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Peter J. Davis
Franklyn P. Cladis
Etsuro K. Motoyama

SMITH'S Anesthesia for Infants and Children

EIGHTH EDITION

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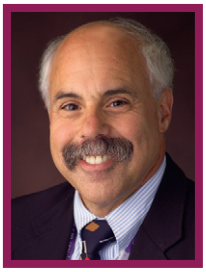
Anesthesia for Infants and Children

EIGHTH EDITION



Peter J. Davis, MD, FAAP
Professor
Department of Anesthesiology
Department of Pediatrics
University of Pittsburgh School of Medicine;
Anesthesiologist-in-Chief
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Franklyn P. Cladis, MD
Assistant Professor
Department of Anesthesiology
University of Pittsburgh School of Medicine
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Etsuro K. Motoyama, MD, FAAP
Professor Emeritus
Department of Anesthesiology
Department of Pediatrics (Pulmonology)
University of Pittsburgh School of Medicine;
Former Director, Pediatric Pulmonology Laboratory
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

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1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

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Acquisitions Editor: Natasha Andjelkovic
Developmental Editor: Julie Mirra
Publishing Services Manager: Anne Altepeter
Team Manager: Radhika Pallamparthy
Senior Project Manager: Cheryl A. Abbott
Project Manager: Antony Prince
Design Direction: Steven Stave

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Dr. Robert Moors Smith

The eighth edition of *Smith's Anesthesia for Infants and Children* is dedicated to Dr. Robert Moors Smith, who died on November 25, 2009, 2 weeks before he would have been 97. The eulogy published by the Harvard Medical School's Office of Communications began with this statement: "The Harvard Medical School flag is at half-mast today in memory of Robert M. Smith, MD, Clinical Professor of Anesthesia, former Chief of Anesthesiology at Children's Hospital Boston and pioneer in clinical anesthesiology in children." This was an extraordinary tribute from an institution that has produced literally hundreds of world leaders in medicine.

Dr. Smith was one of the most distinguished pioneers of modern anesthesia for children in the world. In the United States he was considered the "Father of Pediatric Anesthesiology." During his tenure at Children's Hospital Boston, Dr. Smith was a superb and compassionate clinician and educator who continually advanced practices in pediatric anesthesia and kept abreast with the fast progress of increasingly complex surgery on smaller and younger patients. He was an early advocate of compassionate patient safety—more than 30 years before the term even existed.

Along with Dr. Margo Deming of Philadelphia, Dr. Smith was an early supporter of endotracheal intubation with sterile and child-appropriate–sized tubes to prevent aspiration and postintubation croup. He also encouraged the wrapping of small children to prevent heat loss. In the early 1950s when the monitoring of infants and children consisted of visual observation of the patient and intermittent palpation of the patient's radial pulse, Dr. Smith pioneered a new approach of continuous physiological monitoring. By using a stethoscope taped on the chest wall over the trachea and heart, Dr. Smith could assess ongoing changes in heart and breath sounds. Furthermore, Dr. Smith, together with Ms. Betty Lank, his chief nurse anesthetist, developed a homemade latex infant blood pressure cuff (referred to as the *Smith cuff*) and advocated its routine use for patient safety when inhaled anesthetics consisted of diethylether and cyclopropane. These advancements were early steps in the development of elaborate physiological monitoring systems that are essential for safe anesthesia care today.

In 1959, Dr. Smith published the first comprehensive textbook for pediatric anesthesia, entitled *Anesthesia for Infants and Children*. It was well received among practitioners and trainees in pediatric anesthesia and soon became a classic, often referred to as the "Bible of Pediatric Anesthesia." For the ensuing 20 years until his retirement from Harvard in 1980, Dr. Smith revised and expanded the book through the fourth edition, as he kept abreast with the rapid progress in the practice and science of pediatric anesthesia and other pediatric surgical specialties. Shortly thereafter, Dr. Smith asked the current editors to assume the editorship. To continue his vision, the book was modified and expanded to a multi-authored volume and was renamed *Smith's Anesthesia for Infants and Children* in Dr. Smith's honor. The fifth through the seventh editions were published between 1990 and 2006. With this eighth edition, *Smith's Anesthesia for Infants and Children* has been in publication for more than half a century, making it the longest ongoing textbook of pediatric anesthesiology in the world. It has been a great honor and privilege for us to carry on Dr. Smith's legacy.

Contributors

Ann G. Bailey, MD
Professor, Anesthesiology and Pediatrics
University of North Carolina
Chapel Hill, North Carolina

David Barinholtz, MD
President and CEO, Mobile Anesthesiologists, LLC
Chicago, Illinois

Victor C. Baum, MD
Professor, Anesthesiology and Pediatrics
Executive Vice-Chair, Department of Anesthesiology
Director, Cardiac Anesthesia
University of Virginia
Charlottesville, Virginia

David S. Beebe, MD
Professor, Department of Anesthesiology
University of Minnesota
Minneapolis, Minnesota

Kumar G. Belani, MBBS, MS
Professor, Departments of Anesthesiology, Medicine, and Pediatrics
University of Minnesota
Minneapolis, Minnesota

Richard Berkowitz, MD
Chairman and Medical Director, Department of Anesthesiology and Pain Medicine
Community Hospital
Munster, Indiana;
Visiting Associate Professor, Department of Anesthesiology and Pediatrics
University of Illinois College of Medicine
Chicago, Illinois

Bruno Bissonnette, MD, FRCPC
Professor Emeritus of Anesthesia
University of Toronto
Toronto, Ontario;
Founder and President, Children of the World Anesthesia Foundation
Rimouski, Quebec

Adrian Bosenberg, MB ChB, FFA(SA)
Professor, University of Washington School of Medicine;
Director, Regional Anesthesia Services
Seattle Children's Hospital
Seattle, Washington

Barbara W. Brandom, MD
Professor, Department of Anesthesiology
University of Pittsburgh School of Medicine;
Attending Physician, Department of Anesthesiology
Children's Hospital of Pittsburgh of UPMC;
Director, North American Malignant Hyperthermia Registry of MHAUS
Pittsburgh, Pennsylvania

Claire Brett, MD
Professor, Clinical Anesthesia and Pediatrics
Department of Anesthesiology and Perioperative Care
University of California, San Francisco
San Francisco, California

Robert B. Bryskin, MD
Regional Anesthesia Coordinator
Nemours Children's Hospitals;
Assistant Professor, Anesthesiology
College of Medicine, Mayo Clinic
Jacksonville, Florida

Patrick Callahan, MD
Assistant Professor of Anesthesiology
University of Pittsburgh School of Medicine
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Franklyn P. Cladis, MD
Assistant Professor
Department of Anesthesiology
University of Pittsburgh School of Medicine
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

David E. Cohen, MD
Associate Professor, Anesthesiology and Critical Care and Pediatrics
University of Pennsylvania;
Perioperative Medical Director, The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Ira Todd Cohen, MD, MEd
Professor, Anesthesiology and Pediatrics
Director of Education, Department of Anesthesiology and Pain Medicine
Children's National Medical Center
Washington, DC

Andrew Davidson, MBBS, MD
Associate Professor, University of Melbourne;
Staff Anaesthetist, Royal Children's Hospital;
Head, Clinical Research Development
Murdoch Children's Research Institute
Melbourne, Victoria, Australia

Jessica Davis, BA, JD, LLM
Adjunct Professor, Widener University School of Law
Wilmington, Delaware

Peter J. Davis, MD, FAAP
Professor
Department of Anesthesiology
Department of Pediatrics
University of Pittsburgh School of Medicine;
Anesthesiologist-in-Chief
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Duncan de Souza, MD, FRCP(C)
Assistant Professor, Anesthesiology and Pediatrics
Department of Anesthesiology
University of Virginia
Charlottesville, Virginia

Nina Deutsch, MD
Assistant Professor, Anesthesiology and Pediatrics
Children's National Medical Center
Washington, DC

James A. DiNardo, MD, FAAP
Associate Professor of Anesthesia
Harvard Medical School;
Senior Associate in Cardiac Anesthesia
Program Director, Pediatric Cardiac Anesthesia Fellowship
Children's Hospital Boston
Boston, Massachusetts

Peter Ehrlich, MD, Msc, RCPS(C), FACS
Associate Professor of Surgery, Section of Pediatric Surgery
University of Michigan Medical School;
Medical Director, Pediatric Trauma
University of Michigan CS Mott Children's Hospital
Ann Arbor, Michigan

Demetrius Ellis, MD
Professor, Nephrology and Pediatrics
University of Pittsburgh School of Medicine;
Director, Pediatric Nephrology
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Jeffrey M. Feldman, MD, MSE
Division Chief, General Anesthesia
Children's Hospital of Philadelphia;
Associate Professor, Clinical Anesthesia
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Kathryn Felmet, MD
Assistant Professor, Critical Care Medicine and Pediatrics
University of Pittsburgh School of Medicine
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

John E. Fiadjoe, MD
Assistant Professor, Anesthesia
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Jonathan D. Finder, MD
Professor of Pediatrics
University of Pittsburgh School of Medicine
Clinical Director, Pulmonary Medicine
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Randall P. Flick, MD, MPH, FAAP
Associate Professor of Anesthesiology
Chair, Division of Pediatric Anesthesiology
Medical Director, Eugenio Litta Children's Hospital
Mayo Clinic
Rochester, Minnesota

Michelle Fortier, PhD
Licensed Psychologist
Center for the Advancement of Pediatric Health
University of California Irvine School of Medicine;
Department of Anesthesiology and Perioperative Care
Center for Pain Management
Orange, California

Salvatore R. Goodwin, MD
Associate Professor, Anesthesiology
Mayo Medical School
Rochester, Minnesota;
Chairman, Department of Anesthesia
Nemours Children's Clinic
Jacksonville, Florida

George A. Gregory, MD
Professor Emeritus of Anesthesia and Pediatrics
University of California, San Francisco
San Francisco, California

Lorelei Grunwaldt, MD
Assistant Professor of Surgery
University of Pittsburgh School of Medicine
Division of Pediatric Plastic Surgery
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Dawit T. Haile, MD
Instructor of Anesthesiology
Mayo Clinic
Rochester, Minnesota

Steven Hall, MD
Arthur C. King Professor of Pediatric Anesthesia
Feinberg School of Medicine
Northwestern University;
Anesthesiologist-in-Chief
Children's Memorial Hospital
Chicago, Illinois

Gregory Hammer, MD
Professor, Anesthesia and Pediatrics
Stanford University School of Medicine;
Associate Director, Pediatric ICU
Director, Pediatric Anesthesia Research
Lucile Packard Children's Hospital at Stanford
Stanford, California

Michael W. Hauser, MD
Staff Anesthesiologist
Cleveland Clinic
Cleveland, Ohio

Eugenie S. Heitmiller, MD
Associate Professor, Anesthesiology and Pediatrics
Department of Anesthesiology and Critical Care Medicine
The Johns Hopkins University School of Medicine;
Vice Chairman for Clinical Affairs
Department of Anesthesiology and Critical Care Medicine
The Johns Hopkins Hospital
Baltimore, Maryland

Andrew Herlich, DMD, MD
Professor of Anesthesia, Department of Anesthesiology
University of Pittsburgh School of Medicine;
Chief of Anesthesia, UPMC Mercy Hospital
Pittsburgh, Pennsylvania

Robert S. Holzman, MD, FAAP
Associate Professor of Anesthesia
Harvard Medical School;
Senior Associate, Perioperative Anesthesia
Children's Hospital Boston
Boston, Massachusetts

Elizabeth A. Hunt, MD, MPH, PhD
Assistant Professor, Department of Anesthesiology and Critical Care Medicine
The Johns Hopkins University School of Medicine;
Drs. David S. and Marilyn M. Zamierowski Director
The Johns Hopkins Medicine Simulation Center
Baltimore, Maryland

Nathalia Jimenez, MD, MPH
Assistant Professor, Department of Anesthesiology and Pain Medicine
University of Washington School of Medicine
Seattle Children's Hospital
Seattle, Washington

Lori T. Justice, MD, FAAP
Clinical Staff Pediatric Anesthesiologist
Children's Anesthesiologists, PC
East Tennessee Children's Hospital
Knoxville, Tennessee

Zeev N. Kain, MD, MBA
Professor, Anesthesiology and Pediatrics and Psychiatry and Human Behavior
Chair, Department of Anesthesiology and Perioperative Care
Associate Dean of Clinical Operations, School of Medicine
University of California, Irvine
Orange, California

Evan Kharasch, MD, PhD
Vice Chancellor for Research
Russell D. and Mary B. Shelden Professor of Anesthesiology
Director, Division of Clinical and Translational Research
Department of Anesthesiology;
Professor of Biochemistry and Molecular Biophysics
Washington University in St. Louis
St. Louis, Missouri

Sabine Kost-Byerly, MD, FAAP
Director, Pediatric Pain Management
Department of Anesthesiology and Critical Care Medicine
The Johns Hopkins Hospital;
Associate Professor of Anesthesiology
The Johns Hopkins University School of Medicine
Baltimore, Maryland

Elliot J. Krane, MD
Professor, Department of Anesthesia and Pediatrics
Stanford University School of Medicine
Stanford, California;
Director of Pain Management
Lucile Packard Children's Hospital at Stanford
Palo Alto, California

Barry D. Kussman, MBBCh, FFA (SA)
Assistant Professor of Anesthesia
Harvard Medical School;
Senior Associate in Cardiac Anesthesia
Children's Hospital Boston
Boston, Massachusetts

Ira S. Landsman, MD
Associate Professor, Department of Anesthesiology and Pediatrics;
Chief, Division of Pediatric Anesthesiology
Vanderbilt University Medical Center
Nashville, Tennessee

Ronald S. Litman, DO
Attending Anesthesiologist
The Children's Hospital of Philadelphia;
Professor, Anesthesiology and Pediatrics
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Joseph Losee, MD, FACS, FAAP
Professor of Surgery and Pediatrics
University of Pittsburgh School of Medicine
Chief, Division Pediatric Plastic Surgery
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Igor Luginbuehl, MD
Associate Professor of Anesthesia
Department of Anesthesia and Pain Medicine
The Hospital for Sick Children
Toronto, Ontario

Anne M. Lynn, MD
Professor, Department of Anesthesiology
and Pain Medicine
Adjunct Professor, Pediatrics
University of Washington School of Medicine
Seattle Children's Hospital
Seattle, Washington

Thomas J. Mancuso, MD
Associate Professor of Anesthesia
Harvard Medical School;
Senior Associate in Anesthesia
Children's Hospital Boston
Boston, Massachusetts

Brian P. Martin, DMD
Clinical Assistant Professor
University of Pittsburgh School of Dental
Medicine;
Chief, Division of Pediatric Dentistry
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Keira Mason, MD
Associate Professor of Anesthesia
Harvard Medical School;
Director, Department of Radiology, Anesthesia,
and Sedation
Children's Hospital Boston
Boston, Massachusetts

William J. Mauermann, MD
Assistant Professor of Anesthesia
Mayo Clinic
Rochester, Minnesota

Lynne G. Maxwell, MD
Associate Professor of Anesthesiology and Critical Care
University of Pennsylvania
Senior Anesthesiologist
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

George M. McDaniel, MD, MS
Assistant Professor of Pediatrics and Internal
Medicine
Director, Pediatric Electrophysiology
University of Virginia
Charlottesville, Virginia

Francis X. McGowan, Jr., MD
Professor of Anesthesia
Harvard Medical School;
Chief, Division of Cardiac Anesthesia
Director, Anesthesia and Critical Care
Medicine
Research Laboratory
Children's Hospital Boston
Boston, Massachusetts

Constance L. Monitto, MD
Assistant Professor, Anesthesiology and Critical
Care Medicine
The Johns Hopkins University School
of Medicine
Baltimore, Maryland

Philip G. Morgan, MD
Professor, Department of Anesthesiology
University of Washington;
Seattle Children's Research Institute
Seattle, Washington

Etsuro K. Motoyama, MD, FAAP
Professor Emeritus
Department of Anesthesiology
Department of Pediatrics (Pulmonology)
University of Pittsburgh School of Medicine;
Former Director, Pediatric Pulmonology Laboratory
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Julie Niezgoda, MD
Pediatric Anesthesiology
Children's Hospital Cleveland Clinic
Cleveland Clinic
Cleveland, Ohio

David M. Polaner, MD, FAAP
Professor of Anesthesiology and Pediatrics
University of Colorado School of Medicine;
Attending Pediatric Anesthesiologist
Chief, Acute Pain Service
Anesthesia Informatics
The Children's Hospital, Denver
Aurora, Colorado

Paul Reynolds, MD
Uma and Sujit Pandit Professor and Chief of Pediatric
Anesthesiology
Department of Anesthesiology
University of Michigan
Ann Arbor, Michigan

Mark A. Rockoff, MD
Professor of Anesthesia
Harvard Medical School;
Vice-Chairman, Department of Anesthesiology, Perioperative and Pain Medicine
Children's Hospital Boston
Boston, Massachusetts

Thomas Romanelli, MD, FAAP
Clinical Instructor, Harvard Medical School;
Consultant Anesthesiologist
Shriners Burns Hospital Boston;
Assistant in Anesthesia
Massachusetts General Hospital
Boston, Massachusetts

Allison Kinder Ross, MD
Associate Professor and Chief, Division of Pediatric Anesthesia
Duke University Medical Center
Durham, North Carolina

Joseph A. Scattoloni, MD
Clinical Lecturer, Department of Anesthesia
Section of Pediatric Anesthesia
University of Michigan Health System
Ann Arbor, Michigan

Jamie McElrath Schwartz, MD
Assistant Professor, Departments of Anesthesiology and Critical Care Medicine and Pediatrics
The Johns Hopkins University School of Medicine
Baltimore, Maryland

Robert J. Sclabassi, MD, PhD, DABNM, FASNM
Attending Neurophysiologist
Chief, Intraoperative Monitoring Service
West Penn Alleghany Health System
Pittsburgh, Pennsylvania

Victor L. Scott, II, BSc, MD
Professor of Anesthesiology, Department of Anesthesiology
University of Pittsburgh School of Medicine
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Donald H. Shaffner, MD
Associate Professor, Department of Anesthesiology
Critical Care Medicine and Pediatrics
The Johns Hopkins University School of Medicine
Baltimore, Maryland

Avinash C. Shukla, MBBS, FRCA
Associate in Cardiac Anesthesia
Children's Hospital Boston
Boston, Massachusetts

[†]Robert M. Smith, MD
Clinical Professor Emeritus of Anesthesia
Harvard Medical School and Children's Hospital Boston
Boston, Massachusetts

[†]Deceased.

Kyle Soltys, MD
Assistant Professor of Surgery
University of Pittsburgh School of Medicine
Thomas E. Starzl Transplant Institute
Hillman Center For Pediatric Transplantation
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Sulpicio G. Soriano, MD
Children's Hospital Boston Endowed Chair in Pediatric Neuroanesthesia
Associate Professor of Anesthesia
Harvard Medical School;
Senior Associate, Department of Anesthesiology, Perioperative and Pain Medicine
Children's Hospital Boston
Boston, Massachusetts

Brian P. Struyk, MD
Assistant Professor, Clinical Anesthesiology and Critical Care
University of Pennsylvania School of Medicine;
Director, Radiology Anesthesia
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Kevin J. Sullivan, MD
Assistant Professor of Anesthesiology
Rochester, Minnesota;
Clinical Associate Professor of Pediatrics
University of Florida Health Science Center
Jacksonville, Florida;
Staff Pediatric Anesthesiologist, Critical Care Physician, and Medical Director
Pediatric Intensive Care Unit
Wolfson Children's Hospital
Jacksonville, Florida

Jennifer Thomas, MBChB, FFA (SA), BSc (Ed)
Associate Professor, Department of Pediatric Anaesthesia
Red Cross War Memorial Children's Hospital
University of Cape Town
Cape Town, Western Cape, South Africa

Stevan P. Tofovic, MD, PhD, FAHA, FASN
Assistant Professor of Medicine
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

Kha Tran, MD
Assistant Professor of Anesthesia and Critical Care Medicine
University of Pennsylvania School of Medicine;
Attending Anesthesiologist and Clinical Director, Fetal Anesthesia Team
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Donald C. Tyler, MD, MBA
Associate Professor of Anesthesiology and Critical Care
University of Pennsylvania
Department of Anesthesiology and Critical Care Medicine
The Hospital of the University of Pennsylvania and Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Robert D. Valley, MD
Professor of Anesthesiology and Pediatrics
University of North Carolina School of Medicine
Chapel Hill, North Carolina

Monica S. Vavilala, MD
Associate Professor, Department of Anesthesiology and Pain Medicine and Pediatrics
Adjunct Associate Professor, Neurological Surgery and Radiology
University of Washington;
Associate Director, Harborview Injury Prevention and Research Center
Seattle, Washington

Lisa Vecchione, DMD, MDS
Director, Orthodontic Services
Cleft-Craniofacial Center
Children's Hospital of Pittsburgh of UPMC;
Assistant Clinical Professor of Surgery
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

Kerri M. Wahl, MD, FRCP(C)
Associate Professor, Department of Anesthesiology
Duke University Medical Center
Durham, North Carolina

Jay A. Werkhaven, MD
Associate Professor and Director, Pediatric Otolaryngology
Vanderbilt Bill Wilkerson Center for Otolaryngology and Communication Sciences
Vanderbilt University
Nashville, Tennessee

Susan Woelfel, MD
Associate Professor of Anesthesiology
University of Pittsburgh School of Medicine
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Myron Yaster, MD
Richard J. Traystman Professor
Departments of Anesthesiology, Critical Care Medicine, and Pediatrics
The Johns Hopkins University School of Medicine
Baltimore, Maryland

Aaron L. Zuckerberg, MD
Director, Pediatric Anesthesia and Critical Care Medicine
Director, Children's Diagnostic Center Department of Pediatrics and Anesthesia
Sinai Hospital;
Assistant Professor, Department of Pediatrics
University of Maryland Medical School;
Director of Pediatric Anesthesia, Department of Anesthesia, NAPA/MD
Baltimore, Maryland

Contributors to the Supplemental Material

Cuneyt M. Alper, MD
Professor of Otolaryngology
University of Pittsburgh School of Medicine
Division of Pediatric Otolaryngology
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Lawrence M. Borland, MD
Associate Professor
Departments of Anesthesiology and Pediatrics
University of Pittsburgh School of Medicine
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Robert B. Bryskin, MD
Regional Anesthesia Coordinator
Nemours Children's Hospitals;
Assistant Professor, Anesthesiology
College of Medicine, Mayo Clinic
Jacksonville, Florida

James G. Cain, MD
Visiting Associate Professor
Department of Anesthesiology
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

Franklyn P. Cladis, MD
Assistant Professor
Department of Anesthesiology
University of Pittsburgh School of Medicine
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Peter J. Davis, MD, FAAP
Professor
Department of Anesthesiology
Department of Pediatrics
University of Pittsburgh School of Medicine;
Anesthesiologist-in-Chief
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

William A. Devine
Curator of the Frank E. Sherman, MD, and Cora C. Lenox, MD, Heart Museum
Department of Pathology
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Joseph E. Dohar, MD, MS, FAAP, FACS
Professor of Otolaryngology
University of Pittsburgh School of Medicine;
Clinical Director, Pediatric Voice, Resonance, and Swallowing Center
Department of Otolaryngology
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Christopher M. Grande, MD, MPH
Anesthesiologist and Intensivist
Executive Director, International Trauma Anesthesia and Critical Care Society (ITACCS)
Baltimore, Maryland

Gregory Hammer, MD
Professor, Departments of Anesthesia and Pediatrics
Stanford University School of Medicine;
Associate Director, Pediatric ICU
Director, Pediatric Anesthesia Research
Lucile Packard Children's Hospital at Stanford
Stanford, California

Timothy D. Kane, MD, FACS
Associate Professor of Surgery and Pediatrics
George Washington University School of Medicine
Children's National Medical Center and Sheikh Zayed Institute for Pediatric Surgical Innovation
Washington, DC

Lizabeth M. Lanford, MD
Clinical Assistant Professor of Pediatrics
University of Pittsburgh School of Medicine
Division of Pediatric Cardiology
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

George V. Mazariegos, MD
Professor of Surgery and Critical Care
University of Pittsburgh School of Medicine;
Chief, Pediatric Transplantation
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Etsuro K. Motoyama, MD, FAAP
Professor Emeritus
Department of Anesthesiology
Department of Pediatrics (Pulmonology)
University of Pittsburgh School of Medicine;
Former Director, Pediatric Pulmonology Laboratory
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Douglas A. Potoka, MD
Assistant Professor of Surgery
University of Pittsburgh School of Medicine
Department of Pediatric General and Thoracic Surgery
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Paul Reynolds, MD
Uma and Sujit Pandit Professor and Chief of Pediatric Anesthesiology
Department of Anesthesiology
University of Michigan
Ann Arbor, Michigan

Allison Kinder Ross, MD
Associate Professor and Chief
Division of Pediatric Anesthesia
Duke University Medical Center
Durham, North Carolina

Kenneth P. Rothfield, MD
Chairman, Department of Anesthesiology
Saint Agnes Hospital
Baltimore, Maryland

Victor L. Scott, II, BSc, MD
Professor of Anesthesiology
Department of Anesthesiology
University of Pittsburgh School of Medicine
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Robert F. Yellon, MD, FACS
Professor, Department of Otolaryngology
University of Pittsburgh School of Medicine;
Director of Clinical Services
Department of Pediatric Otolaryngology
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Foreword to the Eighth Edition

Dr. Robert Moors Smith, a distinguished pioneer of modern pediatric anesthesia who was known as the "Father of Pediatric Anesthesia" in the United States, passed away on November 25, 2009, 2 weeks before he would have turned 97. In 1959, Dr. Smith wrote the first comprehensive textbook, *Anesthesia for Infants and Children,* specifically dedicated to the anesthetic management and care of children when pediatric anesthesia was in its infancy and the essentials of pediatric anesthesia practice were barely taking form.

During the following 2 decades as pediatric anesthesia expanded along with the rapid development and expansion of pediatric surgery, Dr. Smith published three additional revised and updated editions with few contributors. The book remained popular as the primary reference source of pediatric anesthesia practice and was often referred to as the "Bible" for practicing pediatric anesthesiologists.

After the fourth edition was published in 1980 and before his retirement from Children's Hospital Boston and Harvard Medical School, Dr. Smith transferred the honor and responsibility of continuing the legacy of his textbook to me, a former fellow and associate in the 1960s and one of the few contributors to the later editions.

From the 1980s and onward, we witnessed continual, if not exponential, expansions in pediatric anesthesia and related fields, with the expansion of pediatric surgical subspecialties and techniques, including the development of neonatal and pediatric intensive care units and intensive care medicine; improvements in anesthesia-related equipment, monitors, and newer anesthetic and adjuvant drugs; establishment of clinical practice standards; expansions in postgraduate anesthesiology training programs; and the development of clinical and basic research activities directly or indirectly related to anesthesiology, physiology, pharmacology, and cell and molecular biology. It became obvious that a single-author textbook in our subspecialty was no longer feasible or desirable.

I was extremely fortunate to have Dr. Peter J. Davis join me to face the new challenge. Our cordial and productive collaboration has lasted for more than 2 decades and still continues today. Peter and I changed the format of the book and expanded it to a multi-author textbook. We published the fifth edition in 1990 with the modified title *Smith's Anesthesia for Infants and Children* to honor Dr. Smith's legacy (against Dr. Smith's initial protest). In subsequent editions in 1996 (sixth edition) and 2006 (seventh edition), we added new chapters authored by experts in specific fields to keep up with the development and expansion of science and practice of pediatric anesthesia, including critical care medicine, psychology, regional anesthesia, pain medicine, and bariatric surgery.

Anesthesia for Infants and Children has surpassed half a century of continual publication since the first edition in 1959, and I have been extremely fortunate to have been closely associated with Bob Smith professionally as well as personally since my fellowship days in Boston in the 1960s. (Bob was particularly pleased to note the half-century mark of his publication when I visited him for the last time in the early summer of 2009 in his lifelong hometown of Winchester, Massachusetts.) With the passing of a giant in the field, it is also the time to pass the torch to Peter Davis as the principal editor, with Dr. Franklyn Cladis as a new member, for the eighth edition, which is dedicated to the memory of Dr. Robert Moors Smith and his glorious life as a family man, compassionate pediatric physician, and a kind mentor to former trainees.

Etsuro K. Motoyama, MD, FAAP

Preface

Dr. Robert Moors Smith's legacy is as a pioneer and a great educator in pediatric anesthesia. Long before the terminology became fashionable—before it even existed—Dr. Smith advocated patient monitoring and safety. In the 1950s, when pediatric anesthesia was still in its infancy, he made the use of the precordial stethoscope and the pediatric blood pressure cuff (Smith cuff) a standard of care. In 1959, he wrote a major comprehensive anesthesia textbook, *Anesthesia for Infants and Children,* which was specifically dedicated to the anesthetic management and care of children.

The first four editions of this book were written almost entirely by Dr. Smith himself. The scope of Dr. Smith's scholarship was reflected in the breadth of his firsthand clinical experience, his keen sense of observation, and his ability to apply scientific and technical developments in medicine and anesthesia to the field of pediatric anesthesia. In 1988, Dr. Smith became the first pediatric anesthesiologist to receive the Distinguished Service Award from the American Society of Anesthesiologists.

In 1980, with Dr. Smith's retirement from the Harvard Medical School faculty and the anesthesia directorship of Children's Hospital Boston, the task of updating this classic textbook was bestowed upon Drs. Motoyama and Davis. The fifth edition, published in 1990, was multi-authored and was reorganized to include new subjects of importance in the ever-expanding field of anesthesiology and pediatric anesthesiology in particular. In the fifth edition, the editors tried to maintain Dr. Smith's compassion, philosophy, and emphasis on the personal approach to patients. To honor his pioneering work and leadership (and against Dr. Smith's initial strong resistance), the title of the fifth edition of the textbook was modified to read *Smith's Anesthesia for Infants and Children.*

In 1996, the sixth edition of the textbook was published. New developments with inhaled anesthetic agents (sevoflurane and desflurane), intravenous agents (propofol), neuromuscular-blocking agents, and anesthetic adjuncts, coupled with changes in the approach to pediatric pain management and airway management, were highlights.

In 2006, the seventh edition further expanded those areas of development. The roles of airway management, regional anesthesia, new local anesthetic agents, and innovative regional anesthetic techniques had been further developed. Newer intravenous anesthetic agents and adjuncts were also included in this edition while maintaining Dr. Smith's principles regarding patient safety and compassion.

The eighth edition has been prepared with the same considerations as the previous seven editions: to give anesthesia care providers comprehensive coverage of the physiology, pharmacology, and clinical anesthetic management of infants and children of all ages. This edition remains organized into four sections. Part I, Basic Principles, has been updated with major revisions to the chapters Respiratory Physiology in Infants and Children, Cardiovascular Physiology, Regulation of Fluids and Electrolytes, Thermoregulation: Physiology and Perioperative Disturbances, and Pharmacology of Pediatric Anesthesia. A chapter on Behavioral Development has been added to this section to help the clinician to better understand the normal behavioral responses of children. Part II, General Approach to Pediatric Anesthesia, has had a number of changes in the authorship of the chapters. New chapters on Pain Managemant, Blood Conservation, Airway Management, and Regional Anesthesia have been added. In addition, real-time use of ultrasound has been incorporated into the website to further enhance the techniques of regional anesthesia. All other chapters in this section have been updated by the same group of contributors as in the seventh edition. Part III, Clinical Management of Specialized Surgical Problems, contains new material. In response to the increasing number of neonatal and fetal surgeries, a new chapter on Neonatology for Anesthesiologists has been added. This is a chapter designed to explore the physiology, development, and care of high-risk neonates. This chapter complements the chapters Anesthesia for Fetal Surgery and Anesthesia for General Surgery in the Neonate. In addition to Neonatology for Anesthesiologists, a chapter on Anesthesia for Conjoined Twins has been added. The chapters on congenital heart disease have been reorganized and written by new contributors. Other chapters with new contributors include Anesthesia for Plastic Surgery, Anesthesia for Neurosurgery, Anesthesia for Fetal Surgery, and Anesthesia for Burn Injuries. The remaining chapters in this section have been updated by the same group of contributors. Part IV, Associated Problems in Pediatric Anesthesia, contains updated and revised chapters on Cardiopulmonary Resuscitation, Medicolegal and Ethical Aspects, Malignant Hyperthermia, and Systemic Disorders. A new chapter on Critical Care Medicine has been added. Of note, the chapter History of Pediatric Anesthesia has been updated by Dr. Mark A. Rockoff, who had direct consultation with Dr. Robert M. Smith before Dr. Smith's death. The appendixes,

which can be found online at www.expertconsult.com, include an updated list of drugs and their dosages, normal growth curves, normal values for pulmonary function tests in children, and an expanded list of common and uncommon syndromes of clinical importance for pediatric anesthesiologists.

In keeping with the advancement in technology, this edition is now in color and the text material is further supplemented by a website. Videos of airway techniques, single-lung isolation, regional anesthesia, the use of ultrasound, and anatomic disections of congenital heart lesions are accessible with just a click of the mouse. In addition, supplemental materials on organ transplantation, airway lesions, and pediatric syndromes are available.

In summary, considerable developments and progress in the practice of pediatric anesthesia over the past decade are reflected in this new edition. The emphasis on the safety and well-being of our young patients during the perianesthetic period remains unchanged.

Peter J. Davis, MD, FAAP
Franklyn P. Cladis, MD
Etsuro K. Motoyama, MD, FAAP

Acknowledgments

The project of revising a classic medical textbook presents many opportunities and challenges. The chance to review the many new developments that have emerged in pediatric anesthesia since the publication of the last edition of *Smith's Anesthesia for Infants and Children* in 2006 and to evaluate their effects on clinical practice has indeed been exciting. As always, we are deeply indebted to the extraordinary work done and commitment made by Dr. Robert M. Smith. Beginning shortly after World War II, Dr. Smith pioneered pediatric anesthesia in the United States. Between 1959 and 1980, he published the first four editions of his book, *Anesthesia for Infants and Children.* His work made this textbook a classic, establishing a quality and record of longevity. The first through fourth editions were written almost exclusively by Dr. Smith, except for the chapter on respiratory physiology by E.K. Motoyama. Since the late 1980s when Dr. Smith passed the book to Drs. Motoyama and Davis, the subsequent fifth, sixth, and seventh editions have utilized the talents and expertise of many renowned pediatric anesthesiologists throughout North America. The seventh edition had been expanded by the addition of new chapters, new contributors, and an enclosed DVD. The eighth edition brings change to the book in both content and presentation. New chapters and new contributors have further advanced our knowledge base. The presentation of the material has been enhanced by the use of color and by providing access to a website to further supplement the book's written text material. In addition, the editorial components of the book have been changed and expanded. Franklyn Cladis has joined the book's lineage of editors.

Our ability to maintain this book's standard of excellence is not just a reflection of the many gifted contributors but is also a result of the level of support that we have received at work and at home. We wish to thank the staff members of the Department of Anesthesiology at Children's Hospital of Pittsburgh of UPMC and the University of Pittsburgh Medical Center for their support and tolerance.

Our special thanks go to Shannon Barnes, editorial assistant, as well as Susan Danfelt and Patty Klein, administrative assistants, of the Department of Anesthesiology, Children's Hospital of Pittsburgh of UPMC, for their many hours of diligent work on the book. We are also appreciative of Dr. Basil Zitelli, Professor of Pediatrics, University of Pittsburgh at Children's Hospital of Pittsburgh of UPMC, for his generosity in allowing us to use many of the photographs published in his own book, *Atlas of Pediatric Physical Diagnosis*.

Our special thanks also go to Elsevier's Natasha Andjelkovic, acquisitions editor; Julie Mirra, developmental editor; and Cheryl Abbott, senior project manager, for their editorial assistance.

Finally, as with the previous two editions, we are deeply indebted to our family members Katie, Evan, Julie, and Zara Davis; Yoko, Eugene, and Ray Motoyama; and Joseph Losee and Hudson Cladis Losee for remaining loyal, for being understanding, and for providing moral support throughout the lengthy and, at times, seemingly endless project.

Peter J. Davis, MD, FAAP
Franklyn P. Cladis, MD
Etsuro K. Motoyama, MD, FAAP

CHAPTER

1 Special Characteristics of Pediatric Anesthesia

Peter J. Davis, Etsuro K. Motoyama, and Franklyn P. Cladis

CONTENTS

In the past few decades, new scientific knowledge of physiology and pharmacology in developing humans, as well as technologic advancements in equipment and monitoring, has markedly changed the practice of pediatric anesthesia. In addition, further emphasis on patient safety (e.g., correct side-site surgery, correct patient identification, correct procedure, appropriate prophylactic antibiotics) coupled with advances in minimally invasive pediatric surgery, have created a need for better pharmacologic approaches to infants and children, as well as improved skills in pediatric anesthetic management.

As a result of the advancements and emphasis on pediatric subspecialty training and practice, the American Board of Anesthesiology has now come to recognize the subspecialty of pediatric anesthesiology in its certification process.

PERIOPERATIVE MONITORING

In the 1940s and 1950s, the techniques of pediatric anesthesia, as well as the skills of those using and teaching them, evolved more as an art than as a science, as [†]Dr. Robert Smith vividly and eloquently recollects through his firsthand experiences in his chapter on the history of pediatric anesthesia (see Chapter 41, History of Pediatric Anesthesia, as updated by Mark Rockoff). The anesthetic agents and methods available were limited, as was the scientific knowledge of developmental differences in organ-system function and anesthetic effect in infants and children. Monitoring pediatric patients was limited to inspection of chest movement and occasional palpation of the pulse until the late 1940s, when Smith introduced the first physiologic monitoring to pediatric anesthesia by using the precordial stethoscope for continuous auscultation of heartbeat and breath sounds (Smith, 1953; 1968). Until the mid-1960s, many anesthesiologists monitored only the heart rate in infants and small children during anesthesia and surgery. Electrocardiographic and blood-pressure measurements were either too difficult or too extravagant and were thought to provide little or no useful information. Measurements of central venous pressure were thought to be inaccurate and too invasive even in major surgical procedures. The insertion of an indwelling urinary (Foley) catheter in infants was considered invasive and was resisted by surgeons.

Smith also added an additional physiologic monitoring: soft, latex blood-pressure cuffs suitable for newborn and older infants, which encouraged the use of blood pressure monitoring in children (Smith, 1968). The "Smith cuff" (see Chapter 41, History of Pediatric Anesthesia, Fig. 41-4) remained the standard monitoring device in infants and children until the late 1970s, when it began to be replaced by automated blood pressure devices.

The introduction of pulse oximetry for routine clinical use in the early 1990s has been the single most important development in monitoring and patient safety, especially related to pediatric anesthesia, since the advent of the precordial stethoscope in the 1950s (see Chapters 10, Equipment; 11, Monitoring; and 40, Safety and Outcome) (Smith, 1956). Pulse oximetry is superior to clinical observation and other means of monitoring, such as capnography, for the detection of intraoperative hypoxemia (Coté et al., 1988, 1991). In addition, Spears and colleagues (1991) have indicated that experienced pediatric anesthesiologists may not have an "educated hand" or a "feel" adequate to detect changes in pulmonary compliance in infants. Pulse oximetry has revealed that postoperative hypoxemia occurs commonly among otherwise healthy infants and children undergoing simple surgical

[†]Deceased.

procedures, presumably as a result of significant reductions in functional residual capacity (FRC) and resultant airway closure and atelectasis (Motoyama and Glazener, 1986). Consequently, the use of supplemental oxygen in the postanesthesia care unit (PACU) has become a part of routine postanesthetic care (see Chapter 3, Respiratory Physiology).

Although pulse oximetry greatly improved patient monitoring, there were some limitations, namely motion artifact and inaccuracy in low-flow states, and in children with levels of low oxygen saturation (e.g., cyanotic congenital heart disease). Advances have been made in the new generation of pulse oximetry, most notably through the use of Masimo Signal Extraction Technology (SET). This device minimizes the effect of motion artifact, improves accuracy, and has been shown to have advantages over the existing system in low-flow states, mild hypothermia, and moving patients (Malviya et al., 2000; Hay et al., 2002; Irita et al., 2003).

Monitoring of cerebral function and blood flow, as well as infrared brain oximetry have advanced the anesthetic care and perioperative management of infants and children with congenital heart disease and traumatic brain injuries. Depth of anesthesia can be difficult to assess in children, and anesthetic overdose was a major cause of anesthesia-associated cardiac arrest and mortality. Depth-of-anesthesia monitors (bisectral index monitor [BIS], Patient State Index, Narcotrend) have been used in children and have been associated with the administration of less anesthetic agent and faster recovery from anesthesia. However, because these monitors use electroencephalography and a sophisticated algorithm to predict consciousness, the reliability of these monitors in children younger than 1 year old is limited.

In addition to advances in monitors for individual patients, hospital, patient, and outside-agency initiatives have focused on more global issues. Issues of patient safety, side-site markings, time outs, and proper patient identification together with the appropriate administration of prophylactic antibiotics have now become major priorities for health care systems. The World Health Organization (WHO) checklists have been positive initiatives that have ensured that the correct procedure is performed on the correct patient, as well as fostered better communication among health care workers. In anesthesia, patient safety continues to be a mantra for the specialty. Improved monitoring, better use of anesthetic agents, and the development of improved airway devices coupled with advancements in minimally invasive surgery, continue to advance the frontiers of pediatric anesthesia as a specialty medicine, as well as improve patient outcome and patient safety.

ANESTHETIC AGENTS

More than a decade after the release of isoflurane for clinical use, two volatile anesthetics, desflurane and sevoflurane, became available in the 1990s in most industrialized countries. Although these two agents are dissimilar in many ways, they share common physiochemical and pharmacologic characteristics: very low blood-gas partition coefficients (0.4 and 0.6, respectively), which are close to those of nitrous oxide and are only fractions of those of halothane and isoflurane; rapid induction of and emergence from surgical anesthesia; and hemodynamic stability (see Chapters 7, Pharmacology; 13, Induction Maintenance and Recovery; and 34, Same-Day Surgical Procedures). In animal models, the use of inhaled anesthetic agents has been shown to attenuate the adverse effects of ischemia in the brain, heart, and kidneys.

Although these newer, less-soluble, inhaled agents allow for faster emergence from anesthesia, emergence excitation or delirium associated with their use has become a major concern to pediatric anesthesiologists (Davis et al., 1994; Sarner et al., 1995; Lerman et al., 1996; Welborn et al., 1996; Cravero et al., 2000; Kuratani and Oi, 2008). Adjuncts, such as opioids, analgesics, serotonin antagonists, and α_1-adrenergic agonists, have been found to decrease the incidence of emergence agitation (Aono et al., 1999; Davis et al., 1999; Galinkin et al., 2000; Cohen et al., 2001; Ko et al., 2001; Kulka et al., 2001; Voepel-Lewis et al., 2003; Lankinen et al., 2006; Aouad et al., 2007; Tazeroualti et al., 2007; Erdil et al., 2009; Bryan et al., 2009; Kim et al., 2009).

Propofol has increasingly been used in pediatric anesthesia as an induction agent, for intravenous sedation, or as the primary agent of a total intravenous technique (Martin et al., 1992). Propofol has the advantage of aiding rapid emergence and causes less nausea and vomiting during the postoperative period, particularly in children with a high risk of vomiting. When administered as a single dose (1 mg/kg) at the end of surgery, propofol has also been shown to decrease the incidence of sevoflurane-associated emergence agitation (Aouad et al., 2007).

Remifentanil, a μ-receptor agonist, is metabolized by nonspecific plasma and tissue esterases. The organ-independent elimination of remifentanil, coupled with its clearance rate (highest in neonates and infants compared with older children), makes its kinetic profile different from that of any other opioids (Davis et al., 1999; Ross et al., 2001). In addition, its ability to provide hemodynamic stability, coupled with its kinetic profile of rapid elimination and nonaccumulation, makes it an attractive anesthetic option for infants and children. Numerous clinical studies have described its use for pediatric anesthesia (Wee et al., 1999; Chiaretti et al., 2000; Davis et al., 2000, 2001; German et al., 2000; Dönmez et al., 2001; Galinkin et al., 2001; Keidan et al., 2001; Chambers et al., 2002; Friesen et al., 2003). When combined, intravenous hypnotic agents (remifentanil and propofol) have been shown to be as effective and of similar duration as propofol and succinylcholine for tracheal intubation.

The development of more predictable, shorter-acting anesthetic agents (see Chapter 7, Pharmacology) has increased the opportunities for pediatric anesthesiologists to provide safe and stable anesthesia with less dependence on the use of neuromuscular blocking agents.

AIRWAY DEVICES AND ADJUNCTS

Significant changes in pediatric airway management that have patient-safety implications have emerged over the past few years. The laryngeal mask airway (LMA), in addition to other supraglottic airway devices (e.g., the King LT-D, the Cobra pharyngeal airway), has become an integral part of pediatric airway management. Although the LMA is not a substitute for the endotracheal tube, LMAs can be safely used for routine anesthesia in both spontaneously ventilated patients and patients requiring pressure-controlled support. The LMA can also be used in the patient with a difficult airway to aid in ventilation and to act as a conduit to endotracheal intubation both with and without a fiber optic bronchoscope.

In addition to supraglottic devices, advances in technology for visualizing the airway have also improved patient safety. Since the larynx could be visualized, at least 50 devices intended for laryngoscopy have been invented. The newer airway-visualization devices have combined better visualizations, video capabilities, and high resolution.

The development and refinement of airway visualization equipment such as the Glidescope, Shikani Seeing Stylet, and the Bullard laryngoscope have added more options to the management of the pediatric airway and literally give the laryngoscopist the ability to see around corners (see Chapters 10, Equipment; and 12, Airway Management).

The variety of pediatric endotracheal tubes (ETTs) has focused on improved materials and designs. ETTs are sized according to the internal diameter; however, the outer diameter (the parameter most likely involved with airway complications) varies according to the manufacturer (Table 1-1). Tube tips are both flat and beveled, and a Murphy eye may or may not be present. The position of the cuff varies with the manufacturer. The use of cuffed endotracheal tubes in pediatrics continues to be controversial. In a multicenter, randomized prospective study of 2246 children from birth to 5 years of age undergoing general anesthesia, Weiss and colleagues (2009) noted that cuffed ETTs compared with uncuffed ETTs did not increase the risk of postextubation stridor (4.4% vs. 4.7%) but did reduce the need for ETT exchanges (2.1% vs. 30.8%). However, the role of cuffed ETTs in neonates and infants who require prolonged ventilation has yet to be determined.

INTRAOPERATIVE AND POSTOPERATIVE ANALGESIA IN NEONATES

It has long been thought that newborn infants do not feel pain the way older children and adults do and therefore do not require anesthetic or analgesic agents (Lippman et al., 1976). Thus, in the past, neonates undergoing surgery were often not afforded the benefits of anesthesia. Later studies, however, indicated that pain experienced by neonates can affect behavioral development (Dixon et al., 1984; Taddio et al., 1995, 2005). Rats exposed to chronic pain without the benefit of anesthesia or analgesia showed varying degrees of neuroapoptosis (Anand et al., 2007). However, to add further controversy to the issue of adequate anesthesia for infants, concerns regarding the neurotoxic effects of both intravenous and inhalational anesthetic agents (GABAminergic and NMDA antagonists) have been raised. Postoperative cognitive dysfunction (POCD) has been noted in adult surgical patients (Johnson et al., 2002; Monk et al., 2008). In adults, POCD may also be a marker for 1-year survival after surgery. Although POCD is an adult phenomenon, animal studies by multiple investigators have raised concerns about anesthetic agents being toxic to the developing brains of infants and small children (Jevtovic-Todorovic et al., 2003, 2008; Mellon et al., 2007; Wang and Slikker, 2008). Early work by Uemura and others (1985) noted that synaptic density was decreased in rats exposed to halothane in utero. Further work with rodents, by multiple investigators, has shown evidence of apoptosis in multiple areas of the central nervous system during the rapid synaptogenesis period. This window of vulnerability appears to be a function of time, dose, and duration of anesthetic exposure. In addition to the histochemical changes of apoptosis, the exposed animals also demonstrated learning and behavioral deficits later in life.

In addition to apoptotic changes that occurred in rodents, Slikker and colleagues have demonstrated neuroapoptotic changes in nonhuman primates (rhesus monkeys) exposed to ketamine (an NMDA antagonist). As with the rodents, ketamine exposure in monkeys resulted in long-lasting deficits in brain function (Dr. Merle Poule, personal communication on the Safety of Key Inhaled and Intravenous Drugs in Pediatric Anesthesia [SAFEKIDS] Scientific Workshop, November 2009, White Oaks Campus Symposium). How these animal studies relate to human findings is unclear to date. However, three clinical studies have been reported, and all three studies are retrospective. Wilder et al. (2009) studied a cohort group of children from Rochester, Minnesota, and noted that children exposed to two or more anesthetics in the first 4 years of life were more likely to have learning

TABLE 1-1. Measured Outer Diameters (OD) of Pediatric Cuffed Tracheal Tubes According to the Internal Diameter (ID) of Tracheal Tubes Supplied by Different Manufacturers

ID	Tracheal Tube Brand	2.5	3.0	3.5	4.0	4.5	5.0	5.5
OD (mm)	Sheridan Tracheal Tube Cuffed Murphy	NA	4.2	4.9	5.5	6.2	6.8	7.5
	Sheridan Tracheal Tube Cuffed Magill	NA	4.3	NA	5.5	NA	6.9	NA
	Mallinckrodt TT High-Contour Murphy	NA	4.4	4.9	5.7	6.3	7.0	7.6
	Mallinckrodt TT High-Contour Murphy P-Series	NA	4.3	5.0	5.7	6.4	6.7	7.7
	Mallinckrodt TT Lo-Contour Magill	NA	4.5	4.9	5.7	6.2	6.9	7.5
	Mallinckrodt TT Lo-Contour Murphy	NA	4.4	5.0	5.6	6.2	7.0	7.5
	Mallinckrodt TT Hi-Lo Murphy	NA	NA	NA	NA	NA	6.9	7.5
	Mallinckrodt TT Safety Flex	NA	5.2	5.5	6.2	6.7	7.2	7.9
	Portex TT-Profile Soft Seal Cuff, Murphy	NA	NA	NA	NA	NA	7.0	7.6
	Rüsch Ruschelit Super Safety Clear Magill	4.0	5.1	5.3	5.9	6.2	6.7	7.2
	Rüsch Ruschelit Super Safety Clear Murphy	NA	NA	NA	NA	NA	6.7	7.3

Modified from Weiss et al.: Shortcomings of cuffed paediatric tracheal tubes. *Brit J Anaesth* 92:78–88, 2004.

disabilities, compared with children exposed to one anesthetic or none at all. Kalkman and others (2009) studied a group of children undergoing urologic surgery before age 6 years and reported that there was a tendency for parents to report more behavioral disturbances than those operated on at a later age. However, in a twin cohort study from the Netherlands, Bartels and coworkers (2009) reported no causal relationship between anesthesia and learning deficits in 1,143 monozygotic twin pairs.

In an effort to determine the impact of anesthetic agents or neurocognitive development, a collaborative partnership between the U.S. Food and Drug Administration (FDA) and the International Anesthesia Research Society has formed Safety of Key Inhaled and Intravenous Drugs in Pediatric Anesthesia (SAFEKIDS), a program designed to fund and promote research in this area.

REGIONAL ANALGESIA IN INFANTS AND CHILDREN

Although conduction analgesia has been used in infants and children since the beginning of the twentieth century, the controversy about whether anesthetic agents can be neurotoxic has caused a resurgence of interest in regional anesthesia (Abajian et al., 1984; Williams et al., 2006).

As newer local anesthetic agents with less systemic toxicity become available, their role in the anesthetic/analgesic management of children is increasing. Studies of levobupivacaine and ropivacaine have demonstrated safety and efficacy in children that is greater than that of bupivacaine, the standard regional anesthetic used in the 1990s (Ivani et al., 1998, 2002, 2003; Hansen et al., 2000, 2001; Lönnqvist et al., 2000; McCann et al., 2001; Karmakar et al., 2002). A single dose of local anesthetics through the caudal and epidural spaces is most often used for a variety of surgical procedures as part of general anesthesia and for postoperative analgesia. Insertion of an epidural catheter for continuous or repeated bolus injections of local anesthetics (often with opioids and other adjunct drugs) for postoperative analgesia has become a common practice in pediatric anesthesia. The addition of adjunct drugs, such as midazolam, neostigmine, tramadol, ketamine, and clonidine, to prolong the neuroaxial blockade from local anesthetic agents has become more popular, even though the safety of these agents on the neuroaxis has not been determined (see Chapters 15, Pain Management; and 16, Regional Anesthesia) (Ansermino et al., 2003; de Beer and Thomas, 2003).

In addition to neuroaxial blockade, specific nerve blocks that are performed with or without ultrasound guidance have become an integral part of pediatric anesthesia (see Chapter 16, Regional Anesthesia). The use of ultrasound has allowed for the administration of smaller volumes of local anesthetic and for more accurate placement of the local anesthetic (Ganesh et al., 2009; Gurnaney et al., 2007; Willschke et al., 2006). The use of catheters in peripheral nerve blocks has also changed the perioperative management for a number of pediatric surgical patients. Continuous peripheral nerve catheters with infusions are being used by pediatric patients at home after they have been discharged from the hospital (Ganesh et al., 2007). The use of these at-home catheters has allowed for shorter hospital stays. In addition, the use of regional techniques with ultrasound guidance, coupled with the natural interest in pain management, has allowed for pediatric anesthesiologists to spearhead pediatric acute and chronic pain management programs.

In addition to advances in anesthetic pharmacology and equipment, advances in the area of pediatric minimal invasive surgery have improved patient morbidity, shortened the length of hospital stays, and improved surgical outcomes (Fujimoto et al., 1999).

Although minimally invasive surgery (MIS) imposes physiologic challenges in the neonate and small infant, numerous neonatal surgical procedures can nevertheless be successfully approached with such methods, even in infants with single ventricle physiology (Georgeson, 2003; Ponsky and Rothenberg, 2008). The success of MIS has allowed for the evolution of robotic techniques, stealth surgery (scarless surgery), and Natural Orifice Transluminal Endoscopic Surgery (NOTES) (Dutta and Albanese, 2008; Dutta et al., 2008; Isaza et al., 2008).

FUNDAMENTAL DIFFERENCES IN INFANTS AND CHILDREN

Regardless of all the advances in equipment, monitoring, and patient safety initiatives, pediatric anesthesia still requires a special understanding of anatomic, psychological, and physiologic development. The reason for undertaking a special study of pediatric anesthesia is that children, especially infants younger than a few months, differ markedly from adolescents and adults. Many of the important differences, however are not the most obvious. Although the most apparent difference is size, it is the physiologic differences related to general metabolism and immature function of the various organ systems (including the heart, lungs, kidneys, liver, blood, muscles, and central nervous system) that are of major importance to the anesthesiologist.

Psychological Differences

For a child's normal psychological development, continuous support of a nurturing family is indispensable at all stages of development; serious social and emotional deprivation (including separation from the parents during hospitalization), especially during the first 2 years of development, may cause temporary or even lasting damage to psychosocial development (Forman et al., 1987). A young child who is hospitalized for surgery is forced to cope with separation from parents, to adapt to a new environment and strange people, and to experience the pain and discomfort associated with anesthesia and surgery (see Chapters 2, Behavioral Development; and 8, Psychological Aspects).

The most intense fear of an infant or a young child is created by separation from the parents, and it is often conceived as loss of love or abandonment. The sequence of reactions observed is often as follows: angry protest with panicky anxiety, depression and despair, and eventually apathy and detachment (Bowlby, 1973). Older children may be more concerned with painful procedures and the loss of self-control that is implicit with general anesthesia (Forman et al., 1987). Repeated hospitalizations for anesthesia and surgery may be associated with psychosocial disturbances in later childhood (Dombro, 1970). In children who are old enough to experience fear and apprehension during anesthesia and surgery, the emotional factor may be of greater

concern than the physical condition; in fact, it may represent the greatest problem of the perioperative course (see Chapter 8, Psychological Aspects) (Smith, 1980).

All of these responses can and should be reduced or abolished through preventive measures to ease the child's adaptation to the hospitalization, anesthesia, and surgery. The anesthesiologist's role in this process, as well as having a basic understanding of neurobehavioral development, are important (Table 1-2).

TABLE 1-2. Aspects of Developmental Assessment and Common Developmental Milestones

Follows dangling object from midline through a range of 90°	1 mo
Follows dangling object from midline through a range of 180°	3 mo
Consistent conjugate gaze (binocular vision)	4 mo
Alerts or quiets to sound	0-2 mo
Head up 45°	2 mo
Head up 90°	3-4 mo
Weight on forearms	3-5 mo
Weight on hands with arms extended	5-6 mo
Complete head lag, back uniformly rounded	Newborn
Slight head lag	3 mo
Rolls front to back	4-5 mo
Rolls back to front	5-6 mo
Sits with no support	7 mo
Hands predominantly closed	1 mo
Hands predominantly open	3 mo
Foot play	5 mo
Transfers objects from hand to hand	6 mo
Index finger approach to small objects and finger-thumb opposition	10 mo
Plays pat-a-cake	9-10 mo
Pulls to stand	9 mo
Walks with one hand held	12 mo
Runs well	2 y
Social smile	1-2 mo
Smiles at image in mirror	5 mo
Separation anxiety/stranger awareness	6-12 mo
Interactive games: peek-a-boo and pat-a-cake	9-12 mo
Waves "bye-bye"	10 mo
Cooing	2-4 mo
Babbles with labial consonants ("ba, ma, ga")	5-8 mo
Imitates sounds made by others	9-12 mo
First words (≈4-6, including "mama," "dada")	9-12 mo
Understands one-step command (with gesture)	15 mo

Modified from Illingworth RS: *The development of the infant and young child: normal and abnormal,* New York, 1987, Churchill Livingstone; ages are averages based primarily on data from Arnold Gesell.

Differences in Response to Pharmacologic Agents

The extent of the differences among infants, children, and adults in response to the administration of drugs is not just a size conversion. During the first several months after birth, rapid development and growth of organ systems take place, altering the factors involved in uptake, distribution, metabolism, and elimination of anesthetics and related drugs. Interindividual variability of a response to a given drug may be determined by a variety of genetic factors. Genetic influences in biotransformation, metabolism, transport, and receptor site all affect an individual's response to a drug. These changes appear to be responsible for developmental differences in drug response and can be further modified by age-related and environmental-related factors. The pharmacology of anesthetics and adjuvant drugs and their different effects in neonates, infants, and children are discussed in detail in Chapter 7, Pharmacology.

Anatomic and Physiologic Differences

Body Size

As stated, the most striking difference between children and adults is size, but the degree of difference and the variation even within the pediatric age group are hard to appreciate. The contrast between an infant weighing 1 kg and an overgrown and obese adolescent weighing more than 100 kg who appear in succession in the same operating room is overwhelming. It makes considerable difference whether body weight, height, or body surface area is used as the basis for size comparison. As pointed out by Harris (1957), a normal newborn infant who weighs 3 kg is one third the size of an adult in length but $\frac{1}{9}^{th}$ the adult size in body surface area and $\frac{1}{21}$ of adult size in weight (Fig. 1-1). Of these body measurements, body surface area (BSA) is probably the most important, because it closely parallels variations in basal metabolic rate measured in kilocalories per hour per square meter. For this reason, BSA is believed to be a better criterion than age or weight in judging basal fluid and nutritional requirements. For clinical use, however, BSA proves somewhat difficult to determine, although a nomogram such as that of Talbot and associates (1952) facilitates the procedure considerably (Fig. 1-2). For the anesthesiologist who carries a pocket calculator, the following formulas may be useful to calculate BSA:

Formula of DuBois and DuBois (1916)

$$BSA\,(m^2) = 0.007184 \times Height^{0.725} \times Weight^{0.425}$$

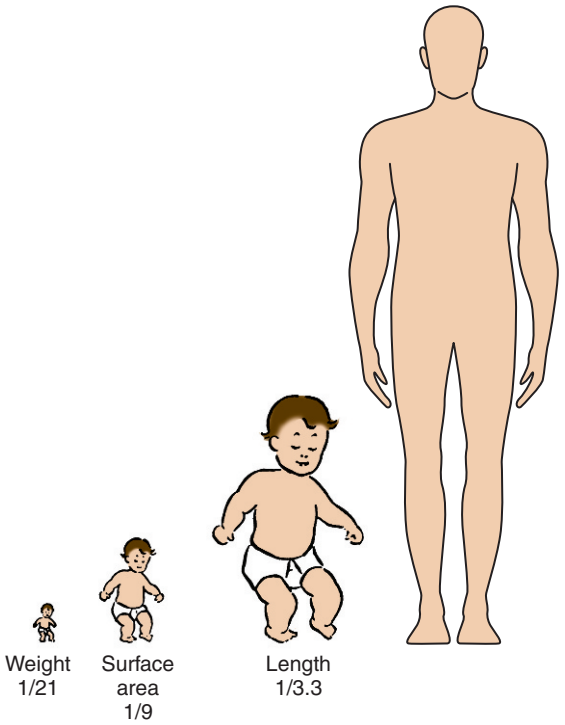
Formula of Gehan and George (1970)

$$BSA\,(m^2) = 0.0235 \times Height^{0.42246} \times Weight^{0.51456}$$

At full-term birth, BSA averages 0.2 m^2, whereas in the adult it averages 1.75 m^2. A table of average height, weight, and BSA is given for reference in Table 1-3. A simpler, crude estimate of BSA for children of average height and weight is given in Table 1-4. The formula:

$$BSA\,(m^2) = (002 \times kg) + 0.40$$

is also reasonably accurate in children of normal physique weighing 21 to 40 kg (Vaughan and Litt, 1987).



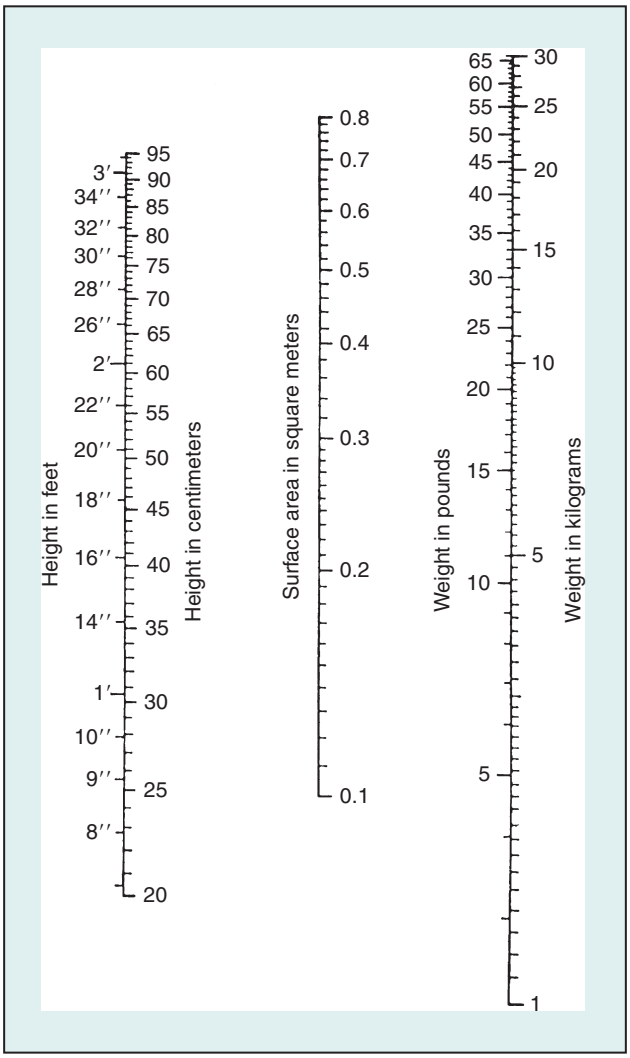
■ **FIGURE 1-1.** Proportions of newborn to adult with respect to weight, surface area, and length. *(From Crawford JD, Terry ME, Rourke GM: Simplification of drug dosage calculation by application of the surface area principle,* Pediatrics *5:785, 1950.)*

The caloric need in relation to BSA of a full-term infant is about 30 kcal/m^2 per hour. It increases to about 50 kcal/m^2 per hour by 2 years of age and then decreases gradually to the adult level of 35 to 40 kcal/m^2 per hour.

Relative Size or Proportion

Less obvious than the difference in overall size is the difference in relative size of body structure in infants and children. This is particularly true with the head, which is large at birth (35 cm in circumference)—in fact, larger than chest circumference. Head circumference increases by 10 cm during the first year and an additional 2 to 3 cm during the second year, when it reaches three-fourths of the adult size (Box 1-1).

At full-term birth, the infant has a short neck and a chin that often meets the chest at the level of the second rib; these infants are prone to upper airway obstruction during sleep. In infants with tracheostomy, the orifice is often buried under the chin unless the head is extended with a roll under the neck. The chest is relatively small in relation to the abdomen, which is protuberant with weak abdominal muscles (Fig. 1-3). Furthermore, the rib cage is cartilaginous and the thorax is too compliant to resist inward recoil of the lungs. In the awake state, the chest wall is maintained relatively rigid with sustained inspiratory muscle tension, which maintains the end-expiratory lung volume functional residual capacity (FRC). Under general anesthesia, however, the muscle tension is abolished and FRC collapses, resulting in airway closure, atelectasis, and venous admixture unless continuous positive airway pressure (CPAP) or positive end-expiratory pressure (PEEP) is maintained.



■ **FIGURE 1-2.** Body surface area nomogram for infants and young children. *(From Talbot NB, Sobel FH, McArthur JW, et al.:* Functional endocrinology from birth through adolescence, *Cambridge, 1952, Harvard University Press.)*

TABLE 1-3. Relation of Age, Height, and Weight to Body Surface Area (BSA)*

Age (y)	Height (cm)	Weight (kg)	BSA (m^2)
Premature	40	1	0.1
Newborn	50	3	0.2
1	75	10	0.47
2	87	12	0.57
3	96	14	0.63
5	109	18	0.74
10	138	32	1.10
13	157	46	1.42
16 (Female)	163	50	1.59
16 (Male)	173	62	1.74

* Based on standard growth chart and the formula of DuBois and DuBois (1916): BSA (m^2) = 0.007184 × Height$^{0.725}$ × Weight$^{0.425}$.

TABLE 1-4. Approximation of Body Surface Area (BSA) Based on Weight

Weight (kg)	Approximate BSA (m^2)
1-5	$0.05 \times kg + 0.05$
6-10	$0.04 \times kg + 0.10$
11-20	$0.03 \times kg + 0.20$
21-40	$0.02 \times kg + 0.40$

Modified from Vaughan VC III, Litt IF: Assessment of growth and development. In Behrman RE, Vaughn VC III, editors: *Nelson's textbook of pediatrics,* ed 13, Philadelphia, 1987, WB Saunders.

Box 1-1 Typical Patterns of Physical Growth

WEIGHT

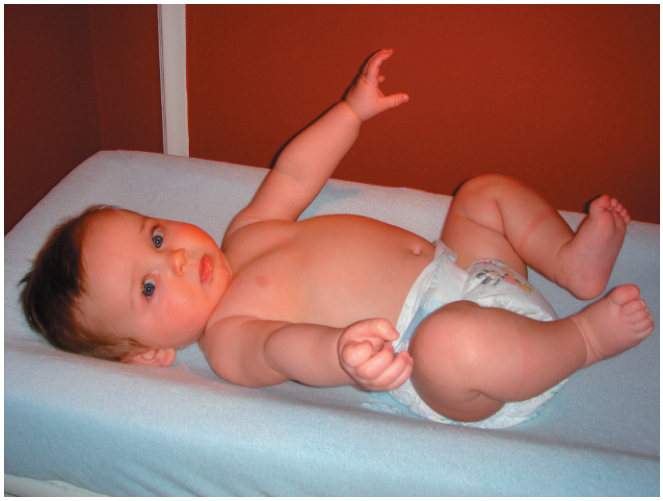
Birth weight (BW) is regained by the tenth to fourteenth day.
Average weight gain per day: 0-6 mo = 20 g; 6-12 mo = 15 g.
BW doubles at ≈4 mo, triples at ≈12 mo, quadruples at ≈24 mo.
During second year, average weight gain per month: ≈0.25 kg.
After age 2 years, average annual gain until adolescence: ≈2.3 kg.

LENGTH/HEIGHT

By end of first year, birth length increases by 50%.
Birth length doubles by age 4 years, triples by 13 years.
Average height gain during second year: ≈12 cm.
After age 2 years, average annual growth until adolescence: ≈5 cm.

HEAD CIRCUMFERENCE

Average head growth per week: 0-2 mo = ≈0.5 cm; 2-6 mo = ≈0.25 cm.
Average total head growth: 0-3 mo = ≈5 cm; 3-6 mo = ≈4 cm; 6-9 mo = ≈2 cm; 9-12 mo = ≈1 cm.



■ **FIGURE 1-3.** A normal infant has a large head, narrow shoulders and chest, and a large abdomen.

Central and Autonomic Nervous Systems

The brain of the neonate is relatively large, weighing about 1/10 of body weight compared with about 1/50 of body weight in the adult. The brain grows rapidly; its weight doubles by 6 months of age and triples by 1 year. By the third week of gestation, the neural plate appears, and by 5 weeks the three main subdivisions of the forebrain, midbrain, and hindbrain are evident. By the eighth week of gestation, neurons migrate to form the cortical layers, and migration is complete by the sixth month. Cell differentiation continues as neurons, astrocytes, aligodendrocytes, and glial cells form. Axons and synaptic connections continually form and remodel. At birth, about one fourth of the neuronal cells are present. The development of cells in the cortex and brain stem is nearly complete by 1 year of age. Myelinization and elaboration of dendritic processes continue well into the third year. Incomplete myelinization is associated with primitive reflexes, such as the Moro and grasp reflexes in the neonate; these are valuable in the assessment of neural development.

At birth the spinal cord extends to the third lumbar vertebra. By the time the infant is 1 year old, the cord has assumed its permanent position, ending at the first lumbar vertebra (Gray, 1973).

In contrast to the central nervous system, the autonomic nervous system is relatively well developed in the newborn. The parasympathetic components of the cardiovascular system are fully functional at birth. The sympathetic components, however, are not fully developed until 4 to 6 months of age (Friedman, 1973). Baroreflexes to maintain blood pressure and heart rate, which involve medullary vasomotor centers (pressor and depressor areas), are functional at birth in awake newborn infants (Moss et al., 1968; Gootman, 1983). In anesthetized newborn animals, however, both pressor and depressor reflexes are diminished (Wear et al., 1982; Gallagher et al., 1987).

The laryngeal reflex is activated by the stimulation of receptors on the face, nose, and upper airways of the newborn. Reflex apnea, bradycardia, or laryngospasm may occur. Various mechanical and chemical stimuli, including water, foreign bodies, and noxious gases, can trigger this response. This protective response is so potent that it can cause death in the newborn (see Chapters 3, Respiratory Physiology; and 4, Cardiovascular Physiology).

Respiratory System

At full-term birth, the lungs are still in the stage of active development. The formation of adult-type alveoli begins at 36 weeks post conception but represents only a fraction of the terminal air sacs with thick septa at full-term birth. It takes more than several years for functional and morphologic development to be completed, with a 10-fold increase in the number of terminal air sacs to 400 to 500 million by 18 months of age, along with the development of rich capillary networks surrounding the alveoli. Similarly, control of breathing during the first several weeks of extrauterine life differs notably from control in older children and adults. Of particular importance is the fact that hypoxemia depresses, rather than stimulates, respiration. Anatomic differences in the airway occur with growth and development. Recently, the concept of the child having a funnel-shaped airway with the cricoid as the narrowest portion of the airway has been challenged. Based on bronchoscopic images, Dalal and colleagues (2009) suggest for infants and children the glottis,

not the cricoid, may be the narrowest portion. The development of the respiratory system and its physiology are detailed in Chapter 3, Respiratory Physiology.

Cardiovascular System

During the first minutes after birth, the newborn infant must change his or her circulatory pattern dramatically from fetal to adult types of circulation to survive in the extrauterine environment. Even for several months after initial adaptation, the pulmonary vascular bed remains exceptionally reactive to hypoxia and acidosis. The heart remains extremely sensitive to volatile anesthetics during early infancy, whereas the central nervous system is relatively insensitive to these anesthetics. Cardiovascular physiology in infants and children is discussed in Chapter 4.

Fluid and Electrolyte Metabolism

Like the lungs, the kidneys are not fully mature at birth, although the formation of nephrons is complete by 36 weeks' gestation. Maturation continues for about 6 months after full-term birth. The glomerular filtration rate (GFR) is lower in the neonate because of the high renal vascular resistance associated with the relatively small surface area for filtration. Despite a low GFR and limited tubular function, the full-term newborn can conserve sodium. Premature infants, however, experience prolonged glomerulotubular imbalance, resulting in sodium wastage and hyponatremia (Spitzer, 1982). On the other hand, both full-term and premature infants are limited in their ability to handle excessive sodium loads. Even after water deprivation, concentrating ability is limited at birth, especially in premature infants. After several days, neonates can produce diluted urine; however, diluting capacity does not mature fully until after 3 to 5 weeks of life (Spitzer, 1978). The premature infant is prone to hyponatremia when sodium supplementation is inadequate or with overhydration. Furthermore, dehydration is detrimental to the neonate regardless of gestational age. The physiology of fluid and electrolyte balance is detailed in Chapter 5, Regulation of Fluids and Electrolytes.

Temperature Regulation

Temperature regulation is of particular interest and importance in pediatric anesthesia. There is a better understanding of the physiology of temperature regulation and the effect of anesthesia on the control mechanisms. General anesthesia is associated with mild to moderate hypothermia, resulting from environmental exposure, anesthesia-induced central thermoregulatory inhibition, redistribution of body heat, and up to 30% reduction in metabolic heat production (Bissonette, 1991). Small infants have disproportionately large BSAs, and heat loss is exaggerated during anesthesia, particularly during the induction of anesthesia, unless the heat loss is actively prevented. General anesthesia decreases but does not completely abolish thermoregulatory threshold temperature to hypothermia. Mild hypothermia can sometimes be beneficial intraoperatively, and profound hypothermia is effectively used during open heart surgery in infants to reduce oxygen consumption. Postoperative hypothermia, however, is detrimental because of marked increases in oxygen consumption, oxygen debt (dysoxia), and resultant metabolic acidosis. Regulation of body temperature is discussed in detail in Chapter 6, Thermoregulation.

SUMMARY

Pediatric anesthesia as a subspecialty has evolved, because the needs of infants and young children are fundamentally different from those of adults. The pediatric anesthesiologist should be aware of the child's cardiovascular, respiratory, renal, neuromuscular, and central nervous system responses to various drugs, as well as to physical and chemical stimuli, such as changes in blood oxygen and carbon dioxide tensions, pH, and body temperature. Their responses are different both qualitatively and quantitatively from those of adults and among different pediatric age groups. More importantly, the pediatric anesthesiologist should always consider the child's emotional needs and create an environment that minimizes or abolishes fear and distress.

There have been many advances in the practice of anesthesia to improve the comfort of young patients since the seventh edition of this book was published in 2006. These advances include a relaxation of preoperative fluid restriction, more focused attention to the child's psychological needs with more extensive use of preoperative sedation via the transmucosal route, the wide use of topical analgesia with a eutectic mixture of local anesthetic cream before intravenous catheterization, expanded use of regional anesthesia with improved accuracy and safety by means of ultrasound devices, and more generalized acceptance of parental presence during anesthetic induction and in the recovery room. Furthermore, a more diverse anesthetic approach has evolved through the combined use of regional analgesia, together with the advent of newer and less soluble volatile anesthetics, intravenous anesthetics, and shorter-acting synthetic opioids and muscle relaxants. Finally, the scope of pediatric anesthesia has significantly expanded with the recent development of organized pain services in most pediatric institutions. As a result, pediatric anesthesiologists have assumed the leading role as pain management specialists, thus further extending anesthesia services and influence beyond the boundary of the operating room.

REFERENCES

Complete references used in this text can be found online at www.expertconsult.com.

CHAPTER 2

Behavioral Development

Julie Niezgoda

CONTENTS

Assessment of growth and development of infants and children typically falls under the domain of the pediatrician or pediatric subspecialist. Delays or deviations from normal often dictate the need to conduct extensive diagnostic evaluations and management strategies. Familiarity with developmental stages may also benefit the pediatric anesthesiologist, allowing the practitioner to recognize the different coping mechanisms children use to respond to the anxiety and stresses throughout the perioperative period. Growth issues, especially failure to thrive, may indicate a serious underlying medical condition that could affect the management and anesthetic plan for children.

A variety of processes are encompassed in growth and development: the formation of tissue; an increase in physical size; the progressive increases in strength and ability to control large and small muscles (gross motor and fine motor development); and the advancement of complexities of thought, problem solving, learning, and verbal skills (cognitive and language development). There is a systematic approach for tracking neurologic development and physical growth in infants, because attainment of milestones is orderly and predictable. However, a wide range exists for normal achievement. The mastering of a particular skill often builds on the achievement of an earlier skill. Delays in one developmental domain may impair development in another (Gessel and Amatruda, 1951). For example, immobility caused by a neuromuscular disorder prevents an infant from exploration of the environment, thus impeding cognitive development. A deficit in one domain might interfere with the ability to assess progress in another area. For example, a child with cerebral palsy who is capable of conceptualizing matching geometric shapes but does not have the gross or fine motor skills necessary to perform the function could erroneously be labeled as developmentally delayed.

It is possible for the anesthesiologist to obtain a gestalt of a child's growth and development level while recording a preoperative history and during the physical examination. However, the anesthesiologist needs to realize that these assessments are usually done by pediatricians over time and are best performed when the child is physically well, familiar with the examiner, and under minimal stress. Therefore, a child who is developing normally could be assessed as delayed during a preoperative assessment.

The goal of this chapter is to review the developmental and behavioral issues faced in routine pediatric practice to help the anesthesiologist tailor an anesthetic plan that is geared to the appropriate age of the child with the goal of decreasing postoperative complications such as behavioral disturbances, emotional reactions, or escalation in medical care. The chapter is divided into sections addressing growth and developmental milestones, including gross motor skills, fine motor skills, cognition, and language, followed by a section of clinical scenarios illustrating the relevance of developmental issues in pediatric anesthesia. The last section contains several common developmental disorders and related anesthetic issues.

PRENATAL GROWTH

The most dramatic events in growth and development occur before birth. These changes are overwhelmingly somatic, with the transformation of a single cell into an infant. The first eight weeks of gestation are known as the embryonic period and encompasses the time when the rudiments of all of the major organs are developed. This period denotes a time that the fetus is highly sensitive to teratogens such as alcohol, tobacco, mercury, thalidomide, and antiepileptic drugs. The average embryo weighs 9 g and has a crown-to-rump length of 5 cm. The fetal stage (more than 9 weeks' gestation) consists of increases in cell number and size and structural remodeling of organ systems (Moore, 1972).

During the third trimester, weight triples and length doubles as body stores of protein, calcium, and fat increase. Low birth weight can result from prematurity, intrauterine growth retardation (small for gestational age, SGA) or both. Large-for-gestational-age (LGA) infants are those whose weight is above the 90th percentile at any gestational age. Deviations from the normal relationship of infant weight gain with increasing gestational age can be multifactorial. Potential causes include maternal diseases (e.g., diabetes, pregnancy-induced hypertension, and seizure disorders), prenatal exposure to toxins (e.g., alcohol, drugs, and tobacco), fetal toxoplasmosis-rubella-cytomegalovirus-herpes simplex-syphilis (TORCHES) infections, genetic abnormalities (e.g., trisomies 13, 18, and 21), fetal congenital malformations (e.g., cardiopulmonary or renal malformations), and maternal malnutrition or placental insufficiency (Kinney and Kumar, 1988).

POSTNATAL GROWTH

Postnatal growth is measured by changes in weight, length, and head circumference plotted chronologically on growth charts. This is an essential component of pediatric health surveillance, because almost any problem involving physiologic, interpersonal, or social domains can adversely affect growth.

Growth milestones are the most predictable, taking into context each child's specific genetic and ethnic influences (Johnson and Blasco, 1997). It is essential to plot the child's growth on gender- and age-appropriate percentile charts. Charts are now available for certain ethnic groups and genetic syndromes such as Trisomy 21 and Turner's syndrome. Deviation from growth over time across percentiles is of greater significance for a child than a single weight measurement. For example, an infant at the fifth percentile of weight for age may be growing normally, may be failing to grow, or may be recovering from growth failure, depending on the trajectory of the growth curve.

Of the three parameters, weight is the most sensitive measurement of well-being and is the first to show deviance as an indication of an underlying problem. Causes of weight loss and failure to thrive include congestive heart failure, metabolic or endocrine disorders, malignancy, infections, and malabsorption problems. Inadequate increases in height over time occur secondary to significant weight loss, and decreased head circumference is the last parameter to change, signifying severe malnutrition. Pathologies such as hydrocephalus or increased intracranial pressure may appear on growth charts as head-circumference measurements that are rapidly increasing and crossing percentiles. Small head size can be associated with craniosynostosis or a syndromic feature. Significant changes in head-circumference measurements in children should alert the anesthesiologist to the potential of underlying neurologic problems.

Because significant weight fluctuation is a potential red flag for serious underlying medical conditions, anesthesiologists should be familiar with the normal weight gain expected for children. It is not unusual for a newborn's weight to decrease by 10% in the first week of life because of the excretion of excess extravascular fluid or possibly poor oral intake. Infants should regain or exceed birth weight by 2 weeks of age and continue to gain approximately 30 g/day, with a gradual decrease to 12 g/day by the first year. Healthy, full-term infants typically double their birth weight at 6 months and triple it by 1 year of age. Many complex formulas are available to estimate the average weight for normal infants and children. A relatively simple calculation to recall is the "rule of tens"; e.g., the weight of a child increases by about 10 pounds per year until approximately 12 to 13 years of age for females and age 16 to 17 years for males. Therefore, one could expect weight gain of 20 pounds by age 2 years, 30 pounds by 3 years, 40 pounds by 4 years, and so on. The weight in pounds can be converted to kilograms by dividing it by 2.2. Length in centimeters is estimated by the following formula: (age in years × 6) + 77.

DEVELOPMENTAL ASSESSMENT

Developmental assessment serves different purposes, depending on the age of the child. In the neonatal period, behavioral assessment can detect a wide range of neurologic impairments. During infancy, assessment serves to reassure parents and to identify sensory, motor, cognitive, and emotional problems early, when they are most amenable to treatment. Middle-childhood and adolescence assessments often help with addressing academic and social problems.

Milestones are useful indicators of mental and physical development and possible deviations from normal. It should be emphasized that milestones represent the average for children to attain and that there can be variable rates of mastery that fall into the normal range. An acceptable developmental screening test must be highly sensitive (detect nearly all children with problems); specific (not identify too many children without problems); have content validity, test-retest, and interrater reliability; and be relatively quick and inexpensive to administer. The most widely used developmental screening test is the Denver Developmental Screening Test (DDST), which provides a pass/fail rating in four domains of developmental milestones: gross motor, fine motor, language, and personal-social. The original DDST was criticized for underidentification of children with developmental disabilities, particularity in the area of language. The reissued DDST-II is a better assessment for language delays, which is important because of the strong link between language and overall cognitive development. Table 2-1 lists the prevalence of some common developmental disabilities (Levy and Hyman, 1993).

TABLE 2-1. Prevalence of Developmental Disabilities

Condition	Prevalence per 1000
Cerebral palsy	2-3
Visual impairment	0.3-0.6
Hearing impairment	0.8-2
Mental retardation	25
Learning disability	75
Attention deficit hyperactivity disorder	150
Behavioral disorders	60-130
Autism	9-10

MOTOR DEVELOPMENT

Primitive Reflexes

The earliest motor neuromaturational markers are primitive reflexes that development during uterine life and generally disappear between the third and sixth months after birth. Newborn movements are largely uncontrolled, with the exception of eye gaze, head turning, and sucking. Development of the infant's central nervous system involves strengthening of the higher cortical center that gradually takes over function of the primitive reflexes. Postural reflexes replace primitive reflexes between three and six months of age as a result of this development (Schott and Rossor, 2003). These reactions allow children to maintain a stable posture even if they are rapidly moved or jolted (Box 2-1).

The asymmetric tonic neck reflex (ATNR) or "fencing posture" is an example of a primitive reflex that is not immediately present at birth because of the high flexor tone of the newborn infant. When the neonate's head is turned to one side, there is increased extensor tone of the upper extremity on the same side and increased flexor tone on the occipital side. The ATNR is a precursor to hand-eye coordination, preparing the infant for gazing along the upper arm and voluntary reaching. The disappearances of this reflex at 4 to 6 months allows the infant mobility to roll over and begin to examine and manipulate objects in the midline with both hands.

The palmar grasp reflex is present at birth and persists until 4 to 6 months of age. When an object is placed in the infant's hand, the fingers close and tightly grasp the object. The grip is strong but unpredictable. The waning of the early grasp reflex allows infants to hold objects in both hands and ultimately to voluntarily let them go.

The Moro reflex is probably the most well-known primitive reflex and is present at birth. It is likely to occur as a startle to a loud noise or sudden changes in head position. The legs and head extend while the arms jerk up and out, followed by adduction of the arms and tightly clenched fists. Bilateral absence of the reflex may mean damage to the infant's central nervous system. Unilateral absence could indicate birth trauma such as a fractured clavicle or brachial plexus injury.

Postural reflexes support control of balance, posture, and movement in a gravity-based environment. The protective equilibrium response can be elicited in a sitting infant by abruptly pushing the infant laterally. The infant will extend the arm on the contralateral side and flex the trunk toward the side of the force to regain the center of gravity (Fig. 2-1). The parachute response develops around 9 months and is a response to a free-fall motion, where the infant extends the extremities in an outward motion to distribute weight over a broader area. Postural reactions are markedly slow in appearance in the infant who has central nervous system damage. Children who fail to gain postural control continue to display traces of primitive reflexes. They also have difficulty with control of movement affecting coordination, fine and gross motor development, and other associated aspects of learning, including reading and writing. Table 2-2 is a list of the average times of appearance and disappearance of the more common primitive reflexes.

Box 2-1 Definitions of Primitive Reflexes

Automatic stepping reflex: Although the infant cannot support his or her weight when a flat surface is presented to the sole of the foot, he or she makes a stepping motion by bringing one foot in front of the other.

Crossed extension reflex: When an extremity is acutely stimulated to withdraw, the flexor muscles in the withdrawing limb contract completely, whereas the extensor muscles relax. The opposite occurs (full extension, with relaxation of contracting muscles) in the opposite limb.

Galant reflex: An infant has the one side of the back stroked moves or swings in that direction.

Moro reflex: When the infant is startled with a loud noise or when the head is lowered suddenly, the head and legs extend and the arms raise up and out. Then the arms are brought in and the fingers close to make fists.

Palmar reflex: When an object is placed into the infant's hand or when the palm of the infant's hand is stroked with an object, the hand closes around the object.

Asymmetric tonic neck reflex ("fencing"): When the infant's head is rotated to one side, the arm on that side straightens and the opposite arm flexes.

Landau reflex: When the infant is held in a horizontal position, he or she raises the head and bring the legs up into a horizontal position. If the head is forced down (flexed) the legs also lower into a vertical position.

Derotational righting reflex: When the infant turns the head one direction, the body leans in the same direction to maintain balance.

Protective equilibrium reflex: When a lateral force is applied to the infant, he or she responds by leaning into the force and extending the contralateral arm.

Parachute reflex: When the infant is facing down and lowered suddenly, the arms extend out in a protective maneuver.

FIGURE 2-1. The protective equilibrium response is demonstrated in an infant being pushed laterally. Note the extended contralateral arm.

TABLE 2-2. Primitive Reflexes

Reflex	Present by (Months)	Gone by (Months)
Automatic stepping	Birth	2
Crossed extension	Birth	2
Galant	Birth	2
Moro	Birth	3-6
Palmar	Birth	4-6
Asymmetric tonic neck ("fencing")	1	4-6
Landau	3	12-24
Derotational head righting	4	Persists
Protective equilibrium	4-6	Persists
Parachute	8-9	Persists

Gross Motor Skills

One principle in neuromaturational development during infancy is that it proceeds from cephalad to caudad and proximal to distal. Thus, arm movement comes before leg movement (Feldman, 2007). The upper extremity attains increasing accuracy in reaching, grasping, transferring, and manipulating objects. Gross motor development in the prone position begins with the infant tightly flexing the upper and lower extremities and evolves to hip extension while lifting the head and shoulders from a table surface around 4 to 6 months of age. When pulled to a sitting position, the newborn has significant head lag, whereas the 6-month-old baby, because of development of muscle tone in the neck, raises the head in anticipation of being pulled up.

Rolling movements start from front to back at approximately 4 months of age as the muscles of the lower extremities strengthen. An infant begins to roll from back to front at about 5 months. The abilities to sit unsupported (about 6 months old) and to pivot while sitting (around 9 to 10 month of age) provide increasing opportunities to manipulate several objects at a time (Needleman, 1996). Once thoracolumbar control is achieved and the sitting position mastered, the child focuses motor development on ambulation and more complex skills. Locomotion begins with commando-style crawling, advances to creeping on hands and knees, and eventually reaches pulling to stand around 9 months of age, with further advancement to cruising around furniture or toys. Standing alone and walking independently occur around the first birthday. Advanced motor achievements correlate with increasing myelinization and cerebellum growth. Walking several steps alone has one of the widest ranges for mastery of all of the gross motor milestones and occurs between 9 and 17 months of age. Milestones of gross motor development are presented in Table 2-3 and Figure 2-2. The accomplishment of locomotion not only expands the infant's exploratory range and offers new opportunities for cognitive and motor growth, but it also increases the potential for physical dangers (Vaughan, 1992).

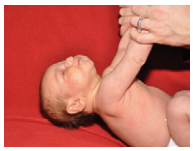
Most children walk with a mature gait, run steadily, and balance on one foot for 1 second by 3½ years of age. The sequence for additional gross motor development is as follows: running, jumping on two feet, balancing on one foot, hopping, and skipping. Finally, more complex activities such as throwing, catching, and kicking balls, riding bicycles, and climbing on playground equipment are mastered. Development beyond walking incorporates improved balance and coordination and progressive narrowing of additional physical support. Complex motor skills also incorporate advanced cognitive and emotional development that is necessary for interactive play with other children. Figure 2-3 shows the red flags to watch for in the abnormal physical development of the infant.

TABLE 2-3. Cognitive and Language Communication Skills Development

Average Age of Attainment (Months)	Cognitive	Language Communication
2	Stares briefly at area when object is removed	Smiles in response to face or voice
4	Stares at own hand	Monosyllabic babble
8	Object permanence—uncovers toy after seeing it covered	Inhibits to "no" Follows one-step command *with* gesture (wave to "come here")
10	Separation anxiety from familiar people	Follows one-step command without gesture ("give it to me")
12	Egocentric play (pretends to drink from cup)	Speaks first real word
18	Cause and effect relationships no longer need to be demonstrated to understand (pushes car to move, winds toy on own) Distraction techniques may no longer succeed	Speaks 20 to 50 words
24	Mental activity is independent of sensory processing or motor manipulation (sees a child in a book with a mask on face and can later reenact event)	Speaks in two-word sentences
36	Capable of symbolic thinking	Speaks in three-word sentences
48	Immature logic is replaced Conventional logic and wisdom	Speaks in four-word sentences Follows three-step commands

1 Month
Prone, lies tightly flexed with pelvis high. Head lags after shoulders when pulled to sit





3 Months
Prone, rests on forearms. Partial head lag when pulled to sit

5 Months
Rolls back to front

6 Months
Sit without support. Lifts head before shoulders when pulled to sit


7 Months
Commando crawl

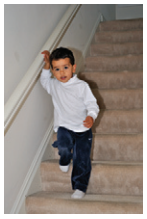
8 Months
Four point kneeling, reaches with one hand. Aquires sitting position without support

10 Months
Cruises around furniture

12 Months
Walks alone

18 Months
Runs

24 Months
Jumps in place, throws overhand, walks down stairs holding rail

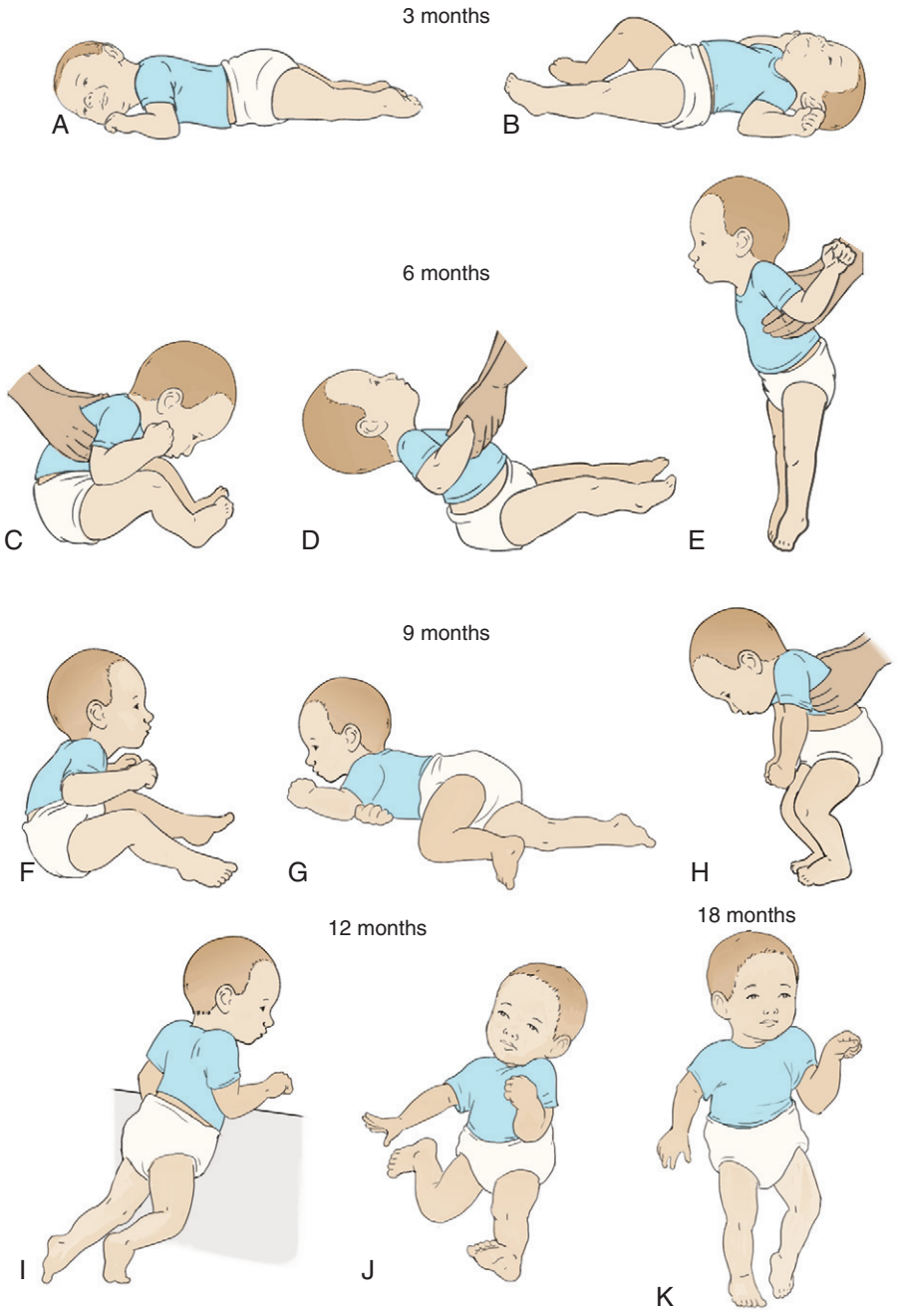


36 Months
Balance on one foot for one second

48 Months
Hopes on one foot

60 Months
Catches a ball

■ **FIGURE 2-2.** Gross motor skills development chart.



■ **FIGURE 2-3.** Abnormal developmental findings. **A,** Difficulty lifting head and stiff legs with little or no movement. **B,** Pushing back with head, keeping hands fisted, and lacking arm movement. **C,** Rounded back, inability to lift head up, and poor head control. **D,** Difficulty bringing arms forward to reach out, arching back, and stiffening legs. **E,** Arms held back and stiff legs. **F,** Using one hand predominantly; rounded back and poor use of arms when sitting. **G,** Difficulty crawling and using only one side of the body to move. **H,** Inability to straighten back and cannot bear weight on legs. **I,** Difficulty getting to standing position because of stiff legs and pointed toes; only using arms to pull up to standing. **J,** Sitting with weight to one side and strongly flexed or stiffly extended arms; using hand to maintain seated position. **K,** Inability to take steps independently, poor standing balance, many falls, and walking on toes. *(Redrawn from* What Every Parent Should Know *[pamphlet], 2006, Pathways Awareness Foundation.)*

Fine Motor Development

At birth, the neonate's fingers and thumbs are typically tightly fisted. Normal development moves from the primitive grasp reflex, where the infant reflexively grabs an object but is unable to release it to a voluntary grasp and release of the object. By 2 to 3 months of age the hands are no longer tightly fisted, and the infant begins to bring them toward the mouth, sucking on the digits for self comfort. Objects can be held in either hand by age 3 months and transferred back and forth by 6 months.

1 Month
Hands tightly fisted

2 Months
Grasps rattle

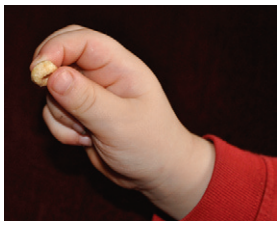
3 Months
Hands unfisted most of the time

4 Months
Reaches for and retains rattle, uses both hands

6 Months
Transfers objects hand to hand, immature hand rake of pellat

10 Months
Pincer grasp between thumb and index finger

12 Months
Pincer grasp between finger tips



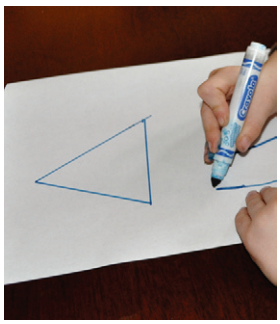
18 Months
Tower of four cubes, scribbles spontaneously

24 Months
Tower of six cubes, turns pages of books one at a time, imitate vertical stroke

36 Months
Copies circle, cuts with small scissors

48 Months
Copies cross, draws a person with three parts

60 Months
Copies triangle



■ **FIGURE 2-4.** Fine motor skills development chart.

In early development, the upper extremities assist with balance and mobility. As the sitting position is mastered with improved balance, the hands become more available for manipulation and exploration. The evolution of the pincer grasp is the highlight of fine motor development during the first year. The infant advances from "raking" small objects into the palm to the finer pincer grasp, allowing opposition of the thumb and the index finger, whereby small items are picked up with precision. Children younger than 18 months of age generally use both hands equally well, and true "handedness" is not established until 36 months (Levine et al., 1999). Advancements in fine motor skills continue throughout the preschool years, when the child develops better eye-hand coordination with which to stack objects or reproduce drawings (e.g., crosses, circles, and triangles). Figure 2-4 lists and demonstrates the chronologic order of fine motor development.

LANGUAGE DEVELOPMENT

Delays in language development are more common than delays in any other developmental domain (Glascoe, 2000). Language includes receptive and expressive skills. Receptive skills are the ability to understand the language, and expressive skills include the ability to make thoughts, ideas, and desires known to others. Because receptive language precedes expressive language, infants respond to several simple statements such as "no," "bye-bye," and "give me" before they are capable of speaking intelligible words. In addition to speech, expression of language can take the forms of gestures, signing, typing, and "body language." Thus, speech and language are not synonymous. The hearing-impaired child or child with cerebral palsy may have normal receptive language skills and intellect to understand dialogue but needs other forms of expressive language to vocalize responses. Conversely, children may talk but fail to communicate; for example, a child with autism may vocalize by using "parrot talk" or echolalia that has no meaningful content and does not represent language.

Language development can be divided into the three stages of pre-speech, naming, and word combination. Pre-speech is characterized by cooing or babbling until around 8 to 10 months of age, when babbling becomes more complex with multiple syllables. Eventually random vocalization ("da-da") is interpreted and reinforced by the parents as a real word, and the child begins to repeat it. The naming period (ages 10 to 18 months) is when the infant realizes that people have names and objects have labels. Once the infant's vocalizations are reinforced as people or things, the infant begins to use them appropriately. At around 12 months of age some infants understand as many as 100 words and can respond to simple commands that are accompanied by gestures. Early into the second year a command without a gesture is understood. Expressive language is slower, and an 18-month-old child has a limited vocabulary of around 25 words. After the realization that words can stand for things, the child's vocabulary expands at a rapid pace. Preschool language development begins with word combination at 18 to 24 months and is the foundation for later success in school. Vocabulary increases from 50 to 100 words to more than 2000 words during this time. Sentence structure advances from two- and three-word phrases to sentences incorporating all of the major grammatic rules. A simple correlate is that a child should increase the number of words in a sentence with advancing age; e.g., two-word sentences by 2 years of age, three-word sentences by age 3 years (Table 2-3).

Language is a critical barometer of both cognitive and emotional development (Coplan, 1995). Mental retardation may first surface as a concern with delayed speech and language development around 2 years of age; however, the average age of diagnosis is 3 to 4 years. All children whose language development is delayed should undergo audiologic testing. If a child's expressive skills are advanced compared with his or her receptive skills (e.g., child speaks five-word sentences but does not understand simple commands), a pervasive development disorder could be the cause.

COGNITIVE DEVELOPMENT

The concept of a developmental line implies that a child passes through successive stages. The psychoanalytic theories of Sigmund Freud and Erik Erikson and the cognitive theory of Jean Piaget describe stages in the development of cognition and emotion that are as qualitatively different as the milestones attained in gross motor development.

At the core of Freudian theory is the idea of biologically determined drives. The core drive is sexual, broadly defined to include sensations that include excitation or tension and satisfaction or release (Freud, 1952). There are discrete stages: oral, anal, oedipal, latent, and genital. During these stages the focus of the sexual drive shifts with maturation and is at first influenced primarily by the parents and subsequently by an enlarging circle of social contacts. Defense mechanisms in early childhood can develop pathologically to disguise the presence of conflict. The emotional health of the child and adult depends on the resolution of the conflicts that arise throughout these stages.

Erikson's chief contribution was to recast Freud's stages in terms of the emerging personality (Erikson, 1963). For example, basic trust, the first of Erickson's psychosocial stages, develops as infants learn that their urgent needs are met regularly. The consistent availability of a trusted adult creates the conditions for secure attachment. The next stage establishes the child's internal sense of either autonomy vs. shame and doubt and corresponds to Freud's anal stage. A sense of either identity or role confusion corresponds to the crisis experienced in Freud's genital stage (puberty) (Table 2-4).

Piaget's name is synonymous with the study of cognitive development. A central tenet of his theory is that cognition is qualitatively different at different stages of development (Hobson, 1985). During the sensorimotor stage, children learn basic things about their relationship with their environment. Thoughts about the nature of objects and their relationships are acted out and tied immediately to sensations and manipulation. With the arrival of language the nature of thinking changes dramatically, and symbols increasingly take the place of things and actions. Stages of preoperational thinking, concrete operations, and formal operations correspond to the different ages of preschool, school age, and adolescence, respectively. At all stages, children are not passive recipients of knowledge but actively seek out experience (assimilation) and use them to build on how things work.

Cognitive development and neuromaturational development are closely related, and it is sometimes difficult to distinguish between the two in the infant and child. Early in the neonatal period, cognitive development begins when the infant responds to visual and auditory stimuli by interacting with surroundings

TABLE 2-4. Classic Stage Theories of the Development of Emotion and Cognition

Theory	0-1 Years (Infancy)	2-3 Years (Toddler)	3-6 Years (Preschool)	6-12 Years (School Age)	12-20 Years (Adolescents)
Freud: psychosexual	Oral	Anal	Oedipal phallic	Latency	Puberty and genital
Erikson: psychosocial	Basic trust	Autonomy vs. shame and doubt	Initiative vs. guilt	Industry vs. inferiority	Identity vs. role confusion
Piaget: cognitive	Sensorimotor (stages I-IV)	Sensorimotor (stages V and VI) Egocentric thought	Preoperational	Concrete operational	Formal operational

to gain information. Activities such as mouthing, shaking, and banging objects provide information to the infant beyond the visual features. Infant exploration begins with the body, with activities such as staring intently at a hand and touching other body parts. These explorations represent an early discovery of "cause and effect," as the infant learns that voluntary movements generate predictable tactile and visual sensations (e.g., kicking the side of the bed moves a mobile). Signs of abnormal cognitive development are outlined in Box 2-2.

A communication system develops between the infant and mother or primary caregiver. Accordingly, the infant begins to display anxiety at the end of this developmental period if the person most familiar to the child is not available. The ability to maintain an image of a person develops before that of an object, and therefore the infant may display separation anxiety when a loved one leaves the room. Object permanence, a major milestone, develops around 9 months when the infant understands that objects continue to exist even if they are covered up and not seen. With locomotion the child explores greater areas and develops a substantial sense of social self, as well as an early appreciation of the behavior standards expected by adults. Interactive and pretend play begins at 30 months, and playing in pairs occurs around 24 to 36 months.

Childhood cognitive development and the effect it has on the child's perception of the hospitalization and surgery are important for the pediatric anesthesiologist to understand in order to help the child deal with the stresses during this time. One out of four children will be hospitalized by age 5 years. Although extreme emotional reactions are rare, at least 60% of children demonstrate signs of stress-related anxiety during the perioperative period. Children between the ages of 1 and 3 years, previously hospitalized children, and children who have undergone turbulent anesthetic inductions are at increased risk for exhibiting adverse postoperative behavioral reactions.

Box 2-2 Abnormal Cognitive Signs

1 month: Failure to be alert to environmental stimuli. May indicate sensory impairment
5 months: Failure to reach for objects. May indicate motor, visual, and/or cognitive deficit
6 months: Absent babbling. May indicate hearing deficit
7 months: Absent stranger anxiety. May be due to multiple care providers (eg, neonatal intensive care unit)
11 months: Inability to localize sound. May indicate unilateral hearing loss

(Modified from Seid M et al.: Perioperative psychosocial interventions for autistic children undergoing ENT surgery, *Int J Ped Otorhinolaryngology*, 40:107, 1997.)

Stress and anxiety can be manifested by behavioral problems such as nightmares, phobias, agitation, avoidance of caregivers, emotional distress, and regressive behaviors (e.g., temper tantrums, bedwetting, and loss of previously acquired developmental milestones). Allowing adequate preoperative evaluation and psychological preparation for both the parent and child based on specific needs relative to the child's developmental stage is a method the anesthesiologist can invoke to reduce the emotional trauma of anesthesia.

Erikson (1963) describes the infants' motivations as dependent on the satisfaction of basic human needs (e.g., food, shelter, and love). According to Freud, the child directs all of his or her energies to the mother and fears her loss because her absence may jeopardize the child's satisfaction creating tension and anxiety. This dependence is the essence of separation anxiety. Before this stage infants are able to accept surrogates and respond favorably to anyone holding them. Once stranger anxiety develops, active participation of the parents during the hospitalization should be encouraged to maintain a sense of security for the child and promote bonding (Thompson and Standford, 1981).

Toddlers have developed ambulation skills that allow exploration, but they are well bonded to their parents and much less willing to be separated, especially when they are stressed. They are too young to understand detailed explanations so procedures should be told in simple, nonthreatening language. Comprehension of conversation is more advanced than verbal expression. The receptive and expressive language discordance often results in frustration on the child's behalf, putting toddlers at increased risk for stormy inductions and postoperative emotional and behavioral reactions. Toddlers also fear pain and bodily harm. Whenever possible, a parent or trusted caregiver should be present for potentially painful or threatening procedures. Children at this age are comforted by a familiar toy or treasured object and respond to magical thinking or stories.

The preschooler's view of the world is egocentric or self-centered. The child is unable to understand or conceptualize another individual's point of view, does not comprehend why people do not understand him or her, and has no appreciation for others' feelings. These children have concerns with bodily integrity and demonstrate the need for reassurances. Anxiety can be allayed by giving the child a sense of mastery and participation, such as allowing him or her to "hold" the mask for induction. Their preoperational thinking is very literal, and it is important to use caution when using similes or metaphors, e.g., if a provider states that the child will be given a "stick" (intravenous line or shot), the child may wait to be handed a tree branch. At this stage, any explanation appears to be more important than the actual content of the explanation. Children given explanations, whether accurate or not, were found to have

fewer postoperative behavioral changes than those who were not given explanations (Bothe and Gladston, 1972). Although the preschooler's vocabulary is improving, cognitively the child may have difficulty remembering a sequence of events or establishing causality, leading to misconceptions about procedures.

School-age children, during the "concrete operations" stage, are more independent. Their activities become goal-oriented, and their language skills develop rapidly. They have a sense of conscience and can appreciate feelings of others. Children are able to draw on previous experience and knowledge to formulate predictions about related issues. They have an increased need for explanation and participation. Rather than giving children choices in the operating room (e.g., intravenous injection vs. mask for going to sleep), details about the procedure and options available for the child should be discussed preoperatively in a nonthreatening environment (McGraw, 1994).

Adolescents are caught in a difficult period between childhood and adulthood. Physically, they are maturing and may feel self-conscious about their bodies. Psychologically, they are striving to know who they are. Adolescents have developed the ability to recognize and exhibit mature defense mechanisms (e.g., the adolescent whose appendicitis "at least gets me out of my math test"). They are more likely to cooperate with a physician perceived to be attentive and nonjudgmental. Concerns regarding coping, pain, losing control, waking up prematurely, not waking up, and dying are very real for teenagers. Clear explanations and assurances should be provided regarding these issues. The need for independence and privacy is important and should be respected.

CLINICAL RELEVANCE OF GROWTH AND DEVELOPMENT IN PEDIATRIC ANESTHESIA

An overview of basic growth and development can be obtained in a preoperative consultation by reviewing the history and observing for gross and fine motor milestones during the physical examination. A 1-month-old infant displaying well-developed extensor tone when suspended in a ventral position might be interpreted by the parent as having advanced motor development when, in reality, issues of an upper motor neuron lesion should be considered. Other signs of spasticity are early rolling, pulling to a direct stand at 4 months of age, and walking on the toes. Persistent closing of fists beyond 3 months of age could be the earliest indication of neuromotor dysfunction. An afebrile 2-month-old baby with tachypnea, rales, audible murmur, and failure to gain weight should raise concerns about a significant cardiac lesion and the need for a cardiac consultation. A 7-month-old infant with poor head control who is unable to sit without support or to lift his or her chest off the table in the prone position may indicate hypotonia and a possible neuromuscular disorder. Spontaneous postures, such as "frog legging" when prone or scissoring may provide visual physical clues of hypotonia or spasticity, respectively. At 9 months of age, the child should stand erect on a parent's lap or cruise around office furniture, and the 12-month-old child will want to get down and walk. Weakness in the 3- or 4-year-old child may be best discovered by observing the quality of stationary posture and transition movements. Gower's sign (arising from sitting on the floor to standing using the hands to "walk up" the legs) is a classic example of pelvic girdle and quadriceps muscular weakness. Fine motor evaluation can be easily evaluated by handing the infant a tongue depressor or toy. The newborn infant should grasp it reflexively; by 4 months of age, the infant should reach and retain the object, and by the age of 6 months, the child can transfer an object from hand to hand. The development of fine pincer grasp by 12 months of age allows the child to pick up small objects with precision, and increases the risk for foreign body aspiration. The observation of a child who constantly uses one hand while neglecting the other should prompt the clinician to examine the contralateral upper extremity for weakness associated with hemiparesis.

Abnormal head size, significant weight gain or loss, and short-stature issues may be indicative of genetic issues. The presence of three or more dysmorphic features should raise concerns of a syndromic feature with possible difficult airway issues. Almost 75% of superficial dysmorphic features can be found by examining the head, hands, and skin.

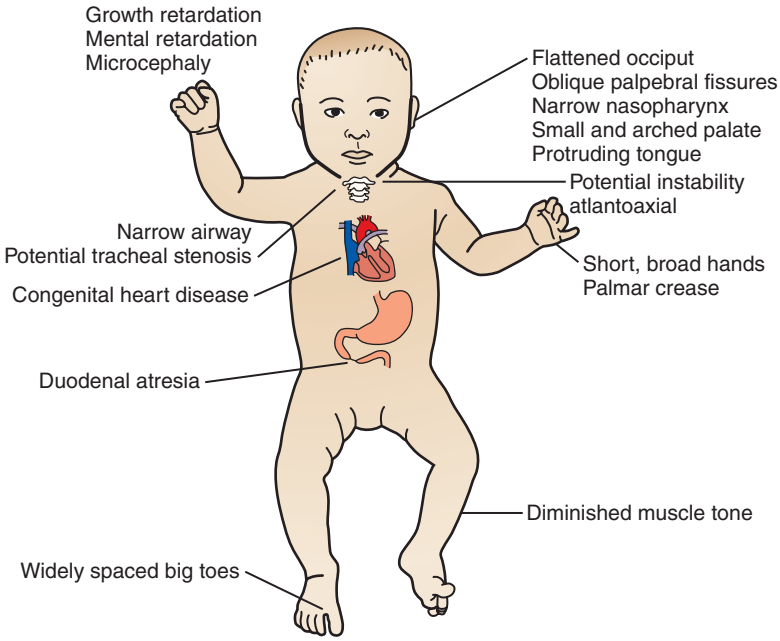
Down's Syndrome

Down's syndrome is the most common genetic abnormality worldwide, with an estimated prevalence of 1 out of 800 children (Sherman et al., 2007). Although this syndrome was described centuries earlier, Dr. John Langon Down first reported its clinical description in 1866 (Megarbane et al., 2009). Down's syndrome is the most recognizable and best known chromosomal disorder. The extra copy in chromosome 21 affects several organs and results in a wide spectrum of phenotypical changes (Hartway, 2009). Down's syndrome is usually identified soon after birth by a characteristic pattern of dysmorphic features (Fig. 2-5) (Ranweiler, 2009). The diagnosis is confirmed by karyotype analysis with trisomy 21 present in 95% of persons with this syndrome (Gardiner and Davisson, 2000).

Perioperative responsibility is shared between the anesthesiologist and the surgeon. The anesthesiologist is responsible for preoperative risk evaluation, perioperative management, and subsequent patient optimization (Hartley et al., 1998). The preoperative evaluation provides the best opportunity to stratify the potential risks, because children with Down's syndrome often have multiple congenital anomalies, each of which has anesthetic implications (Fig. 2-5) (Santamaria et al., 2007). Important considerations in the operative management of these patients include assessment of their behavioral development, atlantoaxial instability, airway narrowing, and respiratory and cardiac malformations; these are critical issues that require special attention when considering anesthesia (Bhattarai et al., 2008). Wherever possible, preoperative therapeutic interventions must be initiated to reduce the risks associated with these concurrent diseases (Borland et al., 2004). For the anesthesiologist, a system-based approach to the patient with Down's syndrome may be most useful. For a complete discussion of the anesthetic concerns related to Down's Syndrome, see Chapter 36, Systemic Disorders.

Behavioral Considerations

Down's syndrome is the most common cause of mental retardation, which is characterized by developmental delays, language and memory deficits, and other cognitive abnormalities (Roizen and Patterson, 2003). The child's cognitive state and psychological status often allow the anesthesia provider to ascertain the appropriate technique based on the child's needs.



■ **FIGURE 2-5.** The congenital anomalies of Down's syndrome. *(Modified from Ranweiler R: Assessment and care of the newborn with Down syndrome,* Adv Neonatal Care *9:17, 2009; and Santamaria LB, Di Paola C, Mafrica F, et al: Preanesthetic evaluation and assessment of children with Down's syndrome,* The Scientific World Journal *7:242, 2007.)*

Older children and young adults with Down's syndrome have a higher prevalence of early Alzheimer's disease, further impairing cognitive function (Nieuwenhuis-Mark, 2009). Interestingly, children up to 6 years of age show age-related gains in adaptive function, but older children show no correlation between age and adaptive function (Dykens et al., 2006). In addition, the incidence of seizure disorders in those with Down's syndrome is 5% to 10% (Stafstrom et al., 1991).

Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder (ADHD) is a disorder of inattention, hyperactivity, and impulsivity that affects 8% to 12% of children worldwide, with boys overrepresented by a ratio of about 3:1 (Biederman and Faraone, 2005). During child and adolescent development, ADHD is associated with greater risks for low academic achievement, poor school performance, retention in grade level, school suspensions and expulsions, poor peer and family relations, anxiety and depression, aggression, conduct problems, and delinquency (Barkley, 1997). The means of inheritance acquisition is probably multifactorial, but family, twin, and adoption studies have documented a strong genetic basis for ADHD (Thapar et al., 1999). The cellular theory suggests the frontosubcortical cerebellar regions of the brain have inadequate dopamine and noradrenaline to effectively provide inhibitory regulation (Biederman and Faraone, 2005).

Both the American Academy of Pediatrics (AAP) and the American Academy of Child and Adolescent Psychiatry (AACA) recommend psychoactive medications for children, adolescents, and adults with ADHD. These medications are classified as stimulants or nonstimulants. Perioperative consequences of these medications include resistance to premedication, cardiovascular instability, altered anesthesia requirements (monitored anesthesia care), lower seizure thresholds, and increased postoperative nausea and vomiting (Forsyth et al., 2006).

As an example of medication interaction, one patient required large doses of midazolam while receiving methylphenidate (Ririe et al., 1997). ADHD drugs are associated with increased blood pressure as a result of increased catecholamine levels, but the chronic use of stimulants can deplete these stores or downregulate catecholamine receptors. Prolonged hypotension has been reported in older patients with ADHD, and cardiac arrest (requiring cardiopulmonary resuscitation) during anesthetic induction was reported in a teenager (Bohringer et al., 2000; Perruchoud and Chollett-Rivier, 2008).

Medications such as buproprion are associated with seizures in a dose-related manner. The seizure threshold can be lowered by concomitant administration of drugs such as antipsychotics, antidepressants, systemic steroids, tramadol, and sedating antihistamines. In addition, bupropion inhibits the enzyme responsible for converting tramadol to morphine, thereby reducing the analgesic effect of tramadol (Corner et al., 2002).

These cases highlight the potential difficulties of the drug–drug interactions while a patient is undergoing general anesthesia. Based on these observations, the anesthesiologist should request more details about the medications a patient is taking for ADHD, particularly if they are stimulants or nonstimulants, and the length of time the patient has been taking the medications. As in cardiac arrest, the implications and ramifications of anesthesia can be quite significant (Tables 2-5 and 2-6) (Perruchoud and Chollett-Rivier, 2008).

Autism

Autism affects 5 to 7 in 10,000 births, is found in all racial, ethnic, and social backgrounds, and is four times more common in males than females (Rudolph and Rudolph, 2003). Current data suggest that the actual rate is 40 out of 10, 000 births and that one out of every 150 children in the United States is affected (Rutter, 2005). Autism is now recognized a psychiatric childhood disorder, and is listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) under the section of Pervasive Developmental Disorders (PDD). The diagnostic criteria for autistic disorders include qualitative impairments in social interactions, impairment in verbal and nonverbal communications, restricted range of interests, and resistance to

TABLE 2-5. The Mechanisms of Action of Commonly Used ADHD Medications

Commonly Used Drug	Mechanism of Action
Methylphenidate (Ritalin)	Blocks the reuptake of norepinephrine and dopamine Stimulates the cerebral cortex similarly to amphetamines
Dexamphetamine (Dexedrin)	Promotes the release of catecholamines through sympathomimetic amines, primarily dopamine and norepinephrine Competitively inhibits catecholamine reuptake by the presynaptic nerve terminal
Buproprion (Wellbutrin)	Inhibits the neuronal uptake of norepinephrine and dopamine
Atomoxetine, 25 mg (Strattera)	Selectively inhibits norepinephrine reuptake by the presynaptic nerve terminal

From Forsyth I et al.: Attention deficit hyperactivity disorder and anesthesia, *Paediatric anaesthesia,* 16:371, 2006.

change (APA, 2000). These children exhibit hyperactivity and patterns of behavior, activity, and interests that are restrictive, repetitive, and stereotyped.

The etiology is unknown in the vast majority of the cases. However, there is a small minority of patients with notable coexisting medical diseases, including macrocephaly (15% to 35%), seizure disorders (30%), fragile X syndrome (2% to 8%), and tuberous sclerosis (1% to 3%) (Box 2-2) (Bailey and Rutter, 1991; Williams et al., 2008).

TABLE 2-6. Possible Drug–Drug Interactions with ADHD

Potential Side Effects	Medications
Sympathomimetic drugs that may produce exaggerated cardiovascular effects	Ephedrine, tramadol, SSRIs, MAOIs, tricyclics, herbal remedies, and dietary supplements (e.g., ephedra, St. John's wort)
Stimulants with potential to increase anesthetic requirements	Methylphenidate, dexamphetamine
Stimulants with potential to exacerbate seizure activity	Tramadol, detropropoxyphene, SSRIs, tricyclics

From Forsyth I et al.: Attention deficit hyperactivity disorder and anesthesia, *Paediatric anaesthesia,* 16:371, 2006.
SSRI, Selective serotonin reuptake inhibitor; *MAOI,* monoamine oxidase inhibitor.

Children with autism can present perioperative challenges to a pediatric anesthesia team (van der Walt and Moran, 2001). They are less able to understand the need for the procedures involved in surgery and have difficulty adjusting to the new routine of the hospital visit. Their perioperative anxiety level can be very high, and it may be difficult for them to interact with strangers, even caring and attentive perioperative staff. They are more sensitive to the visual and auditory stimuli of the hospital, particularly in the operating room, and even simple tactile stimuli such as the face mask may overwhelm their senses. Overall, these children are at high risk for severe distress and anxiety; consequently, morbidity and cost may be increased, and patient and parental satisfaction may be decreased.

Premedication varies depending on the requirements of each child, as well as the preferences of the individual anesthesiologist, who might generally use oral, intramuscular, or intravenous medications. Most institutions employ oral midazolam 0.5 mg/kg; however, the side effects are unpredictable and may not allow optimal anesthetic induction (Rainey and van der Walt, 1998). Ketamine is also an effective preoperative sedative, available in intravenous, intramuscular, and oral dosing. Oral ketamine has a 17% bioavailability, compared with 93% when given intramuscularly or intravenously (Clements et al., 1982). An effective transmucosal dosing combines ketamine 3 mg/kg mixed with midazolam 0.5 mg/kg (Funk et al., 2000).

If possible, the patient should undergo conditioning to become familiar with the hospital and the upcoming procedure (Nelson and Amplo, 2009). Diminished waiting time in the preoperative area can lessen fear and stress. Short, clear commands, with empathic positive and negative reinforcements, can help guide the patient through this difficult ordeal. Anesthesia management can be optimized by judicial use of premedication and parental presence during induction. The actual administration of an adequate dose of premedication can be the biggest challenge for the anesthesiologist working with an uncooperative or frightened child with delayed cognitive abilities. A balanced approach can help minimize the use of force, which is sometimes necessary, but nonetheless upsetting to the patient, the family, and the perioperative team. A discussion regarding the potential use of restraints during the perioperative period is imperative to clearly define the caregiver's expectations regarding this treatment modality. In summary, children with autism can present perioperative challenges, but thoughtful psychosocial and medical interventions can improve patient and parent satisfaction.

For questions and answers on topics in this chapter, go to "Chapter Questions" at www.expertconsult.com.

REFERENCES

Complete references used in this text can be found online at www.expertconsult.com.

CHAPTER 3

Respiratory Physiology in Infants and Children

Etsuro K. Motoyama and Jonathan D. Finder

CONTENTS

Among many physiologic adaptations for the survival of humans at birth, cardiorespiratory adaptation is by far the most crucial. The respiratory and circulatory systems must be developed sufficiently in utero for the newborn infant to withstand drastic changes at birth—from the fetal circulatory pattern with liquid-filled lungs to air breathing with transitional circulatory adaptation in a matter of a few minutes. The newborn infant must exercise an effective neuronal drive and respiratory muscles to displace the liquid filling the airway system and to introduce sufficient air against the surface force in order to establish sufficient alveolar surface for gas exchange. At the same time, pulmonary blood vessels must dilate rapidly to increase pulmonary blood flow and to establish adequate regional alveolar ventilation/pulmonary perfusion ($\dot{V}_A/\dot{Q}_P$) for sufficient pulmonary gas exchange. The neonatal adaptation of lung mechanics and respiratory control takes several weeks to complete. Beyond this immediate neonatal period, the infant's lungs continue to mature at a rapid pace, and postnatal

development of the lungs and the thorax surrounding the lungs continues well beyond the first year of life. Respiratory function in infants and toddlers, especially during the first several months of life, as with cardiovascular system and hepatic function, is both qualitatively and quantitatively different from that in older children and adults, and so is their responses to pharmacologic agents, especially anesthetics.

This chapter reviews clinically relevant aspects of the development of the respiratory system and function in infants and children and their application to pediatric anesthesia. Such knowledge is indispensable for the proper care of infants and children before, during, and after general anesthesia and surgery, as well as for the care of those with respiratory insufficiency.

The respiratory system consists of the respiratory centers in the brainstem; the central and peripheral chemoreceptors; the phrenic, intercostal, hypoglossal (efferent), and vagal (afferent) nerves; the thorax (including the thoracic cage; the muscles of the chest, abdomen, and diaphragm); the upper (extrathoracic) and lower (intrathoracic) airways; the lungs; and the pulmonary vascular system. The principal function of the respiratory system is to maintain the oxygen and carbon dioxide (CO_2) equilibrium in the body. The lungs also make an important contribution to the regulation of acid-base (pH) balance. The maintenance of body temperature (via loss of water through the lungs) is an additional but secondary function of the lungs. The lungs are also an important organ of metabolism.

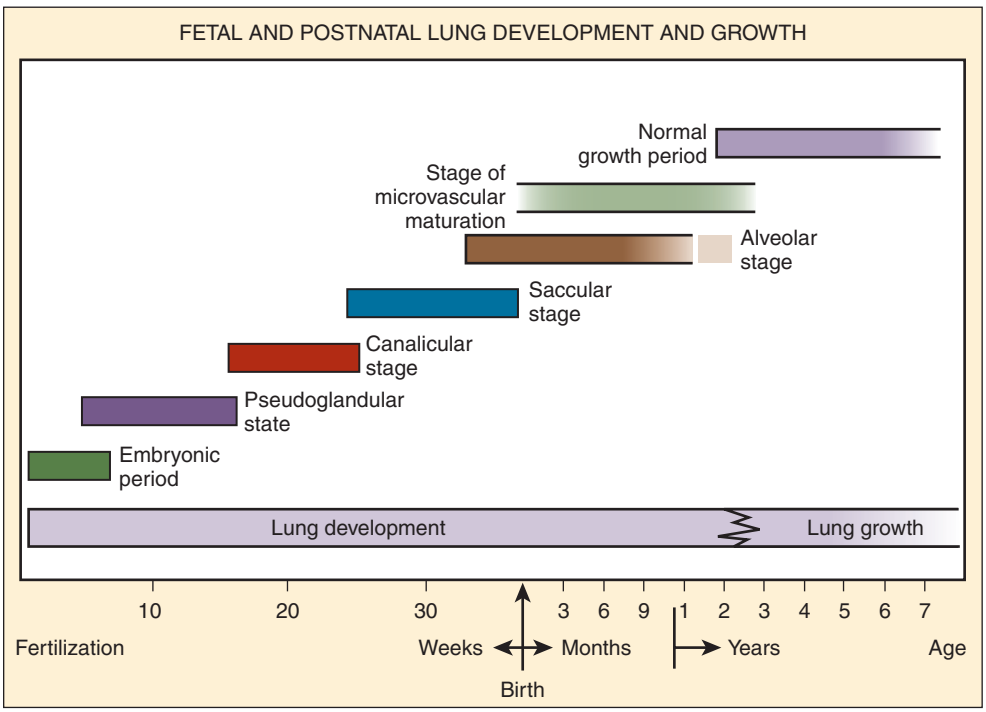
DEVELOPMENT OF THE RESPIRATORY SYSTEM

Prenatal Development of the Lungs

The morphologic development of the human lung is seen as early as several weeks into the embryonic period and continues well into the first decade of postnatal life and beyond (Fig. 3-1). The fetal lungs begin to form within the first several weeks of the embryonic period, when the fetus is merely 3 mm in length. A groove appears in the ventral aspect of the foregut, creating a small pouch. The outgrowth of the endodermal cavity, with a mass of surrounding mesenchymal tissue, projects into the pleuroperitoneal cavity and forms lung buds. The future alveolar membranes and mucous glands are derived from the endoderm, whereas the cartilage, muscle, elastic tissue, and lymph vessels originate from the mesenchymal elements surrounding the lung buds (Emery, 1969).

During the pseudoglandular period, which extends until 17 weeks' gestation, the budding of the bronchi and lung growth rapidly take place, forming a loose mass of connective tissue. The morphologic development of the human lung is illustrated in Figure 3-2. By 16 weeks' gestation, preacinar branching of the airways (down to the terminal bronchioli) is complete (Reid, 1967). A disturbance of the free expansion of the developing lung during this stage, as occurs with diaphragmatic hernia, results in hypoplasia of the airways and lung tissue (Areechon and Reid, 1963). During the canalicular period, in midgestation, the future respiratory bronchioli develop as the relative amount of connective tissue diminishes. Capillaries grow adjacent to the respiratory bronchioli, and the whole lung becomes more vascular (Emery, 1969).

At about 24 weeks' gestation, the lung enters the terminal sac period, which is characterized by the appearance of clusters of terminal air sacs, termed *saccules,* with flattened epithelium (Hislop and Reid, 1974). These saccules are large and irregular with thick septa and have few capillaries in comparison with the adult alveoli (Boyden, 1969). At about 26 to 28 weeks' gestation, proliferation of the capillary network surrounding the terminal air spaces becomes sufficient for pulmonary gas exchange (Potter, 1961). These morphologic developments may occur earlier in some premature infants (born at 24 to 25 weeks' gestation) who have survived through neonatal intensive care. Starting at 28 weeks' gestation, air space wall



■ **FIGURE 3-1.** Stages of human lung development and their timing. Note the overlap between stages, particularly between the alveolar stage and the stage of microvascular maturation. Open-ended bars indicate uncertainty as to exact timing. *(From Zeltner TB, Burri PH: The postnatal development and growth of the human lung. II. morphology,* Respir Physiol *67:269, 1987.)*

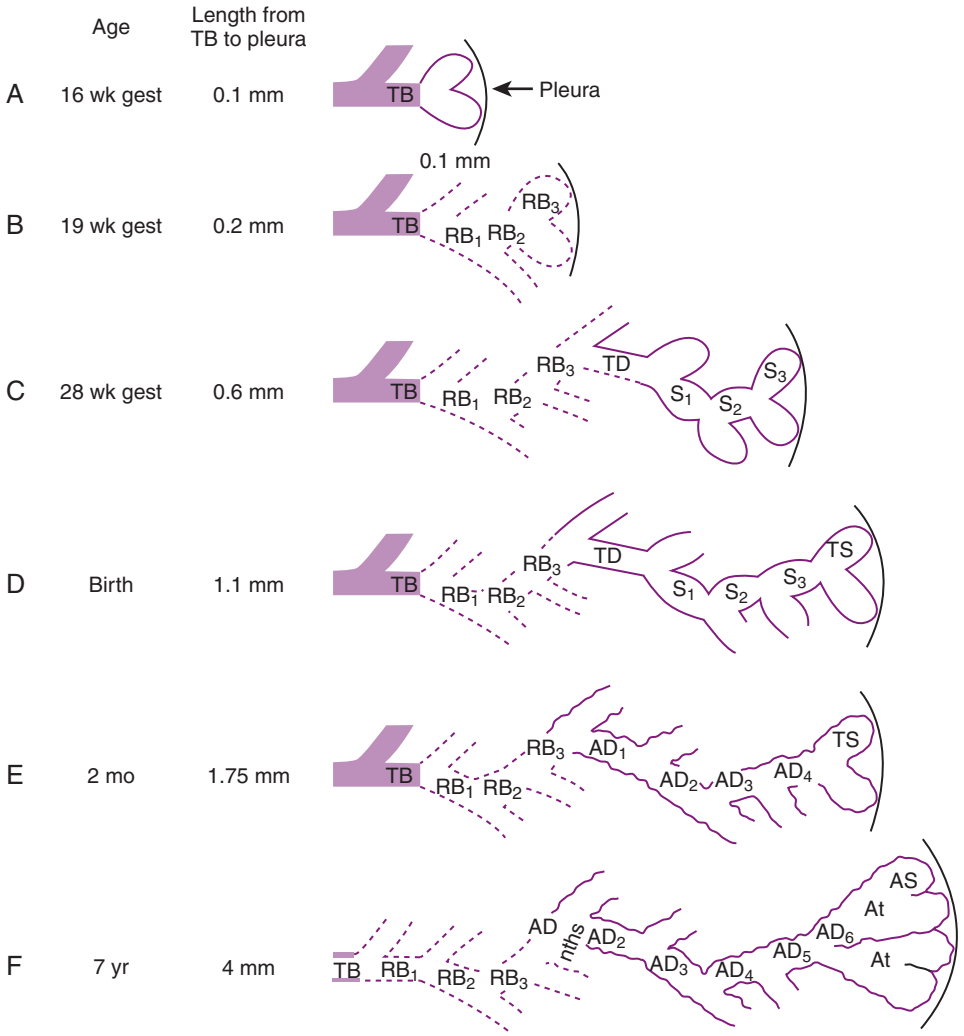


FIGURE 3-2. Development of the acinus in human lungs at various ages. *TB,* Terminal bronchiole; *RB,* respiratory bronchiole; *TD,* transitional duct; *S,* saccule; *TS,* terminal saccule; *AD,* alveolar duct; *At,* atrium; *AS,* alveolar sac, *(From Hislop A, Reid L: Development of the acinus in the human lung,* Thorax *29:90, 1974.)*

thickness decreases rapidly. From this period onward toward term, there is further lengthening of saccules with possible growth of additional generations of air spaces. Some mammalian species, such as the rat, have no mature alveoli at birth (Burri, 1974). In contrast, alveolar development from saccules begins in some human fetuses as early as 32 weeks' gestation, but alveoli are not uniformly present until 36 weeks' gestation (Langston et al., 1984). Most alveolar formation in humans takes place postnatally during the first 12 to 18 months of postnatal life, and development of respiratory bronchioles by transformation of preexisting terminal airways does not take place until after birth (Langston et al., 1984).

The fetal lung produces a large quantity of liquid, which expands the airways while the larynx is closed. This expansion produces the growth factor, such as human bombesin, and helps to stimulate lung growth and development (Sunday et al., 1988). The lung fluid is periodically expelled into the uterine cavity and contributes about one third of the total amniotic fluid. Prenatal ligation or occlusion of the trachea was tried in the 1990s with some success for the treatment of the fetus with congenital diaphragmatic hernia (Harrison et al., 1993). This treatment causes the expansion of the fetal airways and results in an accelerated growth of the otherwise hypoplastic lung.

The type II pneumocytes, which produce pulmonary surfactant that forms the alveolar lining layer, reduces surface tension and stabilizes air spaces after air breathing, appear at about 24 to 26 weeks' gestation but occasionally as early as 20 weeks (Spear et al., 1969; Lauweryns, 1970). Idiopathic (or infantile) respiratory distress syndrome (IRDS), also known as hyaline membrane disease (HMD), which occurs in premature infants, is caused by the immaturity of the lungs with their insufficient pulmonary surfactant production and their inactivation by plasma proteins exudating onto the alveolar surface (see Surface Activity and Pulmonary Surfactant).

Experimental evidence from animals indicates that certain pharmacologic agents such as cortisol and thyroxin administered to the mother or directly to the fetus accelerate the maturation of the lungs, resulting in the early appearance of type II pneumocytes and surfactant (deLemos et al., 1970; Motoyama et al., 1971; Wu et al., 1973; Smith and Bogues, 1982; Rooney, 1985). Liggins and Howie (1972) reported accelerated maturation of human fetal lungs after the administration of corticosteroids to mothers 24 to 48 hours before the delivery of premature babies. Despite initial concern that steroids might potentially be toxic to other organs of the fetus, particularly to the development of the central nervous system, prenatal glucocorticoid therapy has been used widely since the 1980s to induce lung maturation and surfactant synthesis in mothers at risk of premature delivery (Avery, 1984; Avery et al., 1986).

NEONATAL RESPIRATORY ADAPTATION

Respiratory rhythmogenesis occurs in the fetus long before partition. The clamping of the umbilical cord and increasing arterial oxygen tensions and relative hyperoxia with air breathing (but not transient hypoxia) initiate and maintain rhythmic breathing at birth.

To introduce air into the fluid-filled lungs at birth, the newborn infant must overcome large surface force with the first few breaths. Usually a negative pressure of 30 cm H_2O is necessary to introduce air into the fluid-filled lungs. In some normal full-term infants, even with sufficient surfactant, a force of as much as –70 cm H_2O or more must be exerted to overcome the surface force (Fig. 3-3) (Karlberg et al., 1962). Usually fluid is rapidly expelled via the upper airways. The residual fluid leaves the lungs through the pulmonary capillaries and lymphatic channels over the first few days of life, and changes in compliance parallel this time course. All changes are delayed in the premature infant.

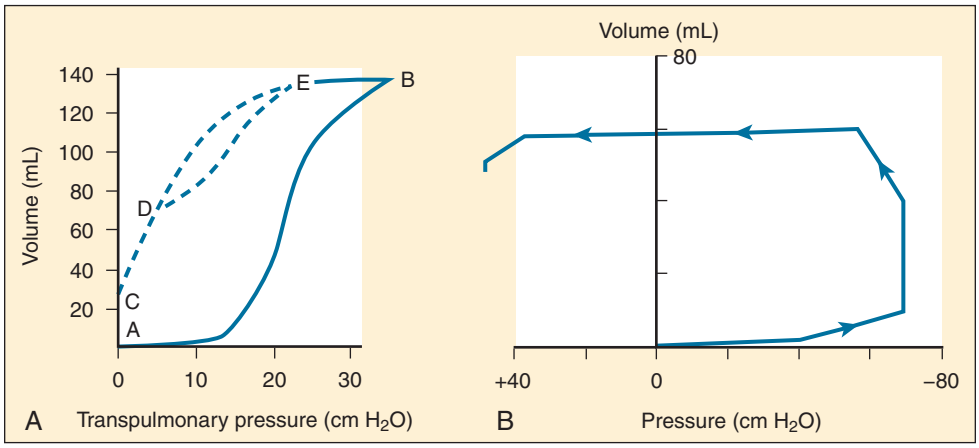
As the lungs expand with air, pulmonary vascular resistance decreases dramatically and pulmonary blood flow increases markedly, thus allowing gas exchange between alveolar air and pulmonary capillaries to occur. Changes in P_{O_2}, P_{CO_2} *(P* stands for *partial pressure),* and pH are largely responsible for the dramatic decrease in pulmonary vascular resistance (Cook et al., 1963). The resultant large increases in pulmonary blood flow and the increase in left atrial pressure with a decrease in right atrial pressure reverse the pressure gradient across the atria and close (initially functionally and eventually anatomically) the foramen ovale, a right-to-left one-way valve. With these adjustments, the cardiopulmonary system approaches adult levels of ventilation/perfusion ($\dot{V}_A/\dot{Q}$ balance within a few days (Nelson et al., 1962, 1963). The process of expansion of the lungs during the first few hours of life and the resultant circulatory adaptation for establishing pulmonary gas exchange are greatly influenced by the adequacy of pulmonary surfactant. It should be remembered that these changes are delayed in immature newborns.

Postnatal Development of the Lungs and Thorax

The development and growth of the lungs and surrounding thorax continue with amazing speed during the first year of life. Although the formation of the airway system all the way to the terminal bronchioles is complete by 16 weeks' gestation, alveolar formation begins only at about 36 weeks' gestation. At birth, the number of terminal air sacs (most of which are saccules) is between 20 and 50 million, only one tenth that of fully grown lungs of the child. Most postnatal development of alveoli from primitive saccules occurs during the first year and is essentially completed by 18 months of age (Langston et al., 1984). The morphologic and physiologic development of the lungs, however, continues throughout the first decade of life (Mansell et al., 1972).

During the early postnatal period, the lung volume of infants is disproportionately small in relation to body size. In addition, because of higher metabolic rates in infants (oxygen consumption per unit body weight is twice as high as that of adults), the ventilatory requirement per unit of lung volume in infants is markedly increased. Infants, therefore, have much less reserve of lung volume and surface area for gas exchange. This is the primary reason why infants and young children become rapidly desaturated with hypoventilation or apnea of relatively short duration.

In the neonate, static (elastic) recoil pressure of the lungs is very low (i.e., compliance, normalized for volume, is unusually high), which is not dissimilar to that of geriatric or emphysematous lungs, because the elastic fibers do not develop until the postnatal period (whereas elastic fibers in geriatric lungs are brittle and not functional) (Mansel et al., 1972; Fagan, 1976; Bryan and Wohl, 1986). In addition, the elastic recoil pressure of the infant's thorax (chest wall) is extremely low because of its compliant cartilaginous rib cage with poorly developed thoracic muscle mass, which does not add rigidity. These unique characteristics make infants more prone to lung collapse, especially under general anesthesia when inspiratory muscles are markedly relaxed (see maintenance of FRC below). Throughout



■ **FIGURE 3-3. A,** Typical pressure-volume curve of expansion of a gas-free lung. *A-B,* initial expansion. In the example, approximately 30 cm H_2O pressure will be necessary to overcome surface forces. *C,* Deflation to zero pressure with gas trapping. *D-E,* Subsequent breaths with a further increase in FRC (from *C* to *D*). **B,** Pressure-volume relationships during the first breath of a newborn weighing 4.3 kg. Here, 60 to 70 cm H_2O negative pressure was necessary to overcome the surface forces. *(From Karlberg P et al.: Respiratory studies in newborn infants. II. Pulmonary ventilation and mechanics of breathing in the first minutes of life, including the onset of respiration,* Acta Paediatr Scand *51:121, 1962.)*

infancy and childhood, static recoil pressure of the lungs and thorax steadily increases (compliance, normalized for volume, decreases) toward normal values for young adults (Zapletal et al., 1971; Motoyama, 1977).

The actual size of the airway from the larynx to the bronchioles in infants and children, of course, is much smaller than in adolescents and adults, and flow resistance in absolute terms is extremely high. When normalized for lung volume or body size, however, infants' airway size is relatively much larger; airway resistance is much lower than in adults (Polgar, 1967; Motoyama, 1977; Stocks and Godfrey, 1977). Infants and toddlers, however, are more prone to severe obstruction of the upper and lower airways because their absolute (not relative) airway diameters are much smaller than those in adults. As a consequence, relatively mild airway inflammation, edema, or secretions can lead to far greater degrees of airway obstruction than in adults (e.g., as with subglottic croup [laryngotracheobronchitis] or acute supraglottitis [epiglottitis]).

Further description on the development of the lungs and thorax and their effects on lung function, especially under general anesthesia, are described later in the chapter. Perinatal and postnatal adaptations of respiratory control are included in the following section on the control of breathing.

Prenatal Development of Breathing

Respiratory rhythmogenesis occurs long before parturition. Dawes and others (1970) were the first to demonstrate "breathing" activities with rhythmic diaphragmatic contractions in the fetal lamb. They found it to be episodic and highly variable in frequency. Boddy and Robinson (1971) recorded movement of the human fetal thorax with an ultrasound device and interpreted this as evidence of fetal breathing. Later studies have shown that during the last 10 weeks of pregnancy, fetal breathing is present approximately 30% of the time (Patrick et al., 1980). The breathing rate in the fetus at 30 to 31 weeks' gestation is higher (58 breaths/min) than that in the near-term fetus (47 breaths/min). A significant increase in fetal breathing movements occurs 2 to 3 hours after a maternal meal and is correlated with the increase in the maternal blood sugar level (Patrick et al., 1980).

Spontaneous breathing movements in the fetus occur only during active, or rapid eye movement (REM), sleep and with low-voltage electrocortical activity, and they appear to be independent of the usual chemical and nonchemical stimuli of postnatal breathing (Dawes et al., 1972; Jansen and Chernick, 1983). Later studies, however, have clearly shown that the fetus can respond to chemical stimuli known to modify breathing patterns postnatally (Dawes et al., 1982; Jansen et al., 1982; Rigatto et al., 1988, 1992). In contrast, hypoxemia in the fetus abolishes, rather than stimulates, breathing movements. This may be related to the fact that hypoxemia diminishes the incidence of REM sleep (Boddy et al., 1974). It appears that normally low arterial oxygen tension, or Pa_{O_2} (19 to 23 mm Hg), in the fetus is a normal mechanism inhibiting breathing activities in utero (Rigatto, 1992). Severe hypoxia induces gasping, which is independent of the peripheral chemoreceptors and apparently independent of rhythmic fetal breathing (Jansen and Chernick, 1974).

The near-term fetus is relatively insensitive to Pa_{CO_2} changes. Extreme hypercapnia (Pa_{CO_2} greater than 60 mm Hg) in the fetal lamb, however, can induce rhythmic breathing movement that is preceded by a sudden activation of inspiratory muscle tone with expansion of the thorax and inward movement (inspiration) of amniotic fluid, as much as 30 to 40 mL/kg (an apparent increase in functional residual capacity [FRC]) (Motoyama, unpublished observation). When Pa_{O_2} was reduced, breathing activities ceased, and there was a reversal of the sequence of events noted above (i.e., relaxation of the thorax, decreased FRC as evidenced by outward flow of amniotic fluid) (Motoyama, 2001).

The Hering-Breuer (inflation) reflex is present in the fetus. Distention of the lungs by saline infusion slows the frequency of breathing (Dawes et al., 1982). Transection of the vagi, however, does not change the breathing pattern (Dawes, 1974).

Maternal ingestion of alcoholic beverages abolishes human fetal breathing for up to 1 hour. Fetal breathing movement is also abolished by maternal cigarette smoking. These effects may be related to fetal hypoxemia resulting from changes in placental circulation Jansen and Chernick, 1983). It is not clear why the fetus must "breathe" in utero, when gas exchange is handled by the placental circulation. Dawes (1974) suggested that fetal breathing might represent "prenatal practice" to ensure that the respiratory system is well developed and ready at the moment of birth. Another reason may be that the stretching of the airways and lung parenchyma is an important stimulus for lung development; bilateral phrenic nerve sectioning in the fetal lamb results in hypoplasia of the lungs (Alcorn et al., 1980).

Perinatal Adaptation of Breathing

During normal labor and vaginal delivery, the human fetus goes through a period of transient hypoxia, hypercapnia, and acidemia. The traditional view of the mechanism of the onset of breathing at birth until the 1980s was that the transient fetal asphyxia stimulates the chemoreceptors and produces gasping, which is followed by rhythmic breathing at birth that is aided by thermal, tactile, and other sensory stimuli. Subsequent studies have challenged this concept (Chernick et al., 1975; Baier et al., 1990; Rigatto, 1992). The current concept regarding the mechanism of continuous neonatal breathing is summarized in Box 3-1.

Once the newborn has begun rhythmic breathing, ventilation is adjusted to achieve a lower Pa_{CO_2} than is found in older children and adults (Table 3-1). The reason for this difference is not clear but most likely is related to a poor buffering capacity in the neonate and a ventilatory compensation for metabolic acidosis. The Pa_{O_2} of the infant approximates the adult level within a few weeks of birth (Nelson, 1976).

Box 3-1 Mechanism of Continuous Neonatal Breathing

- The onset of breathing activities occurs not at birth but in utero, as a part of normal fetal development.
- The clamping of the umbilical cord initiates rhythmic breathing.
- Relative hyperoxia with air breathing, compared with low fetal Pa_{O_2}, augments and maintains continuous and rhythmic breathing.
- Continuous breathing is independent of the level of Pa_{CO_2}.
- Breathing is unaffected by carotid denervation.
- Hypoxia depresses or abolishes continuous breathing.

TABLE 3-1. Normal Blood-Gas Values

	Pao_2 (mm Hg)	Sao_2 (%)	$Paco_2$ (mm Hg)	pH
Pregnant woman at term	88*	96	32	7.40
Umbilical vein	31	72*	42	7.35
Umbilical artery	19	38*	51	7.29
1 hour of life (artery)	62	95	28	7.36
24 hours of life (artery)	68	94	29	7.37
Child and adult (artery)	99	97	41	7.40

*Estimated values.

Control of breathing in the neonate evolves gradually during the first month of extrauterine life and beyond and is different from that in older children and adults, especially in the response to hypoxemia and hyperoxia. The neonates' breathing patterns and responses to chemical stimuli are detailed after a general overview of the control of breathing.

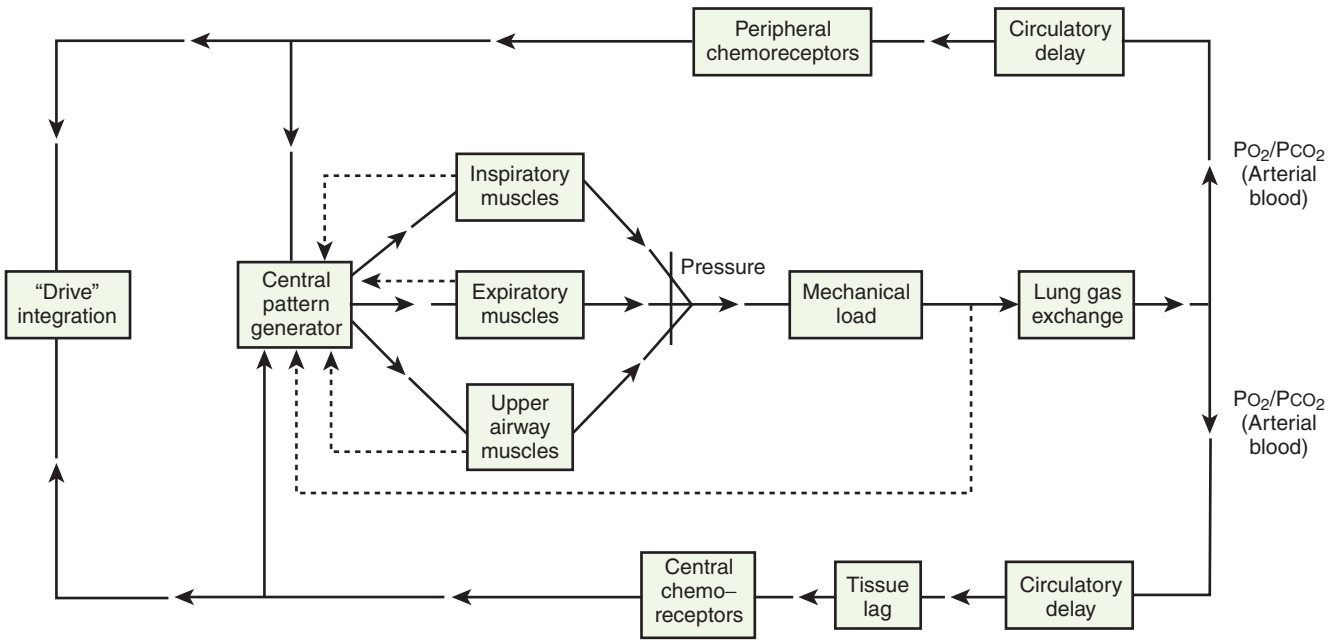
CONTROL OF BREATHING

The mechanism that regulates and maintains pulmonary gas exchange is remarkably efficient. In a normal person, the level of $Paco_2$ is maintained within a very narrow range, whereas oxygen demand and carbon dioxide production vary greatly during rest and exercise. This control is achieved by a precise matching of the level of ventilation to the output of carbon dioxide. Breathing is produced by the coordinated action of a number of inspiratory and expiratory muscles. Inspiration is produced principally by the contraction of the diaphragm, which creates negative intrathoracic pressure that draws air into the lungs. Expiration, on the other hand, is normally produced passively by the elastic recoil of the lungs and thorax. It may be increased actively by the contraction of abdominal and thoracic expiratory muscles during exercise. During the early phase of expiration, sustained contraction of the diaphragm with decreasing intensity (braking action) and the upper airway muscles' activities and narrowing of the glottic aperture impede and smoothen the rate of expiratory flow.

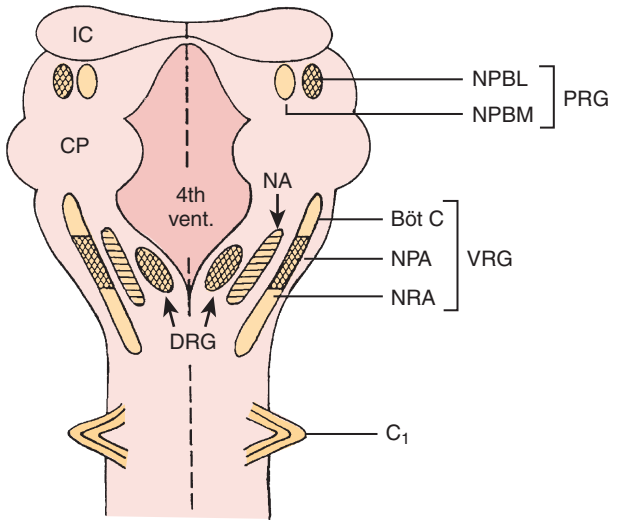
Rhythmic contraction of the respiratory muscles is governed by the respiratory centers in the brainstem and tightly regulated by feedback systems so as to match the level of ventilation to metabolic needs (Fig. 3-4) (Cherniack and Pack, 1988). These feedback mechanisms include central and peripheral chemoreceptors, stretch receptors in the airways and lung parenchyma via the vagal afferent nerves, and segmental reflexes in the spinal cord provided by muscle spindles (Cherniack and Pack, 1988). The control of breathing comprises neural and chemical controls that are closely interrelated.

Neural Control of Breathing

Respiratory neurons in the medulla have inherent rhythmicity even when they are separated from the higher levels of the



■ **FIGURE 3-4.** Block diagram of multi-input, multi-output system that controls ventilation.



■ **FIGURE 3-5.** Schematic representation of the respiratory neurons on the dorsal surface of the brainstem. Cross-hatched areas contain predominantly inspiratory neurons, blank areas contain predominantly expiratory neurons, and dashed areas contain both inspiratory and expiratory neurons. *Böt C,* Bötzinger complex; *C*$_1$ first cervical spinal nerve; *CP,* cerebellar peduncle; *DRG,* dorsal respiratory group; *4th Vent,* fourth ventricle; *IC,* inferior colliculus; *NA,* nucleus ambiguus; *NPA,* nucleus paraambigualis; *NPBL,* nucleus parabrachialis lateralis; *NPBM,* nucleus parabrachialis medialis; *NRA,* nucleus retroambigualis; *PRG,* pontine respiratory group; *VRG,* ventral respiratory group. *(From Tabatabai M, Behnia R: Neurochemical regulation of respiration. In Collins VJ, editor:* Physiological and pharmacological basis of anesthesia, *Philadelphia, 1995, Williams & Wilkins.)*

brainstem. In the cat, respiratory neurons are concentrated in two bilaterally symmetric areas in the medulla near the level of the obex. The dorsal respiratory group of neurons (DRG) is located in the dorsomedial medulla just ventrolateral to the nucleus tractus solitarius and contains predominantly inspiratory neurons. The ventral respiratory group of neurons (VRG), located in the ventrolateral medulla, consists of both inspiratory and expiratory neurons (Fig. 3-5) (von Euler, 1986; Tabatabai and Behnia, 1995; Berger, 2000).

Dorsal Respiratory Group of Neurons

The DRG is spatially associated with the tractus solitarius, which is the principal tract for the ninth and tenth cranial (glossopharyngeal and vagus) nerves. These nerves carry afferent fibers from the airways and lungs, heart, and peripheral arterial chemoreceptors. The DRG may constitute the initial intracranial site for processing some of these visceral sensory afferent inputs into a respiratory motor response (Berger, 2000).

On the basis of lung inflation, three types of neurons have been recognized in the DRG: type Iα *(I* stands for *inspiratory),* type Iβ, and pump (P) cells. Type Iα is inhibited by lung inflation (Cohen, 1981a). The axons of these neurons project to both the phrenic and the external (inspiratory) intercostal motoneurons of the spinal cord. Some type Iα neurons have medullary collaterals that terminate among the inspiratory and expiratory neurons of the ipsilateral VRG (Merrill, 1970).

The second type, Iβ, is excited by lung inflation and receives synaptic inputs from pulmonary stretch receptors. There is controversy as to whether Iβ axons project into the spinal cord respiratory neurons; the possible functional significance of such spinal projections is unknown. Both Iα and Iβ neurons receive excitatory inputs from the central pattern generator (or central inspiratory activity) for breathing, so that when lung inflation is terminated or the vagi in the neck are cut, the rhythmic firing activity of these neurons continues (Cohen, 198la, 1981b; Feldman and Speck, 1983).

The third type of neurons in the DRG receives no input from the central pattern generator. The impulse of these neurons, the P cells, closely follows lung inflation during either spontaneous or controlled ventilation (Berger, 1977). The P cells are assumed to be relay neurons for visceral afferent inputs (Berger, 2000).

The excitation of Iβ neurons by lung inflation is associated with the shortening of inspiratory duration. The Iβ neurons appear to promote inspiration-to-expiration phase-switching by inhibiting Iα neurons. This network seems to be responsible for the Hering-Breuer reflex inhibition of inspiration by lung inflation (Cohen, 198la, 1981b; von Euler, 1986, 1991).

The DRG thus functions as an important primary and possibly secondary relay site for visceral sensory inputs via glossopharyngeal and vagal afferent fibers. Because many of the inspiratory neurons in the DRG project to the contralateral spinal cord and make excitatory connections with phrenic motoneurons, the DRG serves as a source of inspiratory drive to phrenic and possibly to external intercostal motoneurons (Berger, 2000).

Ventral Respiratory Group of Neurons

The VRG extends from the rostral to the caudal end of the medulla and has three subdivisions (Fig. 3-5). The Bötzinger complex, located in the most rostral part of the medulla in the vicinity of the retrofacial nucleus, contains mostly expiratory neurons (Lipski and Merrill, 1980; Merrill et al., 1983). These neurons send inhibitory signals to DRG and VRG neurons and project into the phrenic motoneurons of the spinal cord, causing its inhibition (Bianchi and Barillot, 1982; Merrill et al., 1983). The physiologic significance of these connections may be to ensure inspiratory neuronal silence during expiration (reciprocal inhibition) and to contribute to the "inspiratory off-switch" mechanism.

The nucleus ambiguus (NA) and nucleus paraambigualis (NPA), lying side by side, occupy the middle portion of the VRG. Axons of the respiratory motoneurons originating from the NA project along with other vagal efferent fibers and innervate the laryngeal abductor (inspiratory) and adductor (expiratory) muscles via the recurrent laryngeal nerve (Barillot and Bianchi, 1971; Bastel and Lines, 1975). The NPA contains mainly inspiratory (Iγ) neurons, which respond to lung inflation in a manner similar to that of Iα neurons. The axons of these neurons project both to phrenic and external (inspiratory) intercostal motoneuron pools in the spinal cord. The nucleus retroambigualis (NRA) occupies the caudal part of the VRG and contains expiratory neurons whose axons project into the spinal motoneuron pools for the internal (expiratory) intercostal and abdominal muscles (Merrill, 1970; Miller et al., 1985).

The inspiratory neurons of the DRG send collateral fibers to the inspiratory neurons of the NPA in the VRG. These connections may provide the means for ipsilateral synchronization of the inspiratory activity between the neurons in the DRG

and those in the VRG (Merrill, 1979, 1983). Furthermore, axon collaterals of the inspiratory neurons of the NPA on one side project to the inspiratory neurons of the contralateral NPA, and vice versa. These connections may be responsible for the bilateral synchronization of the medullary inspiratory motoneuron output, as evidenced by synchronous bilateral phrenic nerve activity (Merrill, 1979, 1983).

Pontine Respiratory Group of Neurons

In the dorsolateral portion of the rostral pons, both inspiratory and expiratory neurons have been found. Inspiratory neuronal activity is concentrated ventrolaterally in the region of the nucleus parabrachialis lateralis (NPBL). The expiratory activity is centered more medially in the vicinity of the nucleus parabrachialis medialis (NPBM) (Fig. 3-5) (Cohen, 1979; Mitchell and Berger, 1981). The respiratory neurons of these nuclei are referred to as the pontine respiratory group (PRG), which was, and sometimes still is, called the pneumotaxic center, although the term is generally considered obsolete (Feldman, 1986). There are reciprocal projections between the PRG neurons and the DRG and VRG neurons in the medulla. Electrical stimulation of the PRG produces rapid breathing with premature switching of respiratory phases, whereas transaction of the brainstem at a level caudal to the PRG prolongs inspiratory time (Cohen, 1971; Feldman and Gautier, 1976). Bilateral cervical vagotomies produce a similar pattern of slow breathing with prolonged inspiratory time; a combination of PRG lesions and bilateral vagotomy in the cat results in apneusis (apnea with sustained inspiration) or apneustic breathing (slow rhythmic respiration with marked increase end inspiratory hold) (Feldman and Gaultier, 1976; Feldman, 1986). The PRG probably plays a secondary role in modifying the inspiratory off-switch mechanism (Gautier and Bertrand, 1975; von Euler and Trippenbach, 1975).

Respiratory Rhythm Generation

Rhythmic breathing in mammals can occur in the absence of feedback from peripheral receptors. Because transection of the brain rostral to the pons or high spinal transection has little effect on the respiratory pattern, respiratory rhythmogenesis apparently takes place in the brainstem. The PRG, DRG, and VRG have all been considered as possible sites of the central pattern generator, although its exact location is still unknown (Cohen, 1981b; von Euler, 1983, 1986). A study with an in vitro brainstem preparation of neonatal rats has indicated that respiratory rhythm is generated in the small area in the ventrolateral medulla just rostral to the Bötzinger complex (pre-Bötzinger complex), which contains pacemaker neurons (Smith et al., 1991).

The pre-Bötzinger complex contains a group of neurons that is responsible for respiratory rhythmogenesis (Smith et al., 1991; Pierrefiche et al., 1998; Rekling and Feldman, 1998). Although the specific cellular mechanism responsible for rhythmogenesis is not known, two possible mechanisms have been proposed (Funk and Feldman, 1995; Ramirez and Richter, 1996). One hypothesis is that the pacemaker neurons possess intrinsic properties associated with various voltage- and time-dependent ion channels that are responsible for rhythm generation. Rhythmic activity in these neurons may depend on the presence of an input system that may be necessary to maintain the neuron's membrane potential in a range in which the voltage-dependent properties of the cell's ion channels result in rhythmic behavior. The network hypothesis is the alternative model in which the interaction between the neurons produces respiratory rhythmicity, such as reciprocal inhibition between inhibitory and excitatory neurons and recurrent excitation within any population of neurons (Berger, 2000). The output of this central pattern generator is influenced by various inputs from chemoreceptors (central and peripheral), mechanoreceptors (e.g., pulmonary receptors and muscle and joint receptors), thermoreceptors (central and peripheral), nociceptors, and higher central structures (such as the PRG). The function of these inputs is to modify the breathing pattern to meet and adjust to ever-changing metabolic and behavioral needs (Smith et al., 1991).

Airway and Pulmonary Receptors

The upper airways, trachea and bronchi, lungs, and chest wall have a number of sensory receptors sensitive to mechanical and chemical stimulation. These receptors affect ventilation as well as circulatory and other nonrespiratory functions.

Upper Airway Receptors

Stimulation of receptors in the nose can produce sneezing, apnea, changes in bronchomotor tone, and the diving reflex, which involves both the respiratory and the cardiovascular systems. Stimulation of the epipharynx causes the sniffing reflex, a short, strong inspiration to bring material (mucus, foreign body) in the epipharynx into the pharynx to be swallowed or expelled. The major role of receptors in the pharynx is associated with swallowing. It involves the inhibition of breathing, closure of the larynx, and coordinated contractions of pharyngeal muscles (Widdicombe, 1985; Nishino, 1993; Sant'Ambrogio et al., 1995).

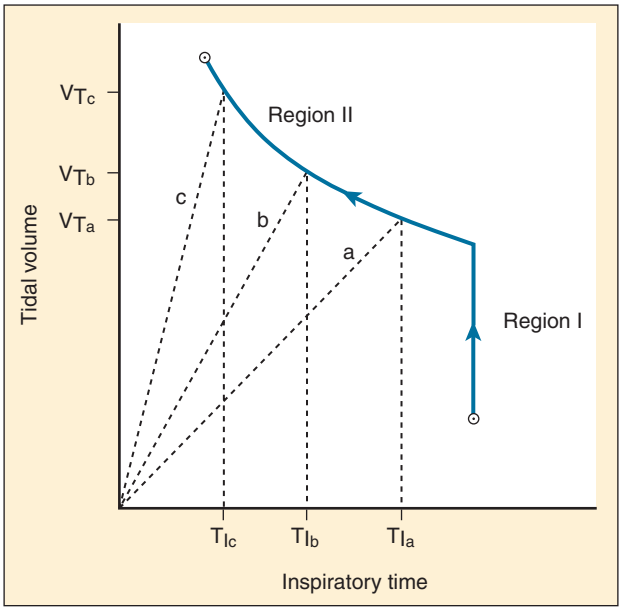
The larynx has a rich innervation of receptors. The activation of these receptors can cause apnea, coughing, and changes in the ventilatory pattern (Widdicombe, 1981, 1985). These reflexes, which influence both the patency of the upper airway and the breathing pattern, are related to transmural pressure and air flow. Based on single-fiber action-potential recordings from the superior laryngeal nerve in the spontaneously breathing dog preparation in which the upper airway is isolated from the lower airways, three types of receptors have been identified: pressure receptors (most common, about 65%), "drive" (or irritant) receptors (stimulated by upper airway muscle activities), and flow or cold receptors (Sant'Ambrogio et al., 1983; Fisher et al., 1985). The laryngeal flow receptors show inspiratory modulation with room air breathing but become silent when inspired air temperature is raised to body temperature and 100% humidity or saturation (Sant'Ambrogio et al., 1985). The activity of pressure receptors increases markedly with upper airway obstruction (Sant'Ambrogio et al., 1983).

Tracheobronchial and Pulmonary Receptors

Three major types of tracheobronchial and pulmonary receptors have been recognized: slowly adapting (pulmonary stretch) receptors and rapidly adapting (irritant or deflation) receptors, both of which lead to myelinated vagal afferent fibers and unmyelinated C-fiber endings (J-receptors). Excellent reviews on pulmonary receptors have been published (Pack, 1981; Widdicombe, 1981; Sant'Ambrogio, 1982; Coleridge and Coleridge, 1984).

Slowly adapting (pulmonary stretch) receptors. Slowly adapting (pulmonary stretch) receptors (SARs) are mechanoreceptors that lie within the submucosal smooth muscles in the membranous posterior wall of the trachea and central airways (Bartlett et al., 1976). A small proportion of the receptors are located in the extrathoracic upper trachea (Berger, 2000). SARs are activated by the distention of the airways during lung inflation and inhibit inspiratory activity (Hering-Breuer inflation reflex), whereas they show little response to steady levels of lung inflation. The Hering-Breuer reflex also produces dilation of the upper airways from the larynx to the bronchi. Although SARs are predominantly mechanoreceptors, hypocapnia stimulates their discharge, and hypercapnia inhibits it (Pack, 1981). In addition, SARs are thought to be responsible for the accelerated heart rate and systemic vasoconstriction observed with moderate lung inflation (Widdicombe, 1974). These effects are abolished by bilateral vagotomy.

Studies by Clark and von Euler (1972) have demonstrated the importance of the inflation reflex in adjusting the pattern of ventilation in the cat and the human. In cats anesthetized with pentobarbital, inspiratory time decreases as tidal volume increases with hypercapnia, indicating the presence of the inflation reflex in the normal tidal volume range. Clark and von Euler demonstrated an inverse hyperbolic relationship between the tidal volume and inspiratory time. In the adult human, inspiratory time is independent of tidal volume until the latter increases to about twice the normal tidal volume, when the inflation reflex appears (Fig. 3-6). In the newborn, particularly the premature newborn, the inflation reflex is present in the eupneic range for a few months (Olinsky et al., 1974).



■ **FIGURE 3-6.** Relationship between tidal volume *(V_T)* and inspiratory time *(T_I)* as ventilation is increased in response to respiratory stimuli. Note that in region I, Vt increases without changes in T_I. Also shown as dashed lines are the V_T trajectories for three different tidal volumes in region II. *(From Berger AJ: Control of breathing. In Murray JF, Nadel JA:* Textbook of respiratory medicine, *Philadelphia, 1994, WB Saunders.)*

Apnea, commonly observed in adult patients at the end of surgery and anesthesia with the endotracheal tube cuff still inflated, may be related to the inflation reflex, because the trachea has a high concentration of stretch receptors (Bartlett et al., 1976; Sant'Ambrogio, 1982). Deflation of the cuff promptly restores rhythmic spontaneous ventilation.

Rapidly adapting (irritant) receptors. Rapidly adapting (irritant) receptors (RARs) are located superficially within the airway epithelial cells, mostly in the region of the carina and the large bronchi (Pack, 1981; Sant'Ambrogio, 1982). RARs respond to both mechanical and chemical stimuli. In contrast to SARs, RARs adapt rapidly to large lung inflation, distortion, or deflation, thus possessing marked dynamic sensitivity (Pack, 1981). RARs are stimulated by cigarette smoke, ammonia, and other irritant gases including inhaled anesthetics, with significant interindividual variability (Sampson and Vidruk, 1975). RARs are stimulated more consistently by histamine and prostaglandins, suggesting their role in response to pathologic states (Coleridge et al., 1976; Sampson and Vidruk, 1977; Vidruk et al., 1977; Berger, 2000). The activation of RARs in the large airways may be responsible for various reflexes, including coughing, bronchoconstriction, and mucus secretion. Stimulation of RARs in the periphery of the lungs may produce hyperpnea. Because RARs are stimulated by deflation of the lungs to produce hyperpnea in animals, they are considered to play an important role in the Hering-Breuer deflation reflex (Sellick and Widdicombe, 1970). This reflex, if it exists in humans, may partly account for increased respiratory drive when the lung volume is abnormally decreased, as in premature infants with IRDS and in pneumothorax.

When vagal conduction is partially blocked by cold, inflation of the lung produces prolonged contraction of the diaphragm and deep inspiration instead of inspiratory inhibition. This reflex, the paradoxical reflex of Head, is most likely mediated by RARs. It may be related to the complementary cycle of respiration, or the sigh mechanism, that functions to reinflate and reaerate parts of the lungs that have collapsed because of increased surface force during quiet, shallow breathing (Mead and Collier, 1959). In the newborn, inflation of the lungs initiates gasping. This mechanism, which was considered to be analogous to the paradoxical reflex of Head, may help to inflate unaerated portions of the newborn lung (Cross et al., 1960).

C-Fiber endings. Most afferent axons arising from the lungs, heart, and other abdominal viscera are slow conducting (slower than 2.5 m/sec), unmyelinated vagal fibers (C-fibers). Extensive studies by Paintal (1973) have suggested the presence of receptors supposedly located near the pulmonary or capillary wall (juxtapulmonary capillary or J-receptors) innervated by such C-fibers. C-fiber endings are stimulated by pulmonary congestion, pulmonary edema, pulmonary microemboli, and irritant gases such as anesthetics. Such stimulation causes apnea followed by rapid, shallow breathing, hypotension, and bradycardia. Stimulation of J-receptors also produces bronchoconstriction and increases mucus secretion. All these responses are abolished by bilateral vagotomy. In addition, stimulation of C-fiber endings can provoke severe reflex contraction of the laryngeal muscles, which may be partly responsible for the laryngospasm observed during induction of anesthesia with isoflurane or halothane.

In addition to receptors within the lung parenchyma (pulmonary C-fiber endings), there appear to be similar

nonmyelinated nerve endings in the bronchial wall (bronchial C-fiber endings) (Coleridge and Coleridge, 1984). Both chemical and, to a lesser degree, mechanical stimuli excite these bronchial C-fiber endings. They are also stimulated by endogenous mediators of inflammation, including histamine, prostaglandins, serotonin, and bradykinin. Such stimulation may be a mechanism of C-fiber involvement in disease states such as pulmonary edema, pulmonary embolism, and asthma (Coleridge and Coleridge, 1984).

The inhalation of irritant gases or particles causes a sensation of tightness or distress in the chest, probably caused by its activation of pulmonary receptors. The pulmonary receptors may contribute to the sensation of dyspnea in lung congestion, atelectasis, and pulmonary edema. Bilateral vagal blockade in patients with lung disease abolished dyspneic sensation and increased breath-holding time (Noble et al., 1970).

Chest-Wall Receptors

The chest-wall muscles, including the diaphragm and the intercostal muscles, contain various types of receptors that can produce respiratory reflexes. This subject has been reviewed extensively (Newsom-Davis, 1974; Duron, 1981). The two types of receptors that have been most extensively studied are muscle spindles, which lie parallel to the extrafusal muscle fibers, and the Golgi tendon organs, which lie in series with the muscle fibers (Berger, 2000).

Muscle spindles are a type of slowly adapting mechanoreceptors that detect muscle stretch. As in other skeletal muscles, the muscle spindles of respiratory muscles are innervated by γ-motoneurons that excite intrafusal fibers of the spindle.

Intercostal muscles have a density of muscle spindles comparable with those of other skeletal muscles. The arrangement of muscle spindles is appropriate for the respiratory muscle load-compensation mechanism (Berger, 2000). By comparison with the intercostal muscles, the diaphragm has a very low density of muscle spindles and is poorly innervated by the γ-motoneurons. Reflex excitation of the diaphragm, however, can be achieved via proprioceptive excitation within the intercostal system (Decima and von Euler, 1969).

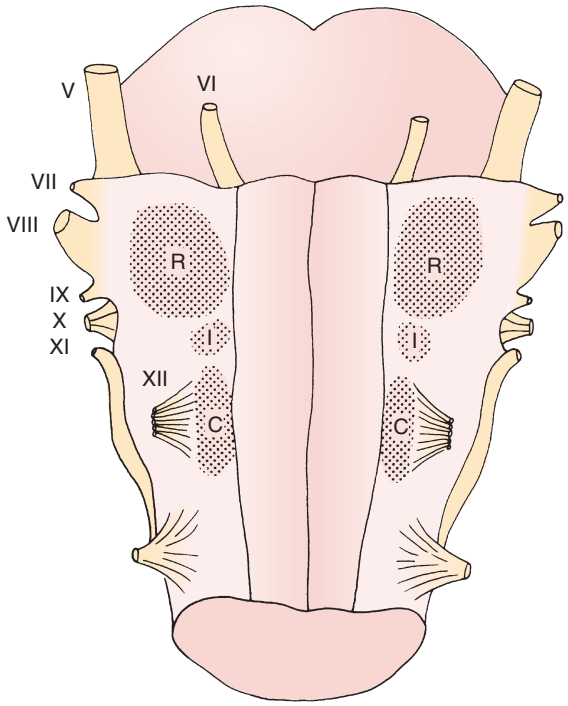
Golgi tendon organs are located at the point of insertion of the muscle fiber into its tendon and, like muscle spindles, are a slowly adapting mechanoreceptor. Activation of the Golgi tendon organs inhibits the homonymous motoneurons, possibly preventing the muscle from being overloaded (Berger, 2000). In the intercostal muscles, fewer Golgi tendon organs are present than muscle spindles, whereas the ratio is reversed in the diaphragm.

Chemical Control of Breathing

Regulation of alveolar ventilation and maintenance of normal arterial P_{CO_2}, pH, and P_{O_2} are the principal functions of the medullary and peripheral chemoreceptors (Leusen, 1972).

Central Chemoreceptors

The medullary, or central, chemoreceptors, located near the surface of the ventrolateral medulla, are anatomically separated from the medullary respiratory center (Fig. 3-7). They respond to changes in hydrogen ion concentration in the adjacent cerebrospinal fluid rather than to changes in arterial P_{CO_2} or pH (Pappenheimer et al., 1965). Since CO_2 rapidly passes through the blood-brain barrier into the cerebrospinal fluid, which has poor buffering capacity, the medullary chemoreceptors are readily stimulated by respiratory acidemia. In contrast, ventilatory responses of the medullary chemoreceptors to acute metabolic acidemia and alkalemia are limited because changes in the hydrogen ion concentration in arterial blood are not rapidly transmitted to the cerebrospinal fluid. In chronic acid-base disturbances, the pH of cerebrospinal fluid (and presumably that of interstitial fluid) surrounding the medullary chemoreceptors is generally maintained close to the normal value of about 7.3 regardless of arterial pH (Mitchell et al., 1965). Under these circumstances, ventilation becomes more dependent on the hypoxic response of peripheral chemoreceptors.



■ **FIGURE 3-7.** View of the ventral surface of the medulla shows the chemosensitive zones. The rostral *(R)* and caudal *(C)* zones are chemosensitive. The intermediate *(I)* zone is not chemosensitive but may have a function in the overall central chemosensory response. The roman numerals indicate the cranial nerves. *(From Berger AJ, Hornbein TF: Control of respiration. In Patton HD et al., editors:* Textbook of physiology, *ed 21, Philadelphia, 1989, WB Saunders.)*

Peripheral Chemoreceptors

The carotid bodies, located near the bifurcation of the common carotid artery, react rapidly to changes in P_{aO_2} and pH. Their contribution to the respiratory drive amounts to about 15% of resting ventilation (Severinghaus, 1972). The carotid body has three types of neural components: type I (glomus) cells, presumably the primary site of chemotransduction; type II (sheath) cells; and sensory nerve fibers (McDonald, 1981). Sensory nerve fibers originate from terminals in apposition to the glomus cells, travel via the carotid sinus nerve to join the glossopharyngeal nerve, and then enter the brainstem. The sheath cells envelop both the glomus cells and the sensory nerve terminals.