influence instructs the epithelium to take a specific developmental pathway (e.g., to differentiate into a type II versus a ciliated epithelial cell). In contrast, permissive inductions allow an already committed cell to express its capabilities (e.g., a type II cell to start secreting surfactant).

■ FETAL LUNG LIQUID SECRETION

Fetal lung liquid secretion is essential for normal lung development. Exactly when the lung begins to secrete fluid is unknown, but the secretion is well established by the second half of gestation and is produced at a rate of 4 to 5 mL/kg/hr. Analysis of fetal lung liquid has demonstrated that it is neither a mere ultrafiltrate of plasma nor aspirated amniotic fluid. The lung fluid relative to plasma has higher concentrations of chloride (155 mM) and potassium (6 mM), similar sodium concentration, and markedly lower bicarbonate (3 mM) concentration. The lung liquid protein concentration is so low that it is comparable with cerebrospinal fluid (0.03 g/dL). Fetal lung liquid secretion is dependent on the active transport of electrolytes into the airspace.

There are two requirements for the active secretion of fluid into the developing airspaces (Fig. 4-7). First, there must be an electrochemical gradient for ion movement that will carry water with it. The source of energy for the active transport is the sodium-potassium adenosine triphosphatase (ATPase) located on the basolateral epithelial cell membrane. As the pump extrudes sodium out of the cell, there is a linked reentry of this sodium along with chloride (and perhaps potassium) back into the cell down sodium's electrochemical gradient. The intracellular chloride concentration rises, and it exits out into the airspace through chloride channels in the apical membrane, driven out by the electrical gradient (the inside of the cell membrane is negative relative to the lumen). The second requirement for ion transport is a very tight epithelial membrane, which is necessary to establish these gradients and to prevent rapid backward flow



■ **FIGURE 4-7.** A model of pathways for active transport of electrolytes by a pulmonary epithelial cell. In fetal life, chloride (Cl) secretion predominates and presumably occurs via the apical Cl channel. After birth, sodium (Na) absorption is dominant. Ouabain inhibits the Na-K ATPase pump, whereas loop diuretics can inhibit the Na:K:2Cl cotransporter, thus impeding Cl secretion. See text for details. (From Welsh M: Electrolyte transport by airway epithelia. Physiol Rev 1987;67:1143–1184.)

of ions and water between the cells. This requirement is met by the extremely tight interepithelial junctions that restrict the movement of these small ions. Data from fetal sheep suggest that the airspace's epithelium is tight and remarkably constant between 50% of gestation and term. Interference with fetal lung liquid secretion or fetal lung distention by liquid results in a maldeveloped lung with a reduced number of terminal airspaces.

THE LUNG AT BIRTH

Many dramatic changes must occur in the lungs during the transition from intrauterine to extrauterine life. The lung's epithelium must change from fluid secretion to fluid absorption, the distal lung units must fill with and retain the inhaled air, and blood flow must increase approximately 20-fold.

Just before birth the lungs contain approximately 30 mL/kg of fetal lung liquid. At the time of birth it is essential that fetal lung liquid secretion decrease so that the lung liquid can be cleared to allow for normal gas exchange. The control mechanisms for this decrease in secretion are incompletely understood, but evidence suggests that catecholamines released before or during the birth process will decrease secretion, possibly by inhibiting chloride ion transport, opening sodium channels in the apex of the epithelial cell, thereby converting it into a sodium reabsorbing membrane, or both. It has also been demonstrated that this effect of catecholamines is dependent on gestational age. In the more immature fetus, β agonists have little effect on lung liquid secretion, and thus the immature fetus may have greater difficulty clearing the airspace fluid when making the transition to breathing air. The process of labor itself will increase the amount of sodium-potassium ATPase activity in the type II epithelial cells; which aspect of labor is important is unknown. Fetal lung liquid is cleared at birth by several mechanisms; approximately one third is squeezed out during the birth process, and the remainder is absorbed by the epithelium; the fluid is then taken up by pulmonary vessels or cleared by the lymphatics. Failure of normal lung water clearance at birth is simply one type of pulmonary edema, and it results in respiratory distress (wet lung syndrome or transient tachypnea of the newborn).

The assessment of lung function in early stages of development is based chiefly on measurement in lambs, which provides insight into the direction of changes that occur with time, although exact analogies to the human subject are speculative. The distensibility of the lung early in gestation is much less than at term. When peak volumes are expressed as milliliters per gram of lung tissue, it is evident that the potential airspace is small with respect to lung mass. The ability to retain air at end-expiration, which depends on the presence of the pulmonary surfactant, does not appear until later in the canalicular stage of development. In the lamb it appears between days 120 and 130 of a 147-day gestation. In the human it appears probably between the 20th and the 24th weeks of gestation, with a wide distribution over this period.

In utero, little blood flows through the lung despite a relatively high perfusion pressure, because of the abundance of pulmonary vascular smooth muscle and the vasoconstrictor effect of the low fetal partial pressure of oxygen (P_{O_2}) (<30 mm Hg). Although during the last trimester, concomitant with surfactant production, blood flow increases to 7% of the cardiac output, it is only at birth that marked increases in the capacity and distensibility of the pulmonary vasculature occur. Several mechanisms are responsible for the changes in circulation. Inflation of the lung with air results in mechanical distention of the vessels, and improvement in oxygenation removes hypoxic vasoconstriction. In addition, the rise in partial pressure of oxygen in arterial blood (Pa_{O_2}) induces granulocytes in the lung to release massive quantities of kinin. This kinin alters the tissue concentrations of prostaglandins and helps to mediate the vasoconstriction of the ductus arteriosus and umbilical vessels and to dilate the pulmonary vascular bed. Both prostacyclin and nitric oxide have a significant regulatory role on pulmonary vascular tone in the perinatal period. The concentration of both prostaglandin 1-synthase and nitric oxide synthase (NOS) increase with development, especially near term. Neonatal lung NOS expression is decreased in persistent pulmonary hypertension of the newborn. With increasing postnatal age, vascular muscle regresses so that the wall/lumen ratio decreases. After about 10 days of extrauterine life, the lumina are wider, regardless of the gestational age of the baby. The events of birth have little effect on other aspects of lung development, including histochemical maturation.

POSTNATAL LUNG GROWTH

The postnatal growth of the lung continues into the adolescent years and perhaps beyond. It is important to remember that the lung of the newborn is not a miniature of the lung of the adult; during growth, tracheal diameter approximately triples, alveolar dimensions increase about fourfold, and alveolar numbers increase about 10-fold while body mass increases about 20-fold. Other anatomic relationships of the infant's and child's lungs are similar to those in the adult's lung (see Figs. 4-1 and 4-2). The internal surface area of the lung maintains a close relationship to body mass (approximately 1 m^2/kg of body weight), and the proportion of total lung weight represented by each lobe is remarkably constant from infancy to adulthood. Average values of lung lobe weight expressed as a percentage of total lung weight are as follows: right upper lobe 19.5%, right middle lobe 8.3%, right lower lobe 25.3%, left upper lobe 22.5%, and left lower lobe 24.6%.

The preacinar blood vessels and airways have developed by 16 weeks' gestation, and although they do increase in size after birth, the majority of postnatal lung growth involves the terminal respiratory unit.

New secondary septa continue to appear on the walls of the saccules and grow into the airspace, thus creating more true alveoli. Alveoli continue to increase in number through segmentation of these primitive alveoli and through transformation of terminal bronchioles into respiratory bronchioles, a process known as alveolarization. The number of alveoli rapidly increases from 20 million to 200 million by the third year of life, but then alveolar multiplication slows.

There is no agreement about when alveolar multiplication ceases (2 vs. 8 years), but few if any new alveoli develop after 8 years of age. Further growth of the airspace then occurs through increases in alveolar dimensions. In the mature adult lung, the number of alveoli varies from 200 million to 600 million, and an individual alveolus is 250 to 350 μm in diameter. The reason for the variable number of alveoli in the adult lung is unknown but seems to be related to total lung volume. Indeed, in the adult there are about 170 alveoli per mm^3 of lung parenchyma.

As alveolar multiplication occurs, new blood vessels appear within the acinus, so the ratio between the numbers of alveoli and arteries remains relatively constant throughout childhood. Branching of conventional arteries continues until 18 months of age, whereas supernumerary arteries continue to appear until 8 years of age.

Throughout childhood there is an increase in the concentration of arteries to alveoli. The alveolar/arterial ratio is 20:1 in the newborn, 12:1 in a 2-year-old child, and 8 to 10:1 in the older child. The muscularization of the arteries lags behind during childhood, with a return to muscularization of more peripheral arteries by adult life (see Fig. 4-7).

■ VENTILATION AND MECHANICS OF BREATHING

The principal function of the lung is to perform gas exchange, that is, to enrich the blood with oxygen and cleanse it of carbon dioxide. An essential feature of normal gas exchange is that the volume and distribution of ventilation are appropriate. Ventilation of the lung depends on the adequacy of the respiratory pump (muscles and chest wall) and the mechanical properties of the airways and gas-exchanging units.

It is traditional and useful to consider mechanical events as belonging to two main categories: the static-elastic properties of the lungs and chest wall and the flow-resistive or dynamic aspects of moving air. Changes in one category may be associated with compensatory changes in the other. Thus, many diseases affect both static and dynamic behavior of the lungs. Often the principal derangement is in the elastic properties of the tissues or in the dimensions of the airways, and the treatment or alleviation of symptoms depends on distinguishing between them.

Before we discuss the mechanical aspects of lung function and gas exchange, it is important to review several basic physical laws concerning the behavior of gases and also the related abbreviations and symbols that will be used.

■ DEFINITIONS AND SYMBOLS

The principal variables for gases are as follows:

V = gas volume
$\dot{V}$ = volume of gas per unit time
P = pressure
F = fractional concentration in dry gas
R = respiratory exchange ratio, carbon dioxide/oxygen
f = frequency
D_L = diffusing capacity of lung

The designation of which volume or pressure is cited requires a small capital letter after the principal variable. Thus, V_{O_2} = volume of oxygen; P_B = barometric pressure.

I = inspired gas
E = expired gas
A = alveolar gas
T = tidal gas
D = dead space gas
B = barometric pressure

When both location of the gas and its species are to be indicated, the order is V_{IO_2}, which means the volume of inspired oxygen.

STPD = standard temperature, pressure, dry (0°C, 760 mm Hg)
BTPS = body temperature, pressure, saturated with water vapor
ATPS = ambient temperature, pressure, saturated with water vapor

The principal designations for blood are as follows:

S = percentage saturation of gas in blood
C = concentration of gas per 100 mL of blood
Q = volume of blood
$\dot{Q}$ = blood flow per minute
a = arterial
$\bar{v}$ = mixed venous
c = capillary

All sites of blood determinations are indicated by lowercase initials. Thus, P_{aCO_2} = partial pressure of carbon dioxide in arterial blood; P_{O_2} = partial pressure of oxygen in mixed venous blood; and P_{aO_2} = partial pressure of oxygen in a capillary.

Properties of Gases

Gases behave as an enormous number of tiny particles in constant motion. Their behavior is governed by the gas laws, which are essential to the understanding of pulmonary physiology.

Dalton's law states that the total pressure exerted by a gas mixture is equal to the sum of the pressures of the individual gases. The pressure exerted by each component is independent of the other gases in the mixture. For instance, at sea level, air saturated with water vapor at a temperature of 37°C has a total pressure equal to the atmospheric or barometric pressure (P_B = 101.3 kilopascals or 30 inches of mercury or 760 mm Hg), with the partial pressures of the components as shown in:

$$P_B = 760 \text{ mm Hg} = P_{H_2O} (47 \text{ mm Hg}) + P_{O_2} (149.2 \text{ mm Hg}) + P_{N_2} (563.5 \text{ mm Hg}) + P_{CO_2} (0.3 \text{ mm Hg})$$

The gas in alveoli contains 5.6% carbon dioxide, BTPS. If P_B = 760 mm Hg, then,

$$P_{ACO_2} = 0.056(760 - 47) = 40 \text{ mm Hg}$$

Boyle's law states that at a constant temperature, the volume of any gas varies inversely as the pressure to which the gas is subjected: PV = k. Because respiratory volume measurements

may be made at different barometric pressures, it is important to know the barometric pressure and to convert to standard pressure, which is considered to be 760 mm Hg.

Charles' law states that if the pressure is constant, the volume of a gas increases in direct proportion to the absolute temperature. At absolute zero (–273°C), molecular motion ceases. With increasing temperature, molecular collisions increase, so that at constant pressure, volume must increase.

In all respiratory calculations, water vapor pressure must be taken into account. The partial pressure of water vapor increases with temperature but is independent of atmospheric pressure. At body temperature (37°C), fully saturated gas has a P_{H_2O} of 47 mm Hg.

Gases may exist in physical solution in a liquid, escape from the liquid, or return to it. At equilibrium, the partial pressure of a gas in a liquid medium exposed to a gas phase is equal in the two phases. Note that in blood the sum of the partial pressures of all the gases does not necessarily equal atmospheric pressure. For example, in venous blood, P_{O_2} has fallen from the 100 mm Hg of the arterial blood to 40 mm Hg, while P_{CO_2} has changed from 40 to 46 mm Hg. Thus, the sum of the partial pressures of O_2, CO_2, and N_2 in venous blood equals 655 mm Hg.

ELASTIC RECOIL OF THE LUNG

The lung is an elastic structure that tends to decrease its size at all volumes. The elasticity of the lung depends on the structural components (although elastic fibers are not essential for normal performance), the geometry of the terminal airspaces, and the presence of an air-liquid interface. When a lung is made airless and is then inflated with liquid, the elastic recoil pressure at large volumes is less than half that of a lung inflated to the same volume with air. Thus, the most significant determinant of the elastic properties of the lung is the presence of an air-liquid interface.

The increase of elastic recoil in the presence of an air-liquid interface results from the forces of surface tension. What is surface tension? When molecules are aligned at an air-liquid interface, they lack opposing molecules on one side. The intermolecular attractive forces are then unbalanced, and the resultant force tends to move molecules away from the interface. The effect is to reduce the area of the surface to a minimum. In the lungs the forces at the air-liquid interface operate to reduce the internal surface area of the lung, and thus they augment elastic recoil. A remarkable property of the material at the alveolar interface, the alveolar lining layer or pulmonary surfactant, is its ability to achieve a high surface tension at large lung volumes and a low surface tension at low volumes. Surfactant is a phospholipid-protein complex that when compressed forms insoluble, folded-surface films of low surface tension. The ability to achieve a low surface tension at low lung volumes tends to stabilize the airspaces and prevent their closure.

The exact method of lung stabilization and the concomitant role of surfactant in this stabilization can be debated. The classic interpretation is that without surfactant the smaller alveoli would tend to empty into the larger alveoli in accordance with the Laplace relationship, which relates the pressure across a surface (P) to surface tension (T) and radius (r) of curvature. For a spherical surface, P = 2T/r. The smaller the radius, the greater is the tendency to collapse.

The difficulty with this hypothesis is that the individual lung units are drawn as independent but communicating bubbles or spheres (Fig. 4-8). This is not representative of structure of the lung because the alveolar walls are planar, not spherical. In addition, the inside wall of one alveolus is the outside wall of the adjacent alveolus. This last explanation has been utilized to develop the interdependence model of lung stability, which indicates that surface and tissue forces interact to maintain the lungs' inherent structure, with the fibrous components playing an important role (see Fig. 4-8).

The elastic recoil of the lung is responsible for the lung's tendency to pull away from the chest wall with the resultant subatmospheric pressure in the pleural space. Lung recoil can therefore be derived from measurement of the pleural pressure when no airflow is occurring and alveolar pressure is zero. (The pressure measurement is taken with the patient holding his breath for a brief period with the glottis open.)

The pressure within the esophagus can be used as an index for mean pleural pressure. This is a reasonable assumption as long as there is no paradoxical rib cage movement. However, it is not a reasonable assumption for premature infants, term infants in rapid eye movement (REM) sleep, and older infants with severe lung disease. For these infants, no average pleural pressure exists, and calculations of resistance and compliance will not be accurate using this method. When pleural pressure is estimated with an esophageal balloon, one must be careful to avoid artifacts resulting from the gravitational pressure of the mediastinum. For this reason, these measurements are best performed with the patient in the upright or lateral rather than the supine position. Once a series of pressure measurements has been made during brief breath-holds at different lung volumes, a pressure-volume curve of the lung can be constructed (Fig. 4-9).

COMPLIANCE OF THE LUNG

The pressure-volume curve of the lung describes two measurements of the elastic properties of the lung: elastic recoil pressure and lung compliance. Elastic recoil pressure is the pressure generated at a given lung volume, whereas compliance is the slope of the pressure-volume curve, or the volume change per unit of pressure:

$$\text{Compliance} = \frac{\Delta\text{volume}}{\Delta\text{pressure}} = \frac{\text{L}}{\text{cm } H_2O}$$

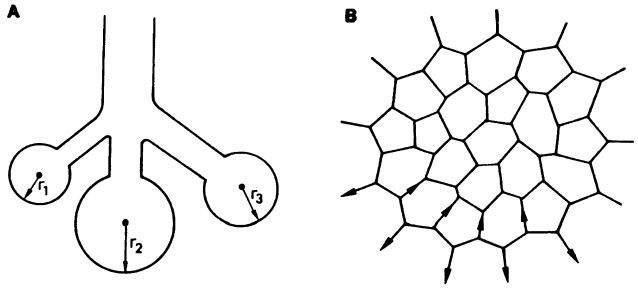
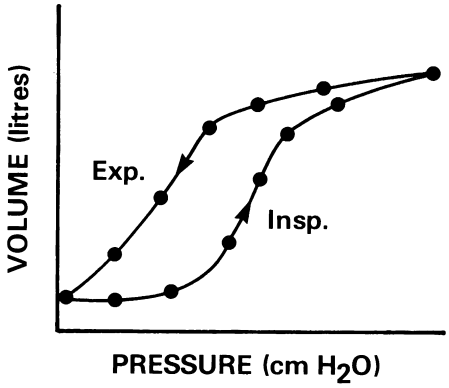


FIGURE 4-8. A, Classic model of the distal lung, in which individual alveoli would be controlled by Laplace's law: $P = 2\gamma/r$. Small alveoli would empty into large alveoli. **B,** Interdependence model of the lung, in which alveoli share common planar and not spherical walls. Any decrease in the size of one alveolus would be stabilized by the adjacent alveoli. (From Weibel ER, Bachofen H: How to stabilize the alveoli. Surfactant or fibers. News Physiol Sci 1987;2:72–75.)



■ **FIGURE 4-9.** Pressure-volume curve of a normal lung. Pleural pressure and lung volume are simultaneously determined during brief breath-holds. Lung compliance is calculated from data obtained on the expiratory portion of the pressure-volume curve.

Compliance depends on the initial lung volume from which the change in volume is measured and the ventilatory events immediately preceding the measurement as well as the properties of the lung itself. At large lung volumes, compliance is lower, because the lung is nearer its elastic limit. If the subject has breathed with a fixed tidal volume for some minutes, portions of the lung are not participating in ventilation, and compliance may be reduced. A few deep breaths, with return to the initial volume, will increase compliance. Thus, a careful description of associated events is required for correct interpretation of the measurement.

Changes in lung compliance occur with age (Table 4-2). Of course, the smaller the subject, the smaller is the change in volume, so that $\Delta V/\Delta P$ is close to 6 mL/cm H_2O in infants, and is 125 to 190 mL/cm H_2O in adults. It is more relevant to a description of the elastic properties of the lung to express the compliance in relation to a unit of lung volume such as the functional residual capacity (FRC). Note that with age, as shown in Table 4-2, the compliance of the lung/FRC, or the specific compliance, changes much less.

It is worth reemphasizing that total lung compliance is a function not only of the lung's tissue and surface tension characteristics but also of its volume. This is especially important to remember when compliance has been measured in newborn infants with respiratory distress syndrome (RDS). The total compliance is a composite of the lung's elastic properties and the number of open lung units. In RDS, sudden changes in total measured compliance (if uncorrected for simultaneously measured lung gas volume) will predominantly, if not exclusively, reflect the opening and closing of individual lung units.

Lung compliance may also be measured during quiet breathing with pressure and volume being recorded at end-inspiration and end-expiration. The resultant value is the dynamic lung compliance. Although dynamic lung compliance does reflect the elastic properties of the normal lung, it is also influenced by the pressure required to move air within the airways. Therefore, dynamic lung compliance increases with increased respiratory rate and with increased airway resistance. Airflow is still occurring within the lung after it has ceased at the mouth, and pleural pressure reflects both the elastic recoil of the lung and the pressure required to overcome the increased airway resistance. Indeed, dynamic lung compliance can be used as a sensitive test of obstructive airway disease.

■ **TABLE 4-2.** Lung compliance (C_L) with age

	mL/cm H_2O	C_L/FRC
Newborns		
3 hr	4.75 ± 1.67	0.041 ± 0.01
24 hr	6.24 ± 1.45	0.055 ± 0.01
Infants		
1 mo–2 yr	7.9	0.038
Children		
Average age 9 yr	77	0.063
Young adult males	184	0.050
Young adult females	125	0.053
Adults over 60 yr	191	0.041

FRC, functional residual capacity.

■ ELASTIC PROPERTIES OF THE CHEST WALL

The chest wall is also an elastic structure, but in contrast to the lung, it tends to push outward at low volumes and inward at high volumes. These phenomena are illustrated when air is introduced into the pleural space: the lung collapses and the chest wall springs outward.

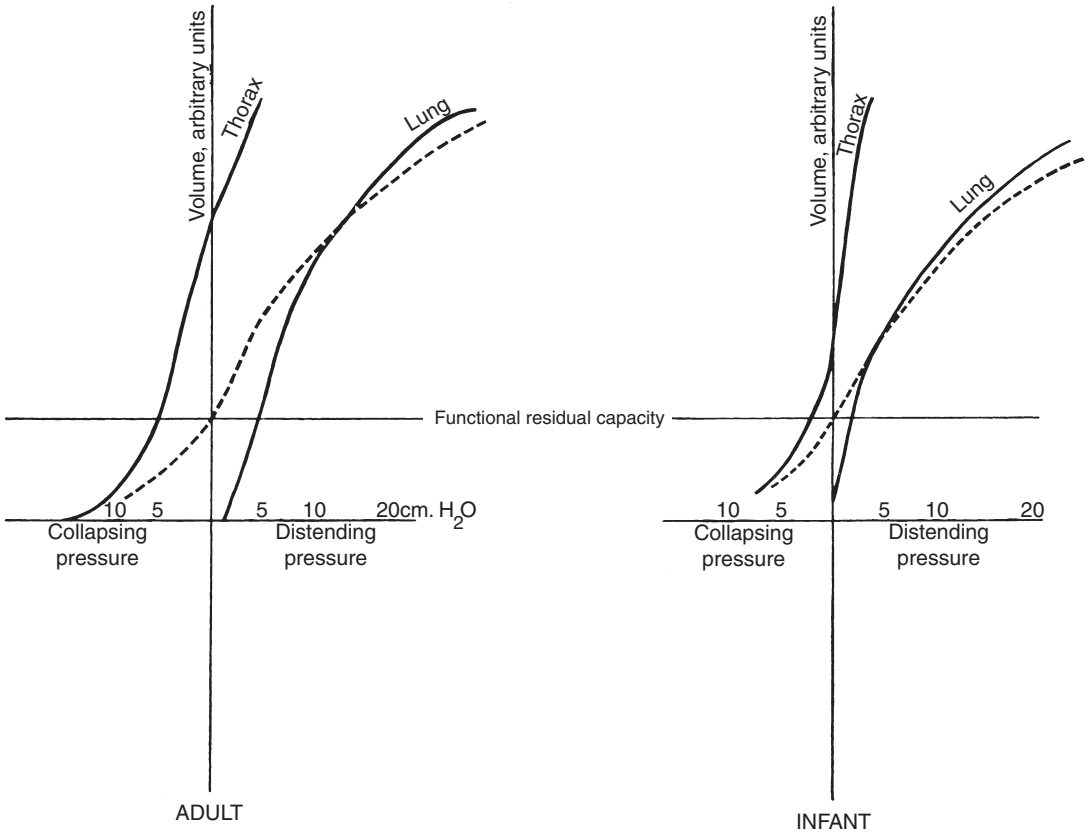
Compliance of the chest wall can be measured by considering the pressure difference between the pleural space or esophagus and the atmosphere, per change in volume. Significant changes in thoracic compliance occur with age (Fig. 4-10). In the range of normal breathing, the thorax of the infant is nearly infinitely compliant. The pressures measured at different lung volumes are about the same across the lung as those measured across lung and thorax together. The functional significance of the high compliance of the neonatal thorax is observed when there is lung disease. The necessarily greater inspiratory effort and more negative pleural pressure can "suck" in the chest wall, resulting in less effective gas exchange and a higher work of breathing.

With advancing age the thorax becomes relatively stiffer. Changes in volume-pressure relations are profitably considered only if referred to a reliable unit, such as a unit of lung volume or a percentage of total lung capacity. Considered on a percentage basis, compliance of the thorax decreases with age. How much of this change is contributed by changes in tissue properties, such as increasing calcification of ribs and connective tissue changes, and how much is a disproportionate growth of the chest wall relative to the lung remains unclear.

■ LUNG VOLUMES

Definition

The partition of commonly used lung volumes can be understood by studying Figure 4-11. The spirogram on the left represents the volume of air breathed in and out by a normal subject. The first portion of the tracing illustrates normal breathing and is called the tidal volume (V_T). The subject then makes a maximal inspiration followed by a maximum expiration: the volume of expired air is the vital capacity (VC). The volume of air that still remains in the lung after a maximal expiration is the residual volume (RV), whereas the volume of air remaining in the lung after a normal passive expiration is the FRC. The maximum amount of air that a subject can have in the lungs is called the total lung capacity (TLC). In healthy young subjects, TLC correlates best with the subject's sitting height.



■ **FIGURE 4-10.** Pressure-volume relations of lungs and thorax in an adult and an infant. The *dashed line* represents the characteristic of lungs and thorax together. Transpulmonary pressure at the resting portion (functional residual capacity) is less in the infant, and thoracic compliance is greater in the infant.

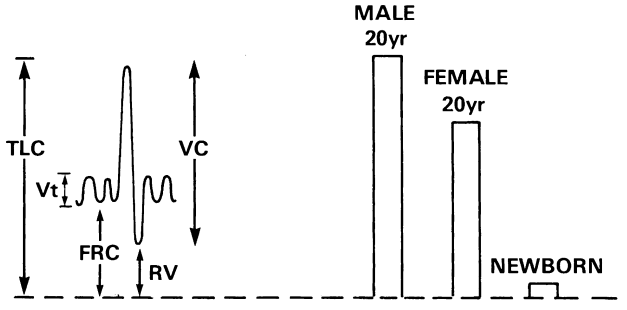
The volumes and capacities of the lungs are determined by many factors, including muscle strength, static-elastic characteristics of the chest wall and lungs, airway status, and patient age and cooperation. TLC is reached when the force generated by maximal voluntary contraction of the inspiratory muscles equals the inward recoil of the lung and chest wall. FRC occurs when the respiratory muscles are relaxed and no external forces are applied; it is therefore the volume at which the inward recoil of the lung is exactly balanced by the outward recoil of the chest wall (see Fig. 4-9).

In healthy children and young adults, end-expiratory lung volume is equivalent to FRC. This is not the case in infants, who breathe at a lung volume higher than FRC. This higher volume seems to be a sensible solution to the infants' problem of having an airway closing volume that exceeds FRC. An infant maintains the expiratory lung volume higher than FRC by a combination of postinspiratory diaphragmatic activity and laryngeal adduction.

The factors determining RV vary with age. In adolescents and young adults, RV occurs when the expiratory muscles cannot compress the chest wall further. In young children and older adults, RV is a function of the patency of small airways and the duration of expiratory effort.

Measurement

Tidal volume and VC can be determined by measuring the expired volume. The measurement of FRC and RV requires another approach. Because both volumes include the air in the lungs that the patient does not normally exhale, they must be measured indirectly. One method uses the principle of dilution of the unknown volume with a known concentration of a gas that is foreign to the lung and only sparingly absorbed, such as helium. The patient breathes from a container with a known volume and concentration of helium in oxygen-enriched air. After sufficient time has elapsed for the gas in the lung to mix and equilibrate with the gas in the container, the concentration of helium in the container is remeasured. Because initial volume × initial concentration of helium = final volume × final concentration of helium, the final volume, which includes gas in the lungs, can be calculated.



■ **FIGURE 4-11.** The lung volumes. The spirogram *(left)* demonstrates normal breathing followed by a maximal inspiratory effort and a maximal expiratory effort. FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity (6.0 L in an average male, 4.2 L in an average female, and 160 mL in an average 3-kg infant; see histograms on *right*); VC, vital capacity; V_T, tidal volume.

The helium dilution method will not measure gas behind closed airways ("trapped gas") or in regions of the lung that are poorly ventilated. There is, however, a method of measuring total gas volume within the thorax that depends on the change in volume that occurs with compression of the gas when breathing against an obstruction. Practically, this measurement requires the patient to be in a body plethysmograph and to pant against a closed shutter. The change in pressure can be measured in the mouthpiece; the change in volume can be recorded with a spirometer attached to the body plethysmograph: $V = P\Delta V/\Delta P$. This method has the advantage of being able to be repeated several times a minute. It has the disadvantage of including some abdominal gas in the measurement.

There have also been concerns about the validity of the plethysmographic technique in patients with obstructive lung disease. This issue has not yet been resolved because the technique has been reported to overestimate the lung volume in adults but underestimate the lung volume in infants with obstructive lung disease.

Interpretation

The major difficulty in detecting abnormalities in lung volumes is that the range of normal values is so large. For example, the mean TLC for a child 140 cm tall is 3.2 L; however, the statistical range of normal (mean ± 2 SD) is 1.9 to 4.3 L. This range of normal values, when expressed as percentage predicted, is even greater for younger children or smaller lung volumes (such as RV). Owing to this wide range of normality, care must be exercised in the interpretation of lung volumes. Measurement of lung volumes is of greatest benefit when repeated over several months to assess the progress of a chronic respiratory illness and the efficacy of treatment.

The VC is one of the most valuable measurements that can be made in a functional assessment, because it is highly reproducible and has a relatively narrow range of normal values. It can be decreased by a wide variety of disease processes, including muscle weakness, loss of lung tissue, obstruction of the airway, and decreased compliance of the chest wall. VC is therefore not a useful tool to discriminate between types of lesions. Its chief role is to assign a value to the degree of impairment and to document changes that occur with therapy or time. In order to decide whether obstructive or restrictive lung disease is present, it is useful to measure expiratory flow rates (see Chapters 9 and 10) and to observe the pattern of abnormalities in the other lung volumes. In obstructive lung disease (e.g., asthma), the smallest lung volumes are affected first: RV increases owing to abnormally high airway resistance at low lung volumes, and as the disease progresses, the FRC increases. Although the increase in FRC (hyperinflation) may rarely be due to loss of lung recoil, the overdistention is usually compensating for partial lower airway obstruction. When the lung volume is increased, intrathoracic airways enlarge, and widespread partial obstruction may be partially relieved by the assumption of a larger resting lung volume. Whereas the total lung capacity is only rarely affected in obstructive disease (such as asthma) in children (in contrast to emphysema in adults), TLC and VC are the first lung volumes to be affected in restrictive diseases of the chest wall (e.g., kyphoscoliosis) or lung (e.g., pulmonary fibrosis).

REGIONAL LUNG VOLUMES

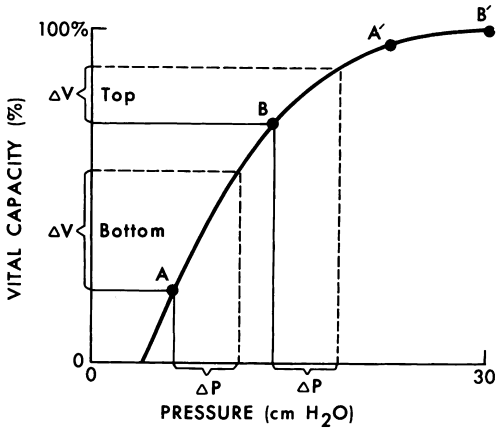
During normal breathing, different areas of the lung have different regional lung volumes; the upper airspaces are inflated more than the lower airspaces. Because static-elastic properties are fairly constant throughout the lung, these different regional lung volumes result from the gradient of pleural pressure that exists from the top to the bottom of the lung. Although gravitational forces are thought to be largely responsible, the mechanisms responsible for this pleural pressure gradient are incompletely understood. In the erect adult lung, the pleural pressure is −8 cm H_2O at the apex and only −2 cm H_2O at the base. The significance of this phenomenon is that when a subject breathes in, the lowermost lung units will receive the majority of the inspired air (Fig. 4-12). This is advantageous because the majority of pulmonary blood flow also goes to the base of the lung, and thus blood flow and ventilation patterns are more closely matched.

DYNAMIC (FLOW-RESISTIVE) PROPERTIES OF THE LUNG

Gas Flow within Airways

The respiratory system must perform work to move gas into and out of the lungs. Because air moves into the lungs during inspiration and out of the lungs during expiration, and because the velocity of airflow increases from small airways to large airways, energy must be expended to accelerate the gas molecules. The respiratory system's resistance to acceleration (inertance) is minimal during quiet breathing and will not be considered further. In contrast, frictional resistance to airflow accounts for one third of the work performed during quiet breathing. The magnitude of pressure loss due to friction is determined by the pattern of flow. Flow may be laminar (streamlined) or turbulent, and which pattern exists depends on the properties of the gas (viscosity, density), the velocity of airflow, and the radius of the airway. In general, there is laminar flow in the small peripheral airways and turbulent flow in the large central airways.

The laws governing the frictional resistance to flow of gases in tubes apply to pulmonary resistance. The equation for



■ **FIGURE 4-12.** Pressure-volume curve of a normal lung *(heavy solid line)*. At functional residual capacity, distending pressure is less at the bottom than at the top; accordingly, alveoli at the bottom *(A)* are smaller (i.e., lower percentage regional vital capacity) than those at the top *(B)*. When a given amount of distending pressure (ΔP) is applied to the lung, alveoli at the bottom increase their volume (ΔV) more than alveoli at the top, owing to the varying steepness of the pressure-volume curve. When fully expanded to total lung capacity (100% VC), alveoli at the bottom *(A′)* are nearly the same size as alveoli at the top *(B′)*, because both points lie on the flat portion of the curve. (From Murray JF: The Normal Lung. Philadelphia: WB Saunders, 1976.)

calculating the pressure gradient required to maintain a laminar flow of air through a tube is given by Poiseuille's law:

$$P = \dot{V}\left(\frac{8l\eta}{\pi r^4}\right)$$

where P is pressure, $\dot{V}$ is flow, l is length, r is radius of the tube, and η is the viscosity of the gas. The viscosity of air is 0.000181 poise at 20°C, or only 1% that of water. Because resistance = pressure/flow, it is clear that the most important determinant of resistance in small airways will be the radius of the tube, which is raised to the fourth power in the denominator of the equation.

The pressure required to maintain turbulent flow is influenced by airway diameter and gas density and is proportional to the square of the gas velocity. The effect of gas density on turbulent flow has both therapeutic implications. Children with viral laryngotracheobronchitis have marked narrowing of the subglottic area, which greatly increases the resistance to airflow. The pressure required to overcome this increased resistance in the large airways, and hence the work of breathing, can be decreased by administering a low-density gas mixture (70% helium, 30% oxygen).

Measurement of Resistance

Resistance (R) is calculated from the equation

$$R = \frac{\text{driving pressure}}{\text{airflow}}$$

The pressure is measured at the two ends of the system—in the case of the lung, at the mouth and at the alveoli—and the corresponding flow is recorded. Measurement of alveolar pressure presents the greatest problem. Several methods have been used to measure alveolar pressure. The most common method employs a body plethysmograph. The subject sits in the airtight box and breathes through a tube connected to a pneumotachometer, an apparatus that measures airflow. When a shutter occludes the tube and airflow ceases, the mouth pressure is assumed to be equal to the alveolar pressure. Airway resistance can then be calculated because airflow, alveolar pressure, and ambient pressure are known.

Total pulmonary resistance can be measured in infants and children by the forced oscillation technique. This measurement includes airway resistance plus the tissue viscous resistance of the lung and chest wall. Nasal resistance is also included in the measurement if the infant is breathing through the nose. Although there are theoretical objections to this technique, it has several advantages. It does not require a body plethysmograph, estimates of pleural pressure, or patient cooperation, and it can be done quickly enough to be used on ill patients. A sinusoidal pressure applied at the upper airway changes the airflow, and the ratio of pressure change to flow change is used to calculate resistance. When the forced oscillations are applied at the so-called resonant frequency of the lung (believed to be 3 to 5 Hz), it is assumed that the force required to overcome elastic resistance of the lung and the force required to overcome inertance are equal and opposite, so that all of the force is dissipated in overcoming flow resistance. This technique has demonstrated that infants with bronchiolitis have about a twofold increase in inspiratory pulmonary resistance and a threefold increase in expiratory resistance.

Several new techniques have been developed that are capable of measuring lung function in infants and young children. Each has its advantages, underlying assumptions, and limitations, and these techniques are discussed in detail in Chapter 9.

Sites of Airway Resistance

The contribution of the upper airway to total airway resistance is substantial. The average nasal resistance of infants by indirect measurements is 13 cm H_2O/L/sec, or nearly half of the total respiratory resistance, as is the case in adults. It is hardly surprising that any compromise of the dimensions of the nasal airways in an infant who is a preferential nose breather will result in retractions and labored breathing. Likewise, even mild edema of the trachea or larynx will impose a significant increase in airway resistance.

In the adult lung, about 80% of the resistance to airflow resides in airways greater than 2 mm in diameter. The vast number of small peripheral airways provides a large cross-sectional area for flow and therefore contributes less than 20% to the airway resistance. Thus, these airways may be the sites of disease that may severely impair ventilation of distal airspaces without appreciably altering the total airway resistance. In the infant lung, however, small peripheral airways may contribute as much as 50% of the total airway resistance, and this proportion does not decrease until about 5 years of age. Thus, the infant and young child are particularly severely affected by diseases that affect the small airways (e.g., bronchiolitis).

Factors Affecting Airway Resistance

Airway resistance is determined by the diameter of the airways, the velocity of airflow, and the physical properties of the gas breathed. The diameter is determined by the balance between the forces tending to narrow the airways and the forces tending to widen them. One of the forces tending to narrow the airways is exerted by the contraction of bronchial smooth muscle. The neural regulation of bronchial smooth muscle tone is mediated by efferent impulses through autonomic nerves. Sympathetic impulses relax the airways, and the parasympathetic impulses constrict them. Bronchi constrict reflexly from irritating inhalants such as sulfur dioxide and some dusts; by arterial hypoxemia and hypercapnia; by embolization of the vessels; by cold; and by some vasoactive mediators, such as acetylcholine, histamine, and bradykinin. They dilate in response to an increase in systemic blood pressure through baroreceptors in the carotid sinus and to sympathomimetic agents such as isoproterenol and epinephrine. The large airways are probably in tonic contraction in health, because in unanesthetized adults, atropine or isoproterenol will decrease airway resistance.

Airway resistance changes with lung volume, but not in a linear manner. Increasing the lung volume to above FRC only minimally decreases airway resistance. In contrast, as lung volume decreases from FRC, resistance rises dramatically and approaches infinity at RV. Although alterations in bronchomotor tone play a role, it is the decrease in lung elastic recoil as lung volume declines that is the predominant mechanism for the change in airway resistance. The recoil of the lung provides a tethering or "guy wire" effect on the airways that tends to increase their diameter. Children of different ages will have different airway resistances owing to the different sizes of their lungs. Therefore, the measurement of airway resistance or its reciprocal, airway conductance, is usually corrected by dividing the airway conductance by the simultaneously measured lung volume.

The resultant specific airway conductance is remarkably constant regardless of the subject's age or height.

Dynamic Airway Compression

During a forced expiration, both the pleural and the peribronchial pressures become positive and tend to narrow the airways; forces tending to keep airways open are the intraluminal pressure and the tethering action of the surrounding lung. During active expiration, however, the intraluminal pressure must decrease along the pathway of airflow from the alveoli to the mouth, where it becomes equal to atmospheric pressure. Therefore, at some point in the airway, intraluminal pressure must equal pleural pressure—the equal pressure point (EPP) (see Chapter 10 and Fig. 10-6). Downstream from the EPP, pleural pressure exceeds intraluminal pressure and thus is a force that tends to narrow the airways. Indeed, during periods of maximum expiratory flow, pleural pressure exceeds the critical closing pressure of the airways, which become narrowed to slits. Despite the cartilaginous support of the larger airways, the membranous portion of the wall of the trachea and large bronchi invaginates under pressure to occlude the airways. Maximum flow under this circumstance is therefore determined by the resistance of the airways located upstream from the EPP, and the driving pressure is the difference between the alveolar pressure and the pressure at the EPP. In disease states in which there is an increased airway resistance, the EPP moves toward the alveoli because of the greater intraluminal pressure drop. Thus, small airways are now compressed during forced expiration with severe flow limitation. With the measurement of pressure-flow and flow-volume curves during forced expiration, it is possible to calculate resistance upstream and downstream from the point of critical closure, or EPP. Increasing the lung volume increases the tethering action of the surrounding lung on the airways, and therefore close attention must be paid to the lung volume at which resistance measurements are made during these studies.

Work of Breathing

The work performed by the respiratory pump is defined by the volume changes of the lungs when the respiratory muscles generate a given pressure. The volume-pressure relationships of the respiratory system depend on properties of the lung and chest wall tissues or the ease with which the airways allow the passage of air. A substantial portion of the pressure generated by the respiratory muscles is applied to produce reversible rearrangements of the structure of the alveolar gas-liquid interface and the fibrous network of the lungs. Another large portion of the effort of the respiratory muscles is directed at producing rearrangements or interactions that are not reversible. The energy spent in such an effort is directly transformed into heat, which is then dissipated into the atmosphere or carried away by the circulating blood. The magnitudes of the work and the pressures derived from these processes generally bear a relationship to the rate of gas flow in and out of the lungs. In this regard, the respiratory system exhibits a resistive behavior for which the driving pressure determines the flow of air. Both the elastic and the resistive components of the work of breathing are usually increased in children with respiratory disease. Establishing a diagnosis and formulating a therapy in these patients is almost always simplified when the clinician distinguishes between conditions that affect primarily the elastic (restrictive respiratory disease) and resistive (obstructive respiratory disease) behaviors of the respiratory system.

DISTRIBUTION OF VENTILATION

The distribution of ventilation will be influenced by several factors of normal lungs. The pleural pressure gradient results in a greater amount of the tidal volume going to the dependent areas of the lung (see Fig. 4-12). In addition, the rate at which an area of the lung fills and empties is related to both airway resistance and compliance. A decrease in airway dimension increases the time required for air to reach the alveoli; a region of low compliance receives less ventilation per unit of time than an area with high compliance. The product of resistance × compliance (time constant) is approximately the same in health for all ventilatory pathways. The unit of this product is time. Note:

$$\text{Resistance} = \frac{\text{pressure}}{\text{flow}} = \frac{\text{cm } H_2O}{\text{L/sec}}$$

and

$$\text{Compliance} = \frac{\Delta\text{volume (L)}}{\Delta\text{pressure (cm } H_2O)}$$

The product, then, is a unit of time, analogous to the time constant in an electrical system, that represents the time taken to accomplish 63% of the volume change.

As mentioned previously, peripheral airways contribute little to overall airway resistance after the age of 5 years. However, in the presence of small airway disease, some areas of the lung have long time constants but those of others are normal. This is particularly evident as the frequency of respiration increases. With increasing frequency, air goes to those areas of the lung with short time constants. These areas then become relatively overdistended, and a greater transpulmonary pressure is required to inspire the same volume of air because alveoli in these relatively normal areas are reaching their elastic limit. Thus, a decreased dynamic compliance with increasing frequency of respiration has been used as a test of small airway disease and indeed may be the only mechanical abnormality detectable in the early stages of diseases such as emphysema and cystic fibrosis.

Airway closure occurs in dependent areas of the lung at low lung volumes. The lung volume above RV at which closure occurs is called the closing volume. In infants, very young children, and older adults, airway closure occurs at FRC and therefore is present during normal tidal breathing. This results in intermittent inadequate ventilation of the respective terminal lung units and leads to abnormal gas exchange, notably to a lower Pa_{O_2} seen in these age groups. It also explains why oxygenation usually can be improved by placing the patient so that the good lung is uppermost in the infant with unilateral lung disease (in young healthy adults the opposite is true).

PULMONARY CIRCULATION

PHYSIOLOGIC CLASSIFICATION OF PULMONARY VESSELS

The pulmonary circulation is the only vascular bed to receive the entire cardiac output. This unique characteristic enables the pulmonary vascular bed to perform a wide variety of homeostatic physiologic functions. It provides an enormously large (80 m^2) yet extremely thin film of blood for gas exchange, filters