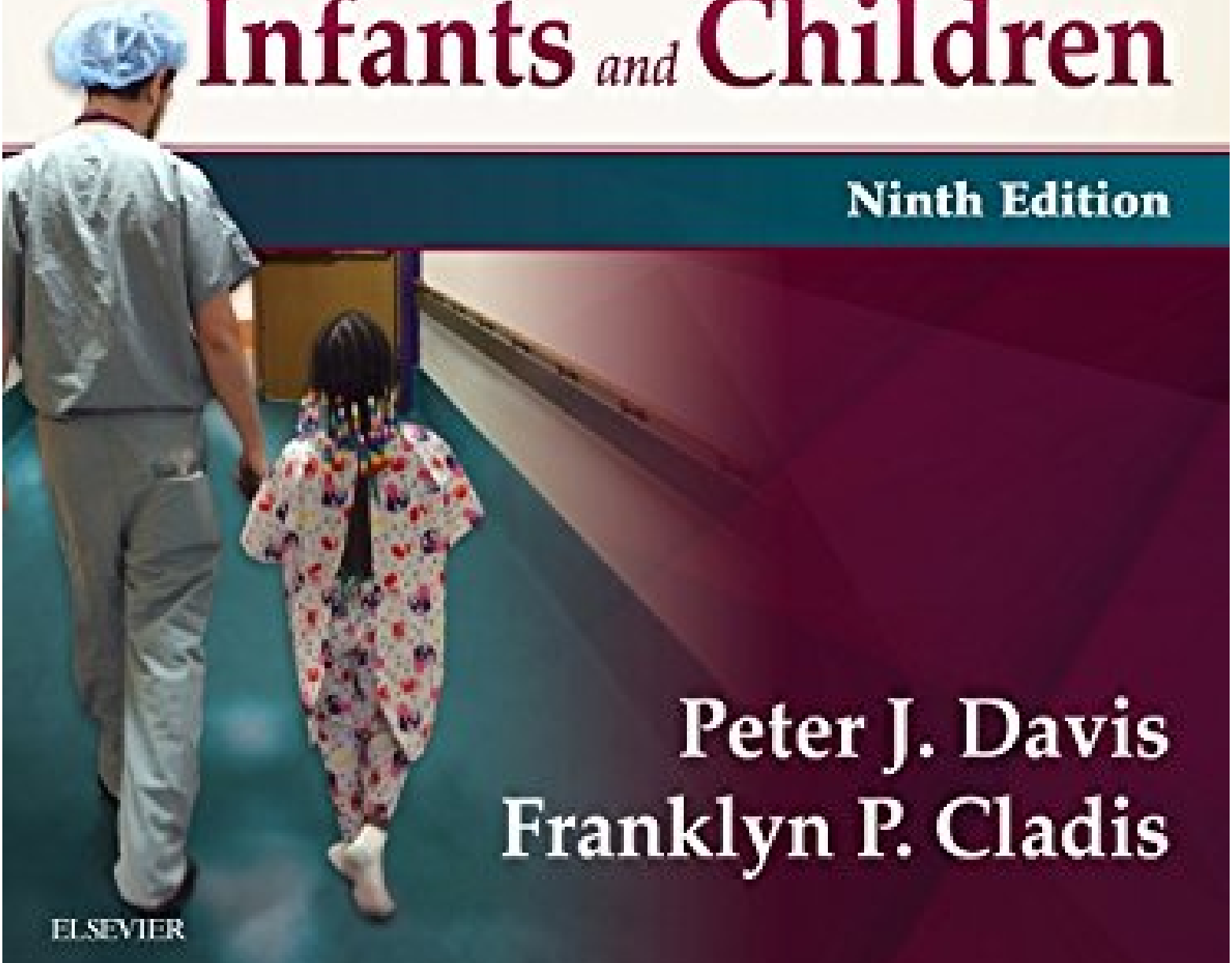
Smith's

Anesthesia for Infants and Children

Ninth Edition



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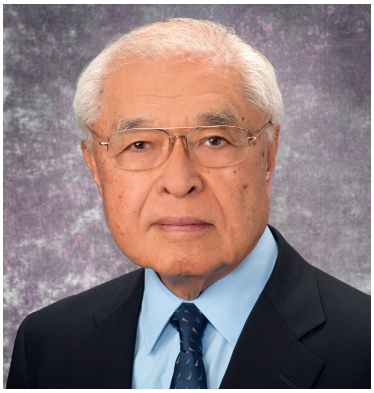

This ninth edition of *Smith's Anesthesia for Infants and Children* is dedicated to Dr. Etsuro K. Motoyama, an academician, researcher, clinician, and mentor. Dr. Motoyama graduated from Chiba University School of Medicine in Japan and completed his anesthesia residency at the Graduate Hospital of the University of Pennsylvania. Dr. Motoyama was a fellow in pediatric anesthesia at the Boston Children's Hospital where he was mentored by Dr. Smith and eventually became his protégé. In addition to clinical training, Dr. Motoyama was also a research fellow in respiratory physiology, studying with Dr. Charles D. Cook at the Harvard Medical School.

Dr. Motoyama's success and academic advancements have been at the Yale School of Medicine and the University of Pittsburgh School of Medicine. He has also received adjunct professor appointments in Japan at the Keio University School of Medicine, Kobe University School of Medicine, and the National Center for Child Health and Development in Tokyo. Among his accomplishments, Dr. Motoyama has helped to pioneer the fields of both pediatric anesthesia and pediatric pulmonology. His basic science research, supported by multiple National Institutes of Health research grants, has been on pulmonary surfactant and bronchopulmonary dysplasia. His clinical research areas have involved (1) the effects of medical preoperative stabilization on outcomes of neonates with congenital diaphragmatic hernia, (2) the differential sensitivity of halothane on airway and thoracic respiratory muscles as a cause of airway obstruction in infants, (3) the effects of anesthesia on FRC, atelectasis, and PEEP, and (4) the longitudinal pulmonary function changes in patients with bronchopulmonary dysplasia and congenital diaphragmatic hernia and in children with early onset scoliosis undergoing repetitive VEPTR thoracoplasties. The ability to perform these pulmonary function studies was made possible by Dr. Motoyama's creation of a specialized device that allowed the patients to be studied while under general anesthesia. His basic science and clinical research contributions have shaped the landscape of pediatric anesthesia, pediatric medicine, and pediatric surgery.

Though currently a Professor Emeritus at the University of Pittsburgh, Dr. Motoyama is still actively engaged in improving the lives of children by providing anesthesia services to pediatric patients in underdeveloped countries. The legacy and spirit of *Smith's Anesthesia for Infants and Children* was maintained when Dr. Smith passed on the responsibilities of the book's editorship to Dr. Motoyama, who edited and co-edited the book's fifth through eighth editions. Though Dr. Motoyama has stepped down from the editorial role in the present edition, the legacies of Drs. Smith and Motoyama continue in the current edition of the book. Through his scientific contributions to the field of pediatric anesthesia as well as through his continued clinical involvement, Dr. Motoyama continues to positively impact the lives of children throughout the world.

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PREFACE

Dr. Robert Smith, a distinguished pioneer in pediatric anesthesia and a great teacher and clinician, wrote the first edition of this book in 1959, a book subsequently referred to as "the bible" of pediatric anesthesia. The forward to the first edition was written by the famous pediatric surgeon Robert E Gross, the William E. Ladd professor of Children's Surgery at the Harvard Medical School. Though his words in the forward were written over 50 years ago, at a time when the specialty of pediatric anesthesia and surgery was in its infant stages, his words and ideas are still poignant and insightful today.

> *During the past decade surgery has made important strides in providing safer and improved methods for handling various problems in infancy and childhood, indeed now making it possible to correct some conditions which were previously thought to be entirely hopeless. Many factors have contributed to these dramatic advances in pediatric surgery. Outstanding among them is the work of anesthesiologists who have focused on the field and have provided well standardized procedures for carrying small and critically ill patients through operations on literally all portions and every system of the body. The surgeon realizes that his chances for success or failure are determined in great measure by the capabilities of the person at the head of the table who is administering the anesthetic.*
>
> *In some medical circles, there seems to be an attitude that the surgical operator is managing the show; in others, the anesthetist has an overly possessive feeling toward the patient. Neither approach is proper. It is best for each to be cognizant of his own problems and also to know of the other's difficulties; both must work together for total care of the patient. Certainly this is the most pleasant way to work, and surely it is the most effective way to conduct a child through a surgical ordeal.*

Since the initial printing of this textbook in 1959, the book has been markedly transformed in its content and in its appearance. The book has gone from mainly a single- to a multi-author book and from a 400-page 7" by 10" book to a 1400-page 11.5" by 8.5" text. As learning styles have changed, so has the format of this book. The book uses multimedia presentations to supplement, emphasize, and reinforce concepts of pediatric anesthesia. However, even with the increases in page number, new information, and media platforms, the basic tenets of anesthesia care and patient compassion, the legacy and tradition of the of the eight previous editions, have been retained.

The ninth edition has been prepared with the same considerations as the previous editions: to give anesthesiology care providers comprehensive coverage of physiology, pharmacology, and clinical anesthetic management of infants and children of all ages. The ninth edition has been reorganized into six main sections. Part I, Basic Physiology and Principles, contains updated chapters on behavioral development and respiratory, cardiovascular, renal, and thermal physiology. The pharmacology chapter in the previous editions has been expanded into its own section. This new Part II, Pharmacology, now has additional authors and specific chapters in developmental pharmacology, intravenous anesthetic agents, inhaled anesthetic agents, opioids, local anesthetic agents, neuromuscular blocking agents, and anesthetic adjuncts. Part III, General Approach, addresses the basic concepts of caring for children as well as the principles involved in the administration of anesthetics to children. The chapters have all been updated. The chapter on regional anesthesia has new authorship and, with the advent of ultrasound guidance and increased popularity in the use of regional anesthesia in infants and children, the reader will be able to access video demonstrations of specific regional anesthetic techniques in children. Part IV, Clinical Management of Specialized Surgical Problems, contains new material written by new authors. The previous edition chapter of Anesthesia for General Abdominal, Thoracic, Urological, and Bariatric Surgery has now been divided into separate chapters to better organize the material. New chapters on sedation and anesthesia for surgical missions have been added. The use of video has been maintained to further supplement the clinical material. The chapter on Neonatology for the Anesthesiologist has been revised into a comprehensive work that updates the anesthesia provider with perinatal outcome data as well as serves as a primer for pediatric anesthesiologists to better understand the pathophysiology of prematurity and the developmental physiology that occur with neonatal growth. This chapter also serves as a rich resource for the chapters on Anesthesia for Fetal Surgery and Anesthesia for General Surgery in Neonates.

In view of the significant number of disorders that pediatric anesthesiologists are confronted with in the everyday care of their patients, Part V, Systemic Disorders and Associated Problems, was created to better organize and provide information for both unusual patient diseases and to address everyday common perioperative anesthetic concerns. Three chapters on obesity, uncommon diseases, and dermatology for the anesthesiologist are new additions to the book. The chapter on dermatology has an extensive number of figures (both in the book and online) of lesions and rashes that anesthesiologists frequently encounter. Part VI, Critical Care in Pediatric Anesthesia, contains revised chapters on critical care medicine, cardiac intensive care, medicolegal and ethical issues, history

of pediatric anesthesia, and cardiopulmonary resuscitation. The CPR chapter contains the latest (2015) recommendations from the American Heart Association. Part VI also includes new chapters on statistics, safety and patient outcomes, and cardiac intensive care.

In keeping with advancements in technology, this edition is in color, and text material is further supplemented by a website. Videos of airway techniques, single-lung isolation, regional anesthesia, the use of ultrasound, and anatomic dissections 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 remain available.

The appendices, which can be found online at 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.

Finally, this edition, like the last edition, also includes online multiple-choice questions with answers and explanations. As with any learning process, it is important for the reader to have some method to affirm that they understood the salient features and to reinforce the learning process. Most chapters have associated questions to aid the reader in understanding of the material

In summary, considerable developments and progress in the practice of pediatric anesthesia are reflected in this new edition. The emphasis on the safety and well-being of young patients during the perianesthetic period remains unchanged—just as Dr Smith would have wanted.

Peter J. Davis, MD, FAAP
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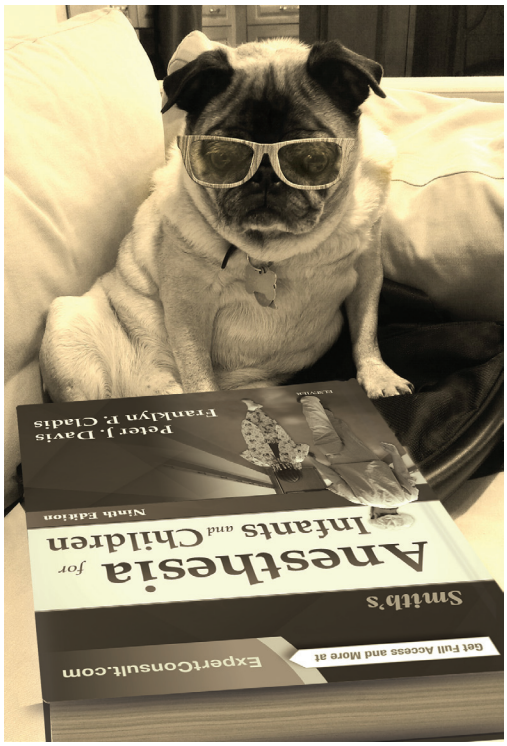

ACKNOWLEDGMENTS

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 2011 and to evaluate their effects on clinical practice has been rewarding. As always, we are deeply indebted to the extraordinary work done and commitment made by Dr. Robert M. Smith in the first four editions that made *Anesthesia for Infants and Children* a classic textbook in pediatric anesthesia.

Our ability to maintain this book's standard of excellence is not just a reflection of the many gifted contributors but 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 for their support and tolerance.

Our special thanks go to Joy Holden 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 Kellie Heap and William Schmitt, Content Strategists; Margaret Nelson, Senior Content Development Specialist; and Clay Broeker, Book Production Specialist, for their editorial assistance.

As with the previous editions, we are deeply indebted to our family members Katie, Evan, Zara, Will, and Hunter Davis; Julie, Andy, and Mugsy Peet Potash; 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. Finally, we are indebted to our patients, who grant us the privilege to care and learn from them as well as keep us humble.

Peter J. Davis, MD, FAAP
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VIDEO CONTENTS

1

Special Characteristics of Pediatric Anesthesia

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

OUTLINE

INTRODUCTION

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 58, "History of Pediatric Anesthesia," updated by Mark A. 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 surgeons resisted its use.

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 58, "History of Pediatric Anesthesia" and Fig. 58-4) remained the standard monitoring device for infants and children until the late 1970s, when automated blood pressure devices began to replace them.

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 Chapter 16, "Equipment," Chapter 17, "Pediatric Anesthesia Monitoring," and Chapter 57, "Safety and Outcome in Pediatric Anesthesia") (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 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

[†]Deceased.

hypothermia, and moving patients (Malviya et al. 2000, Hay et al. 2002, Irita et al. 2003).

Trending of hemoglobin (Hgb) can also be performed with oximetry. Noninvasive pulse co-oximetry (SpHb) has been used in both children and neonates to measure SpHb. Pulse co-oximetry uses pulse oximeter technology that involves sensors with light-emitting diodes of many wavelengths. Patino and colleagues (2014) demonstrated in children undergoing major surgical procedures with anticipated substantial blood loss that SpHb followed the trend in invasively measured Hgb with respect to bias and precision and that the trend accuracy was better than the absolute accuracy. In both term and preterm neonates who weighed less than 3000 grams at birth, Nicholas and colleagues (2015) noted a good agreement between the noninvasive SpHb and the invasive Hgb.

Monitoring of cerebral function and blood flow, as well as infrared brain oximetry, has 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 of age is limited.

More recently, interest has developed in the use of noninvasive monitors to assess fluid responsiveness. Static variables (central venous pressure, pulmonary artery wedge pressure, and left ventricle area) are not reliable predictors of fluid responsiveness. Dynamic indicators that are based on cardiopulmonary interactions in mechanically ventilated patients, such as aortic peak velocity, systolic blood pressure variation (SPV), pulse pressure variation (PPV), and pleth variability index (PVI), have been shown to be predictive in adults. In children, the results of studies involving dynamic variables have been mixed, but it appears that aortic peak velocity is a reliable indicator of fluid responsiveness (Marik et al. 2009, Feldman et al. 2012, Byon et al. 2013, Gan et al. 2013, Pinsky 2014, Nicholas et al. 2015).

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 appropriate administration of prophylactic antibiotics, have now become major priorities for health care systems. World Health Organization (WHO) checklists are 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 1 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 Part II, "Pharmacology"; Chapter 19, "Induction, Maintenance, and Recovery"; and Chapter 42, "Anesthesia for Same-Day Surgery"). 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. 1999a, 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 anesthetic 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 for 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).

Dexmedetomidine is an α_1-adrenergic agonist approved for use as a sedation agent for adult ICU patients (Mason and Lerman 2011). In pediatrics, off-label use of dexmedetomidine is common and has been used in the settings of procedural sedation and ICU sedation. It also has been administered as an adjunct to general anesthesia in order to decrease both opioid and inhalational anesthetic requirements. It has been used to treat junctional ectopic tachycardia in pediatric cardiac patients and has been used successfully for both prophylaxis and treatment of emergence agitation in postoperative surgical patients (Erdil et al. 2009, Jooste et al. 2010, Gupta et al. 2013, Sun et al. 2014). In order to attenuate the biphasic hemodynamic response of dexmedetomidine, the package insert recommends infusing the drug over 10 minutes. However, studies involving rapid bolus administration (less than 3 seconds) of dexmedetomidine in both healthy children and children who had received a heart transplant had minimal clinical significance (Jooste et al. 2010, Hauber et al. 2015).

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 opioid (Davis et al. 1999b, 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 Part II, "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, it 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 Chapter 16, "Equipment" and Chapter 18, "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 2,246 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 for postextubation stridor (4.4% vs. 4.7%) but did reduce the need for ETT exchanges (2.1% vs. 30.8%), thereby reducing the possibility of additional trauma from multiple intubation attempts.

There has been a gradual but steady trend over the last decade toward the routine and exclusive use of cuffed ETTs in pediatric anesthesia including infants (Dullenkopf et al. 2005, Weiss et al. 2009, Litman and Maxwell, 2013, Tobias 2015). Murat (2001) was first to propose the use of cuffed ETTs exclusively for children of all ages with the record of no complications without using uncuffed ETTs for a three-year span in a major children's hospital in Paris. The change in practice of not using uncuffed ETT is due to the recognition that the shape of the glottic opening at the cricoid ring, the narrowest fixed diameter in the upper airways, is more elliptic in shape than circular with a larger anteroposterior (AP) diameter and a narrower transverse diameter (Litman and Maxwell 2013, Dalal et al. 2009). These findings mean that the most appropriate-sized uncuffed ETT (<20 cm H_2O leak pressure) would compress the lateral wall mucosa of the cricoid, causing ischemia even while there are enough anteroposterior spaces left for air leaks (Motoyama, 2009). A recently developed thin-walled (with smaller outer diameter), cuffed endotracheal tube specifically designed for pediatric anesthesia (Microcuff by Kimberly-Clark) has two major modifications: the cuff is made of ultrathin polyurethane, allowing a more effective tracheal seal at a much lower pressure than the pressure known to cause tracheal mucosal necrosis, and the short cuff is located more distally near the tip of the endotracheal tube shaft, allowing more reliable placement of the cuff below the nondistensible cricoid ring, as well as reducing the chance of endobronchial intubation (Dullenkopf et al. 2005, Litman and Maxwell 2013). Whether the new, more costly endotracheal tube actually reduces the incidence of intubation-related airway injury is being investigated.

A main concern with cuffed endotracheal tubes relates to excessive pressure in the cuff. The exact pressure a cuff needs to exert against the wall of the tracheal mucosae to induce ischemia is not known; recommendations range from 20 to 30 cm H_2O. In an observation trial of 200 pediatric patients, Tobias and colleagues (2012) noted that when cuff pressures were measured, 23.5% of the patients had pressures greater than 30. Various devices have been prepared to monitor intracuff pressure (Ramesh et al. 2014, Krishna et al. 2014, Tobias 2015, Kako et al. 2015). The role of cuffed ETTs in neonates and infants who require prolonged ventilation has yet to be determined (Sathyamoorthy et al. 2015).

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 (Lippmann et al. 1976). Thus, in the past, neonates undergoing surgery were often not afforded the benefits of anesthesia.

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

ID	Tracheal Tube Brand	2.5	3	3.5	4	4.5	5	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	7.6
	Mallinckrodt TT High-Contour Murphy P-Series	NA	4.3	5	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	5.6	6.2	7	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	7.6
	Rüsch Ruschelit Super Safety Clear Magill	4	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
	Halyard Microcuff (formerly Kimberly-Clark Healthcare)	NA	4.3	5.0	5.6	6.3	6.7	7.3

ID, Inner diameter; *OD,* outer diameter.
Modified from Weiss M, Dullenkopf A, Gysini C, et al: Shortcomings of cuffed paediatric tracheal tubes, *Br J Anaesth* 2004;92:78–88.

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 have been raised regarding the neurotoxic effects of both intravenous and inhalational anesthetic agents (GABAminergic and NMDA antagonists). 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, Rappaport et al. 2015). Early work by Uemura and coworkers (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.

Neuroapoptotic changes in nonhuman primates (rhesus monkeys) exposed to ketamine (an NMDA antagonist) also occur. As with the rodents, ketamine exposure in monkeys resulted in long-lasting deficits in brain function (Paule et al. 2011). How these animal studies relate to human findings is unclear. However, a number of clinical studies have been reported, and all 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 disabilities, compared with children exposed to one anesthetic or none at all. Kalkman and coworkers (2009) studied a group of children undergoing urologic surgery before 6 years of age and reported that there was a tendency for parents to report more behavioral disturbances than those operated on at a later age. In a group of children anesthetized before 3 years of age, Ing and colleagues (2012) noted an association of anesthesia and neuropsychological outcome and that the deficits in language and abstract reasoning were also present at 10 years of age (Ing et al. 2012). However, not all studies have demonstrated an association of anesthesia with neurocognitive deficits. 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 a cohort of children anesthetized *after* 3 years of age, Ing and associates (2014) noted that language and cognitive function testing were not affected, compared with a control population of children not exposed to anesthetic. Ing and colleagues have noted variations in results that have also been shown to be a function of the outcome measure that was studied (Ing et al. 2014). In an effort to determine the impact of anesthetic agents on neurocognitive development, a collaborative partnership between the U.S. Food and Drug Administration (FDA) and the International Anesthesia Research Society created SmartTots, a program designed to fund and promote research in this area. A recent publication from this collaboration has been the randomized, prospective study that compared neurodevelopmental outcome of infants undergoing either general anesthesia or spinal anesthesia. In infants operated on before 1 year of age and evaluated at 2 years of age, Davidson and colleagues (2016) reported no difference in adverse neurodevelopmental outcomes between the two groups.

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 are 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 Chapter 21, "Pain Management," and Chapter 22, "Regional Anesthesia") (Ansermino et al. 2003, de Beer and Thomas 2003, Walker and Yaksh 2012).

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 22, "Regional Anesthesia") (Boretsky et al. 2013, Visoiu et al. 2014, Hall-Burton and Boretsky 2014, Suresh et al. 2015, Long et al. 2014). The use of ultrasound has allowed for the administration of smaller volumes of local anesthetic and for more accurate placement of the local anesthetic (Willschke et al. 2006, Gurnaney et al. 2007, Ganesh et al. 2009). 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, Gurnaney et al. 2014, Visoiu et al. 2014). The use of these at-home catheters has allowed for shorter hospital stays.

As pediatric regional anesthesia becomes more prevalent, the ability to collect data, audit practice patterns, and report on complications in infants and children undergoing regional anesthesia becomes essential to improving care for children. In this context, the Pediatric Regional Anesthesia Network (PRAN) was formed (Polaner et al. 2012, Long et al. 2014, Taenzer et al. 2014, Suresh et al. 2015).

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 of age, 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 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 Chapter 2, "Behavioral Development" and Chapter 14, "Psychological Aspects of Pediatric Anesthesia").

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 14, "Psychological Aspects of Pediatric Anesthesia") (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, is important (Table 1-2). Anesthesiologists must also be open to new ideas regarding the role of family-centered care, specifically in regard to pediatric patients with psychiatric diagnoses or special needs who may benefit from the presence of service animals. Ambardekar and colleagues (2013) reported on the use of a service animal to help with the induction of anesthesia.

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 Part II, "Pharmacology."

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

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

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.

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 (BSA) 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 the adult size in BSA and of adult size in weight (Fig. 1-1). Of these body measurements, BSA is probably the most important, because it

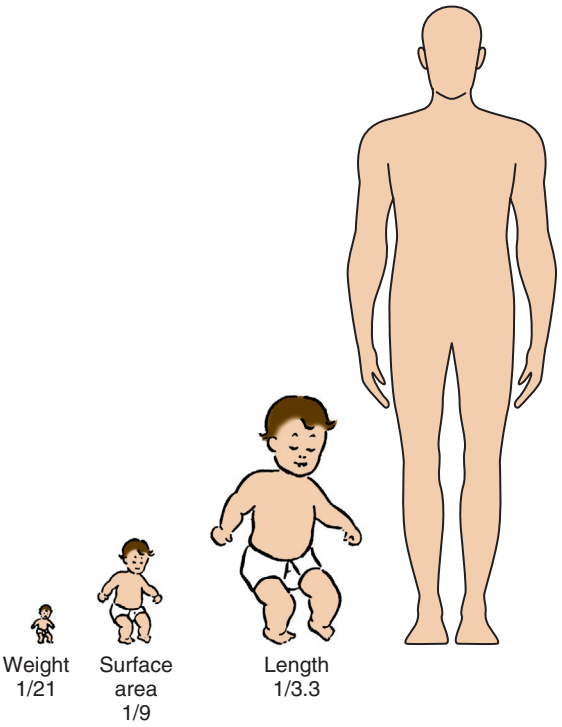

FIG 1-1 Proportions of Newborn to Adult with Respect to Weight, Surface Area, and Length. (Data from Crawford JD, Terry ME, Rourke GM: Simplification of drug dosage calculation by application of the surface area principle, *Pediatrics* 1950;5:785.)

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

Age (years)	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) = $0.007184 \times \text{Height}^{0.725} \times \text{Weight}^{0.425}$.

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)

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

Formula of Gehan and George (1970)

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

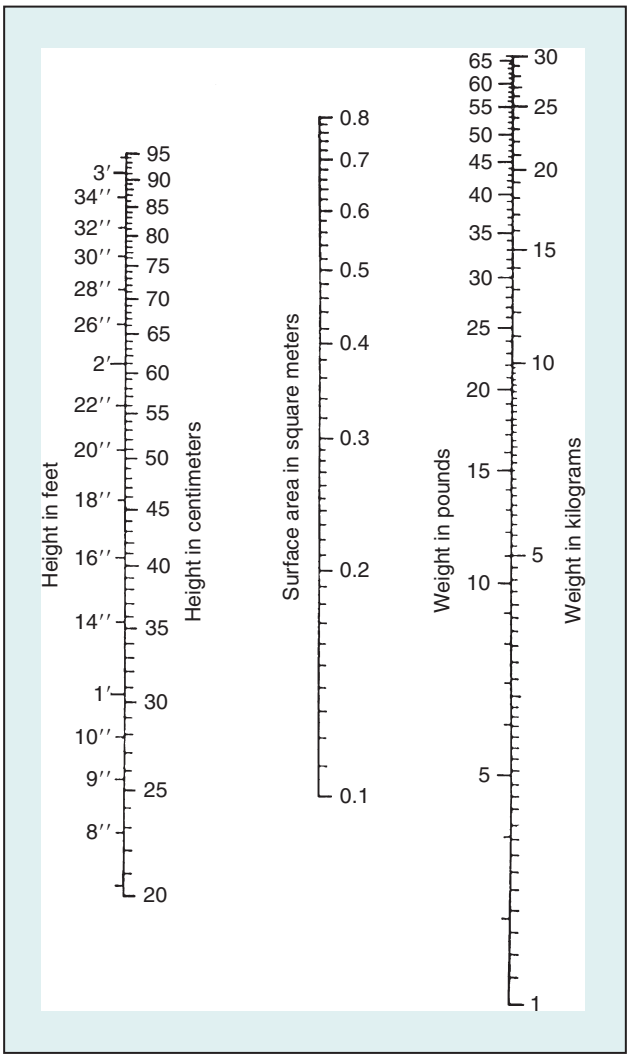

FIG 1-2 Body Surface Area Nomogram for Infants and Young Children. (From Talbot NB, Sobel EH, McArthur JW, Crawford JD: *Functional endocrinology from birth through adolescence,* Cambridge: Harvard University Press, 1952.)

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

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

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

At full-term birth, BSA averages 0.2 m^2, whereas in the adult it averages 1.75 m^2. Table 1-3 shows the relation of age, height, and weight to BSA. A simpler, crude estimate of BSA for children of average height and weight is given in Table 1-4. The formula is also reasonably accurate in children of normal physique weighing 21 to 40 kg (Vaughan and Litt 1987):

$$\text{BSA}\,(m^2) = (0.02 \times \text{kg}) + 0.40$$

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 (i.e., 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.

BOX 1-1 Typical Patterns of Physical Growth

Weight

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

Length/Height

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

Head Circumference

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

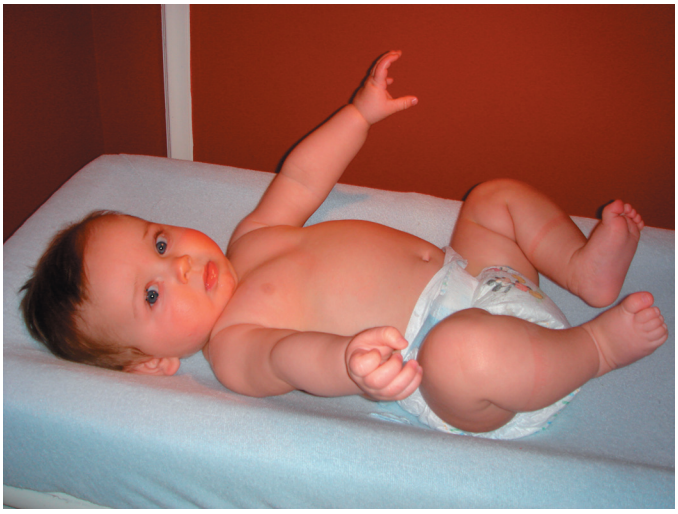

FIG 1-3 A Normal Infant Has a Large Head, Narrow Shoulders and Chest, and a Large Abdomen.

Central and Autonomic Nervous Systems

The brain of a neonate is relatively large, weighing about 1/10 of the body weight compared with about 1/50 of the body weight in an adult. The brain grows rapidly; its weight doubles by 6 months of age and triples by 1 year of age. By the third week of gestation, the neural plate appears, and by 5 weeks' gestation, 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, oligodendrocytes, and glial cells form. Axons and synaptic connections continually form and remodel. Fig. 1-4 plots gestational brain growth as a percentage of brain weight at term (Kinney 2006). 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 of age, 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).

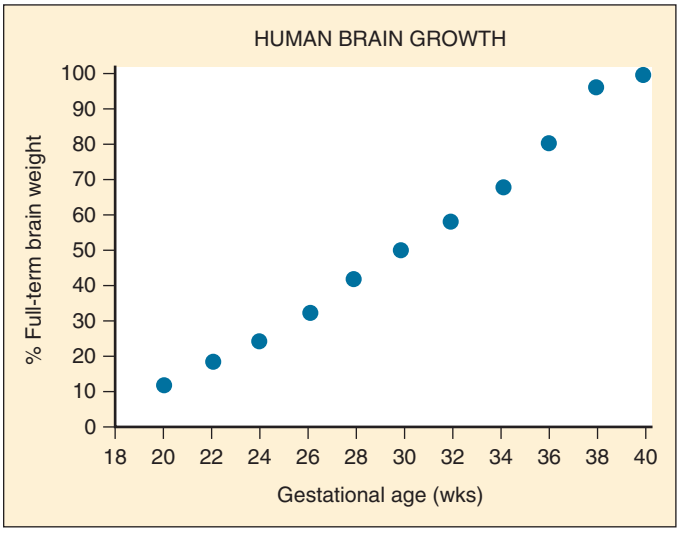

FIG 1-4 Normal Brain Growth from 20 to 40 Weeks' Gestation. Brain weight is expressed as a percentage of term brain weight. (From Kinney HC: The near-term (late preterm) human brain and risk for periventricular leukomalacia: a review, *Semin Perinatol* 2006;30:81-88. Data from Guihard-Costa AM, Larroche JC: Differential growth between the fetal brain and its infratentorial part. *Early Hum Dev.* 1990;23[1]:27-40.)

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 Chapter 3, "Respiratory Physiology" and Chapter 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 postconception 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 age-old concept of the child having a funnel-shaped larynx with the cricoid as the narrowest portion of the airway has been challenged. Findings by Litman and colleagues (2003) using MRI and video-bronchoscopic images by Dalal and colleagues (2009) both revealed that the shape of the infant larynx was more cylindrical (as for adults) than funnel shaped and did not change much with growth.

They also suggest for infants and children that the glottis, not the cricoid, may be the narrowest portion in the paralyzed or cadaveric position (which can be gently widened with an ETT); the cricoid remains to be the solid narrowest segment of the upper airway system. The development of the respiratory system and its anatomy and 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, "Cardiovascular Physiology."

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 a disproportionately large BSA, 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 (Bissonette 1991). 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 over the last decade. 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 general 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, sedatives, 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.

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2

Behavioral Development

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OUTLINE

INTRODUCTION

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 (Gesell 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 having cognitive developmental delay.

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 that might result from the stress of the perioperative process. A great deal of concern has arisen over the past two decades regarding the safety of administering general anesthesia during early childhood. These issues are more complex than the potential behavioral or emotional changes that may result in the postoperative period because of perioperative stress impacting specific developmental stages of the pediatric patient. They relate to the mounting evidence of animal data showing that early exposure to anesthetics can induce apoptotic neurodegeneration and subsequent maladaptive behaviors in immature animals (Rappaport et al. 2015). The relevance of animal data to anesthetic practice is unknown. The final section of this chapter evaluates some of the current published retrospective and ongoing prospective human studies with regard to this topic. To better understand this issue, there is a need for well-designed clinical studies to generate data regarding the neurodevelopmental risks of pediatric anesthesia. The importance of using neuropsychological testing in future pediatric clinical research as a tool for assessing the

neurodegeneration/neurodevelopmental effects of anesthesias on the CNS during this critical period is reviewed.

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 8 weeks of gestation are known as the embryonic period and encompass 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 5th 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 can 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. Notable 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—that is, 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. Expected length in centimeters is estimated by the following formula:

$$(\text{Age in years} \times 6) + 77$$

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 age for children to attain skills 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

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 who 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.

MOTOR DEVELOPMENT

Primitive Reflexes

The earliest motor neuromaturational markers are primitive reflexes that develop 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 3 and 6 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 contralateral side. The ATNR is a precursor to hand-eye coordination, preparing the infant for gazing along the upper arm and voluntary reaching. The disappearance 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.

FIG 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

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 lists the average times of appearance and disappearance of the more common primitive reflexes.

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 Figs. 2-2 and 2-3. 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. Fig. 2-3 shows the red flags to watch for in the abnormal physical development of the infant.

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. 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, Carey, and Crocker 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). Fig. 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.

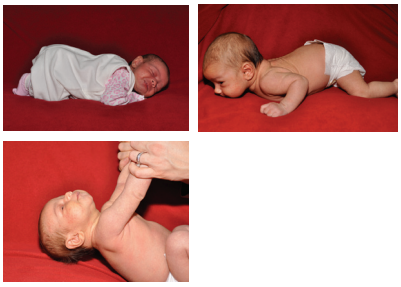
Language development can be divided into the three stages of prespeech, naming, and word combination. Prespeech is characterized by cooing or babbling until around 8 to 10 months of age, when babbling becomes more complex with multiple syllables. Eventually random vocalization ("da-da") is interpreted 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—for example, two-word sentences by 2 years of age, three-word sentences by age 3 years, and so on (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

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
Sits without support. Lifts head before shoulders when pulled to sit

7 Months
Commando crawl

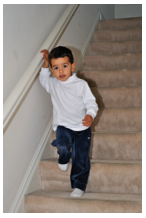
8 Months
Four point kneeling, reaches with one hand. Aquires sitting position without support

10 Months
Cruises around furniture

12 Months
Walks independently

18 Months
Runs

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



36 Months
Balances on one foot for one second

48 Months
Hops on one foot

60 Months
Catches a ball

FIG 2-2 Gross Motor Skills Development Chart.

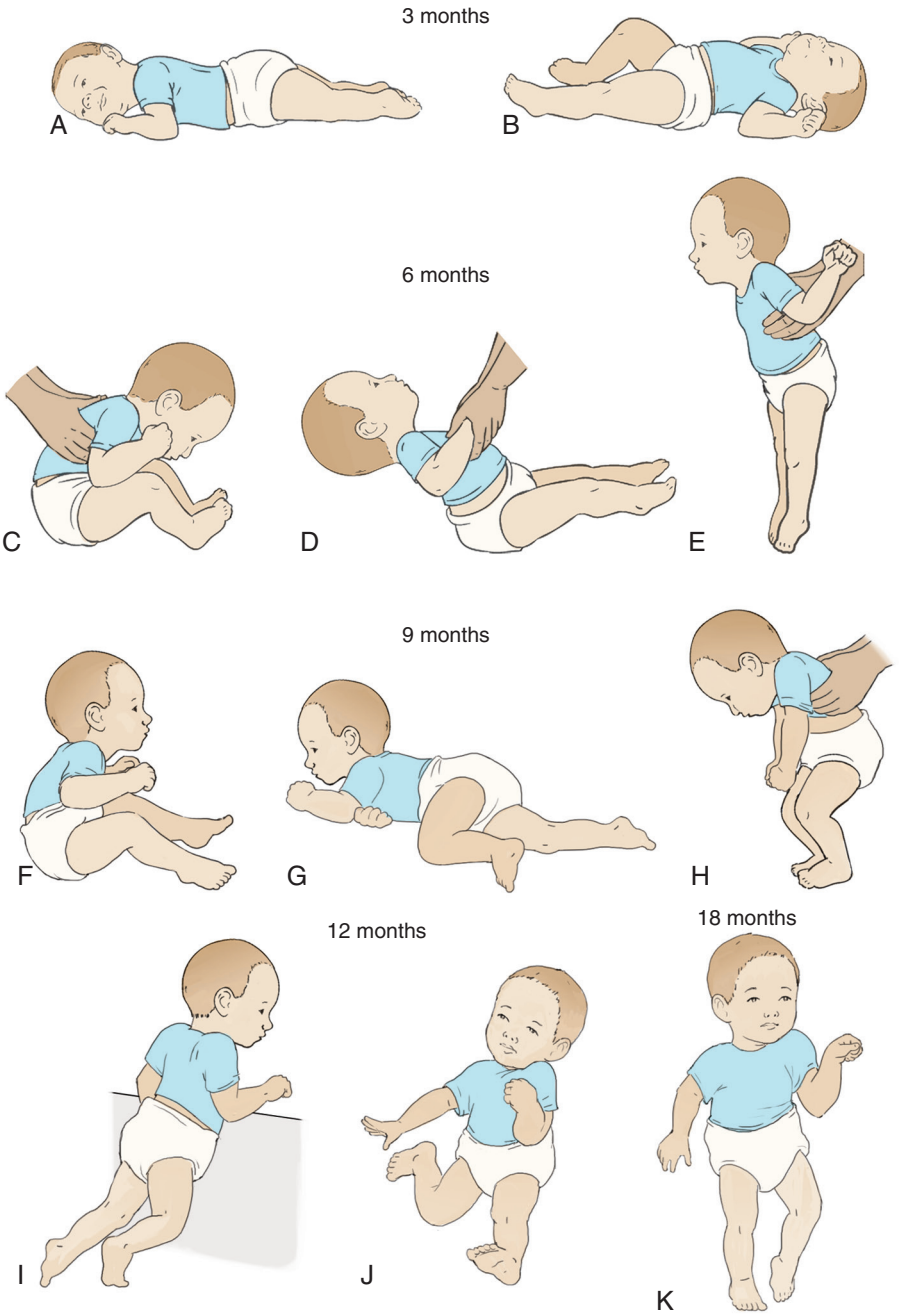


FIG 2-3 Abnormal Developmental Findings. **A,** Difficulty lifting head and stiff legs with little or no movement. **B,** Pushing back with head, keeping hands fisted, and lacking arm movement. **C,** Rounded back, inability to lift head up, and poor head control. **D,** Difficulty bringing arms forward 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.)

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 (1963) chief contribution was to recast Freud's stages in terms of the emerging personality. For example, basic trust, the first of

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

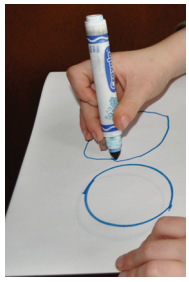
10 Months
Pincer grasp between thumb and index finger

12 Months
Pincer grasp between finger tips

18 Months
Builds a tower of four cubes, scribbles spontaneously

24 Months
Builds a tower of six cubes, turns pages of books one at a time, imitates vertical stroke

36 Months
Copies circle, cuts with small scissors



48 Months
Copies cross, draws a person with three parts

60 Months
Copies triangle

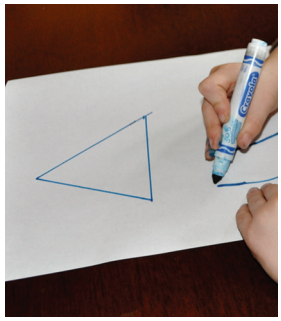


FIG 2-4 Fine Motor Skills Development Chart.

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 versus 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 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 crib moves a mobile). Signs of abnormal cognitive development are outlined in Box 2-2.

A communication system develops between the infant and 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 play and pretend play begin 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 how 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

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

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 (e.g., 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*. 1997;40:107.

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

exhibiting adverse postoperative behavioral reactions. 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, bed-wetting, 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; for example, 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 who were given explanations, whether accurate or not, were found to have fewer postoperative behavioral changes than those who were not given explanations (Bothe and Galdston 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 the 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.

Neurodevelopmental Assessment After Anesthesia in Early Childhood

In the United States today, it is estimated that over 6 million children will receive general anesthesia for both surgical and nonsurgical procedures (Sun et al. 2012). Preclinical studies after exposure to anesthetics common in clinical use completed between 1999 and 2010 have demonstrated neuronal apoptosis or neurodegeneration in the

developing brains of mammals, including rats, mice, and nonhuman primates (Sun 2010). In addition, animals exposed early in development have demonstrated abnormal attention, learning and memory, and behavior changes. While researchers agree that early brain injury results in changes that affect the subsequent acquisition of higher-order cognitive skills (Taylor and Alden 1997), there is little rigorous clinical research that investigates the neurodevelopmental outcome of children after exposure to anesthesia as infants or toddlers. Based on a brief review of this literature, a neuropsychological assessment as a way to evaluate the short- and long-term effects of exposure to anesthesia during infancy and early childhood is described. A comprehensive neuropsychological evaluation completed after anesthesia would elaborate the cognitive and functional status of the child, providing relevant information to guide subsequent treatment and educational interventions.

Investigations of Neurodevelopment After Early Anesthesia

Within the field of anesthesiology, investigations of neurodevelopmental effects have most frequently used a historical cohort design that relies on retrospective "data of convenience" collected for other purposes. One group of studies gleaned data from academic achievement tests administered over the course of the child's school years. The second group used both academic achievement and IQ scores to determine classification of learning disability (LD), which was then applied as a measure of outcome. For a more complete review of this literature, the reader is referred to Beers and colleagues (2014).

Hansen and colleagues (2011) completed a large cohort study to investigate the outcome of children who had been exposed to anesthesia during inguinal hernia repair in infancy by reviewing school records. Outcome was designated as the average composite score attained from a nationally mandated academic achievement test that assessed Danish, foreign languages, mathematics, science, and social studies. Achievement tests were developed to evaluate academic performance, providing standardized assessments of specific skills and knowledge at specific grade levels. Because achievement is relatively fluid and can change from year to year based on a variety of environmental factors (e.g., quality of teaching, school absences), achievement tests differ from tests of intelligence (i.e., IQ) or aptitude, which tend to reflect more stable traits. Perhaps in an effort to address the limitations of academic achievement tests, a study by Wilder and colleagues (2009) identified children who experienced early general anesthesia and were subsequently identified with a learning disability (LD). However, the interpretation of Wilder and colleagues' findings that applied LD status as the outcome variable is confounded by the lack of standardized procedures used to document LD. In the decades since the establishment of the Individuals with Disabilities Education Act (IDEA), inconsistencies in the implementation of guidelines and the misclassification of students in order to provide services for all children requiring academic assistance resulted in a nearly 200% increase in the number of children identified as having LD (IDEA 2004). Because one of the major uses of this educational label is to qualify the child for an Individualized Educational Plan, it has been variously applied by educators, and its usage has been driven to some extent by the resources of the school districts (Beers et al. 2014).

In summary, early investigation of the effects of anesthesia administered during infancy and early childhood used either academic achievement levels or LD status as surrogate measures of neurodevelopmental outcome, providing limited information regarding the status of the brain. As noted by experts in the field of neuropsychology, even the IQ measures used in the definition of LD are highly dependent on school experience and are not particularly sensitive to the status of the central nervous system (Lezak, Howieson, and Loring 2004).

NEUROPSYCHOLOGICAL TESTING AS A TOOL FOR ASSESSING THE NEURODEVELOPMENTAL EFFECTS OF ANESTHESIA

Ing and colleagues (2012) focused on what might be termed the "outcome problem" inherent in cohort studies that use educational test results to ascertain the effects of early anesthetic exposure. They examined the association between exposure before age 3 and cognitive outcome at age 10. These investigators capitalized on the Western Australia Pregnancy Cohort study that applied a battery of age-appropriate neuropsychological instruments. This study is the first of its kind to use neuropsychological test results to delineate neurodevelopmental deficits in discrete cognitive domains and serves to illustrate the advantage of using instruments that are sensitive to the CNS. Children were assessed with a comprehensive battery at age 10. Standardized neuropsychological tests of language function, attention, abstract reasoning, motor skills, and a parent report of behavior were included. Between-group analyses, corrected for multiple comparisons, indicated statistically significant differences on measures of language and abstract reasoning between the exposed and unexposed children. The clinical implication of these findings was evaluated by calculating a disability rating, after adjustment for demographic and gender related variables. A significant difference between the incidence of clinical disability of the exposed and unexposed children on measures of higher-order language abilities and abstract reasoning was delineated. Worthy of comment is the fact that no differences in parent rating scales were found, suggesting that parent surveys are probably not sensitive to cognitive changes that may be associated with exposure, particularly in instances where the exposure is early in the child's history and not associated with a complex medical condition. Sun and colleagues (2012) reported the results of a carefully designed, controlled prospective pilot study that used neuropsychological instruments to investigate a single exposure to anesthesia before the age of 3 years (PANDA). This pilot study established that neuropsychological testing was feasible for younger infants and toddlers. In summary, these two studies indicate that state-of-the-art procedures designed to assess the status of the CNS have clinical utility when developing treatment plans for infants and children exposed to anesthesia.

Developmental Considerations

Over the last 15 years, neuropsychology has gained a developmental perspective and benefits from tests specifically constructed to measure brain function and development during childhood (Goldstein and Beers 2004). Test selection presents a particular challenge and requires particular expertise and training in pediatric (i.e., developmental) neuropsychology. Unlike instruments designed for adults, pediatric instruments differ, depending on the developmental epoch, even though they may be measuring the same cognitive construct. Beers and colleagues (2014) provided a compendium of age-appropriate instruments (i.e., from infancy through later adolescence) to assess the cognitive domains discussed below. This battery, although not developed by consensus, is intended to provide an example of instruments available that might be employed by investigators as they unravel the toxic effects of anesthesiology on the developing brain (Table 2-5).

Cognitive Domains and Associated Neuropsychological Instruments

Lezak and colleagues (2004) defined *neuropsychology* as "an applied science concerned with the behavioral expression of brain dysfunction." They pointed out that one important use of neuropsychological test data is to investigate specific brain disorders with instruments of

TABLE 2-5 Age-Appropriate Instruments Across Cognitive Domains

Task/Age Range (Time)	Description[#]
Global Function Status	
Glasgow Outcome Scale—Extended Pediatric Version (GOS-E Peds)/1 mo–18 yrs (20′)	The GOS-E Peds is a developmentally appropriate semistructured interview designed to measure outcomes after brain injury in infants, children, and adolescents relative to consciousness, independence in the home, independence outside the home, functionality at school, participation in social and leisure activities, and the ability to sustain relationships with family and friends. Scores are calculated in accordance with a categorical scale of 1–8. (Beers et al. 2012)
Intellectual Ability	
Bayley Scales of Infant and Toddler Development, 3rd ed. (BSID-III) Cognitive Scale/1–42 mo (30′)	The BSID-III Cognitive Scale measures sensorimotor development, exploration and manipulation of objects, object relatedness, concept formation, memory, and other aspects of cognitive processing. (Bayley 2006)
Wechsler Preschool and Primary Scale of Intelligence, 4th ed. (WPPSI-IV) Short Form/2:6–7:6 yrs (30′)	The WPPSI-IV short form measures the cognitive ability of preschool and primary-age children and consists of two subtests for ages 2:6–3:11 (Receptive Vocabulary and Block Design) and four subtests for ages 4:0–7:7 (Receptive Vocabulary, Block Design, Matrix Reasoning, and Similarities). Receptive Vocabulary requires children to select the response option that best represents the word the examiner reads aloud. Block Design is a constructional task in which the individual is presented with blocks and asked to replicate designs within a specified time limit. Matrix Reasoning requires individuals to examine an incomplete matrix or series and select the item that would appropriately complete the series. Similarities are composed of both picture and verbal items. Picture items require the child to select the response that is from the same category as two other depicted objects, while verbal items require a description how the two words presented are similar. (Wechsler 2012)
Wechsler Abbreviated Scale of Intelligence, 2nd ed. (WASI-II)/≥6 yrs (30′)	The WASI-II is an abbreviated IQ scale developed to provide a short and reliable measure of intelligence in children, adolescents, and adults. Block Design is a constructional task in which the individual is presented with blocks and asked to replicate designs, examining the individual's visuo-constructional ability, motor speed, and manual dexterity. Vocabulary requires the child to verbally define increasingly difficult vocabulary words, examining the individual's learning ability, fund of general information, concept formation, and expressive language development. Matrix Reasoning requires individuals to examine an incomplete matrix or series and select the item that would appropriately complete the series. In Similarities, an individual is presented with two related pictures or words and must describe how they are similar. (Wechsler 2011)
BSID-III Language Scale/1 mo–3:6 yrs (20′)	The BSID-III Language Scale is composed of both receptive and expressive speech items assessing preverbal behaviors, vocabulary development, and the understanding and use of pronouns and grammar. Early receptive speech items examine behaviors such as sustaining attention when engaged verbally or reacting to sounds in the environment, while later items require that the child comprehend basic elements of speech (e.g., pronouns, plurals, or quantities) and demonstrate the ability to categorize objects. Expressive speech items range from the ability to produce gurgling sounds to the use of prepositions and ability to tell stories. (Bayley 2006)
CELF Preschool, 2nd ed. (CELF-P-2) Concepts and Following Directions/3–6 yrs (10′)	The CELF-5 and its companion instrument, the CELF-P-2, identify language skill deficits in preschool and elementary-age children. The CELF-5 Concepts and Directions subtest provides a measure of receptive speech and requires the ability to interpret, recall, and execute oral commands that contain concepts requiring logical operations. Commands increase in length and complexity over the course of the test. (Semel, Wiig, and Secord 2003)
Clinical Evaluation of Language Fundamentals, 5th ed. (CELF-5) Concepts and Directions/5–21 yrs (10′)	The preschool-age version of this subtest is Concepts and Following Directions included on the CELF-P-2. (Semel, Wiig, and Secord 2013)
Peabody Picture Vocabulary Test, 4th ed. (PPVT-4)/≥2:6 yrs (10–15′)	The PPVT-4 is designed to assess receptive vocabulary skills by presenting increasingly difficult targets words and requiring that the individual identify the picture that corresponds with the target word from a group of four pictures. It is appropriate to compare the results of the PPVT-4 with the EVT-2 to obtain a comprehensive picture of language ability. This test can serve as a surrogate for IQ. *(Alternate Forms Available)* (Dunn and Dunn 2007).
Expressive Vocabulary Test, 2nd ed. (EVT-2)/≥2.6 yrs (10′)	The EVT-2 is designed to assess expressive vocabulary and word retrieval skills and is often compared with PPVT-4 results. These items measure the child's ability to verbally describe objects or actions pictured in the stimulus book, produce synonyms for various target words, or define categories. *(Alternate Forms Available)* (Williams 2007)
Memory and Learning	
California Verbal Learning Test—Children's Version (CVLT-C)/5–16 yrs (45′)	The CVLT-C assesses multiple strategies and processes in learning and recalling verbal material and tests both recall and recognition of words associated with verbal learning of a word list over five trials. After an interference trial, children are asked to recall the original list both immediately and after a 20-minute delay. (Delis et al. 1994)

TABLE 2-5 Age-Appropriate Instruments Across Cognitive Domains—cont'd

Task/Age Range (Time)	Description[#]
NEPSY-II Sentence Repetition/3–6 yrs (5′)	The NEPSY-II Sentence Repetition is designed to assess the child's ability to immediately recall and repeat sentences of increasing complexity. (Korkman, Kirk, and Kemp 2010)
Visual-Spatial Skills	
Beery-Buktenica Developmental Test of Visual Motor Integration, 6th ed. (VMI)/≥2 yrs (5′)	The VMI is an instrument widely used to screen children for visual-motor deficits by asking the child to draw two-dimensional figures of increasing complexity. Standard scores are provided. (Beery, Buktenica, and Beery 2010)
WPPSI-IV Block Design/2:6–7:6 yrs (10′) WASI-II Block Design/6–16 yrs (10′)	Block Design is a constructional task in which the individual is presented with colored blocks and asked to replicate designs, examining the individual's visuo-constructional ability, motor speed, and manual dexterity. The WPPSI-IV format is intended for preschool-age children, with differing forms for ages 2:6–3:11 and 4:0–7:7, while the WISC-IV format assesses older children and adolescents ages 6:0–16:11. (Wechsler 2011, 2012)
Attention and Executive Function	
Behavior Rating Inventory of Executive Function, Preschool Version (BRIEF-P)/2–5 yrs (10–15′) Behavior Rating Inventory of Executive Function (BRIEF)/5–18 yrs (10–15′)	The BRIEF and its companion instrument, the BRIEF-P, are parent-report instruments relating to the child's executive function. The Behavioral Regulation Index measures the child's ability to shift cognitive set and modulate emotions and behavior through age-appropriate inhibition. The Metacognition Index, or the child's self-monitoring behavior, depends on the ability to initiate, plan, organize, and sustain problem solving in working memory. These indexes combine to comprise the Global Executive Composite. (Gioia, Isquith, and Guy 2000; Gioia, Espy, and Isquith 2003)
Motor Function and Processing Speed	
BSID-III Motor Scale/1–42 mos (10′)	The BSID-III Motor Scale is composed of both fine motor and gross motor items assessing perceptual motor integration, motor planning, speed of performance, visual tracking, and object manipulation. (Bayley 2006)
Bruininks-Oseretsky Test of Motor Proficiency, 2nd ed. (BOT-2) Short Form/4–21 yrs (15–20′)	The BOT-2—Short Form is composed of 14 items ranging from the ability to draw lines or copy shapes to mastery of physical activity through tasks such as hopping or the number of push-ups and sit-ups completed during a timed interval. (Bruininks and Bruininks 2005)
NEPSY-II Visuomotor Precision/3–12 yrs (5′)	The NEPSY-II Visuomotor Precision subtest assesses the child's graphomotor speed and accuracy by requiring that he or she draw lines inside of tracks as quickly as possible. Both speed and accuracy scores are provided. (Korkman, Kirk, and Kemp 2010)
Grooved Pegboard Test ≥5 yrs (10′)	Grooved Pegboard is a manipulative dexterity task consisting of a board with 25 randomly keyed slots. Pegs must be rotated before being inserted into the holes. Completion time for each hand and number of dropped pegs are measured. Children ages 5:0 to under 9:0 only complete the first two rows, totaling 10 pegs. (Lafayette Instrument 2002)
WPPSI-IV Animal Coding/4–7:6 yrs (5′)	Coding is a powerful test of the integrity of the CNS as a whole, because it demands speed, attention, visual scanning, and memory. The format for coding varies depending on the age of the child. The youngest children receive the WPPSI-IV Animal Coding subtest, which requires that they work within a specific time frame using the key provided to mark shapes that correspond to various pictured animals. (Wechsler 2012)
*Wechsler Intelligence Scale for Children, 4th ed. (WISC-IV) Coding/6–16 yrs (5′)	Children ages 6:0–7:0 receive the WISC-IV Coding Form A, which requires them to copy symbols that are paired with geometric shapes within the specified time limit. Coding Form B given to children and adolescents ages 8:0–16:11 differs from Coding Form A in that the individual must copy a symbol as it corresponds to a number as opposed to a geometric shape. (Wechsler 2003)
*WISC-IV Symbol Search/6–16 yrs (5′)	Symbol Search is a timed test that requires the individual to scan a group of symbols and indicate whether the target symbol matches any symbols in the search group. Children ages 6:0–7:0 receive Symbol Search A, while children and adolescents age 8:0–16:11 receive Symbol Search B. These forms vary only in the complexity of the designs and the number of items in the search group. (Wechsler 2003)
Behavior	
BSID-III Social Emotional Scale/1–42 mos (15′)	The BSID-III Social-Emotional Scale is a questionnaire completed by the primary caregiver to assess how well the child is meeting the appropriate developmental milestones with regard to his or her social-emotional function. (Bayley 2006)
Child Behavior Checklist (CBCL), Infant/Toddler Version/1:6–4 yrs (10′) Child Behavior Checklist (CBCL), Child Version[44]/5–18 yrs (10′)	The CBCL Infant/Toddler Version (Achenbach and Rescorla 2000) and the CBCL Child Version (Achenbach and Rescorla 2001) are parent-report questionnaires designed to assess the infant's or child's behavior in terms of any internalizing and externalizing symptomatology that may be present related to anxiety, depression, somatic complaints, social difficulties, thought problems, attention problems, oppositional or rule-breaking behavior, aggressive behavior, and/or other behavioral issues.

*Subtest scores combine to form the WISC-IV Processing Speed Index. [#]All variables are continuous unless otherwise noted.
Adapted with permission from Beers SR, Rofey DL, McIntyre KA. Neurodevelopmental assessment after anesthesia in childhood: Review of the literature and recommendations. *J Anes Analg.* 2014;119:661–669.

known sensitivity to central nervous system insult. By convention, carefully validated and standardized neuropsychological tests are organized into the following seven domains (Lezak et al. 2004; Strauss, Sherman, and Spreen 2006).

Intelligence

Intelligence testing provides a general measure of overall ability, social understanding, and practical knowledge. The neuropsychologist uses IQ test results to lay the foundation for tests more sensitive to brain dysfunction rather than to indicate CNS damage (Lezak, Howieson, and Loring 2004).

Language

Key areas evaluated in a general battery include instruments that assess both expressive and receptive speech. In addition, auditory comprehension or the ability to understand and follow complex verbal commends as well as verbal fluency are also frequently assessed.

Learning and Memory

Memory is the capacity to register (i.e., learn), retain, and retrieve information. Neuropsychologists frequently measure memory with respect to verbal, visual, and tactile performance. The field has developed a number of comprehensive memory tests for adults, children, and adolescents that allow for the understanding of how the attendant domains of attention, visual-spatial skills, and executive abilities all impact memory. One limitation of this domain is that memory in children younger than 3 years is usually not developed to the point that traditional assessment techniques are valid.

Visual-Spatial Skills

These skills generally refer to visual-perceptual, visual-spatial, or visual-constructional abilities. Visual-perceptual tasks often assess aspects of visual inattention that can range from impulsivity to more localizing symptoms of visual neglect. Other visual-spatial skills require the individual's ability to rotate his or her own body in space, to match the angle of line from a mixed array, or to perform visual discriminations by matching a discrete segment to an integrated design. Constructional problems usually involve drawing/copying or building, emphasizing tasks that may generalize to deficits in daily living skills.

Attention and Executive Function

This complex domain includes measures of abstract reasoning encompassing the ability to filter out nonessential competing stimuli through focusing, sustaining, and/or dividing attention in order to organize material, solve novel problems, and maintain mental flexibility using input for other brain regions (e.g., memory; visual-spatial information). Novel problem-solving and organizational abilities are frequently referred to as executive function because the activities serve to manage and coordinate both cognition and behavior. Because tests of executive function by definition depend on novelty, they are highly vulnerable to practice effects, and thus it is not appropriate to apply the same measures over time as might be required in longitudinal studies.

Motor and Psychomotor Abilities

A comprehensive neuropsychological evaluation frequently includes measures assessing dexterity and strength in the upper extremities. Performance on these tests can be compared with respect to right versus left hands, allowing for the individual to act as his or her own control. This comparison informs as to the relative integrity of the two brain hemispheres. In children, performance on a simple task that requires both a controlled motor behavior and speed provides much information regarding impulsivity and other aspects of problem-solving style. "Psychomotor" instruments add a cognitive challenge to an otherwise simple task such as copying symbols or inserting pegs into a board, providing an assessment of brain function under challenging circumstances.

SUMMARY

There is a systematic approach for tracking neurologic development and physical growth in infants and children because attainment of these milestones is orderly, predictable, and unchanged over time. Knowing the range of normal growth and development allows the pediatric anesthesiologist to identify delays or deviations from normal that may exist preoperatively or develop postoperatively. Postoperative changes in children after exposure to anesthetic agents or the overall nuances of the perioperative process may result in gross emotional or behavioral disturbances that are easily delineated or may be demonstrated by more subtle brain injury that affects the acquisition of higher-order cognitive function. Any alterations after anesthesia are important to adequately diagnose to initiate interventions and management strategies.

Animal studies have documented that anesthesia holds the potential to damage the immature nervous system, and cohort studies completed with children have provided the foundation for the exploration of the iatrogenic effects of anesthesia administered during infancy and early childhood. Although these early studies relied on testing originally designed for the purpose of classifying school progress or identifying those in need of specialized educational services, they provided the basis for future controlled, prospective studies that investigate outcome after anesthesia. The methodology of neuropsychological testing, initially developed to assess the integrity of the CNS in adults, now includes valid, comparable instruments to assess children across the age range. Thus neuropsychological testing provides investigators with highly sensitive, robust measures of outcome that can be applied not only in prospective research studies but also in the clinical setting. As investigators and clinicians seek to weigh the risks and benefits of anesthesia exposures, this method is likely to play an important role assessing the overall integrity of the brain, identifying deficits within specific cognitive domains, and providing relevant treatment recommendations.

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

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3

Respiratory Physiology

Etsuro K. Motoyama and Jonathan D. Finder

OUTLINE

INTRODUCTION

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 ($\dot{V}_A/Q$) balance 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, as 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 during the perianesthetic period, 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; alveoli and lung parenchyma; and the pulmonary vascular

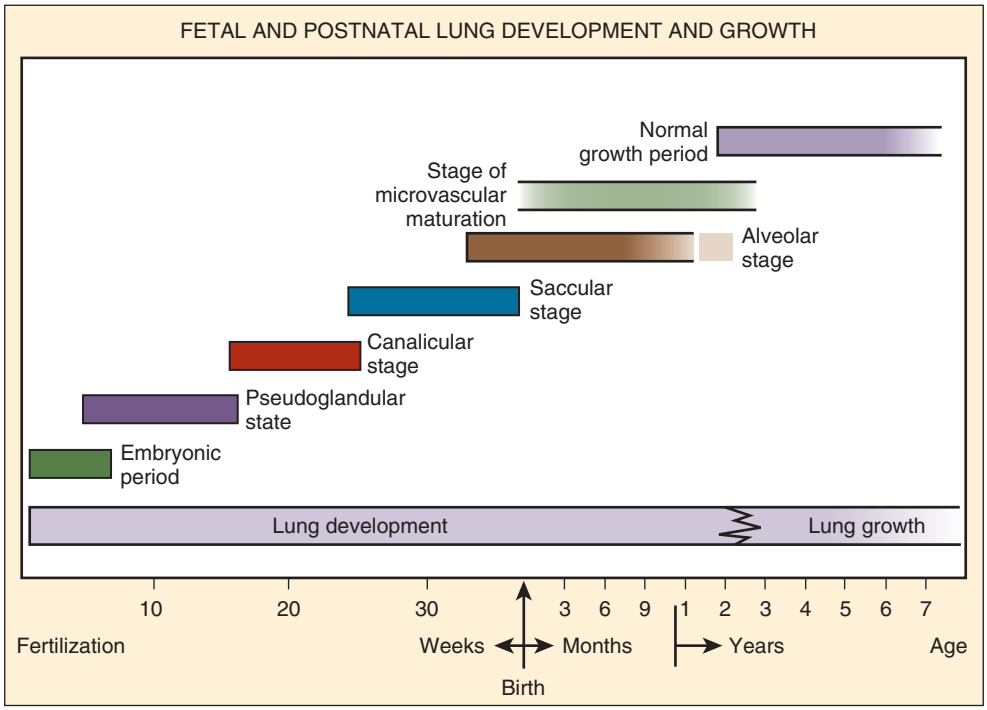

FIG 3-1 Stages of Human Lung Development and Their Timing. Note the overlap between stages, particularly between the alveolar stage and the stage of microvascular maturation. Open-ended bars indicate uncertainty as to exact timing. (From Zeltner TB, Burri PH. The postnatal development and growth of the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

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 Fig. 3-2. By 16 weeks' gestation, preacinar branching of the airways (down to the terminal bronchiol) is completed (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 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. 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 of airways per se stimulates and produces growth factors, such as human bombesin (also known as gastrin-releasing peptide) from pulmonary endocrine cells, which stimulates airway branching and accelerates lung growth and development (Sunday et al. 1988; Sunday 1996). The fetal larynx is periodically relaxed, and lung fluid is expelled into the uterine cavity and contributes about one-third of the total amniotic fluid; the

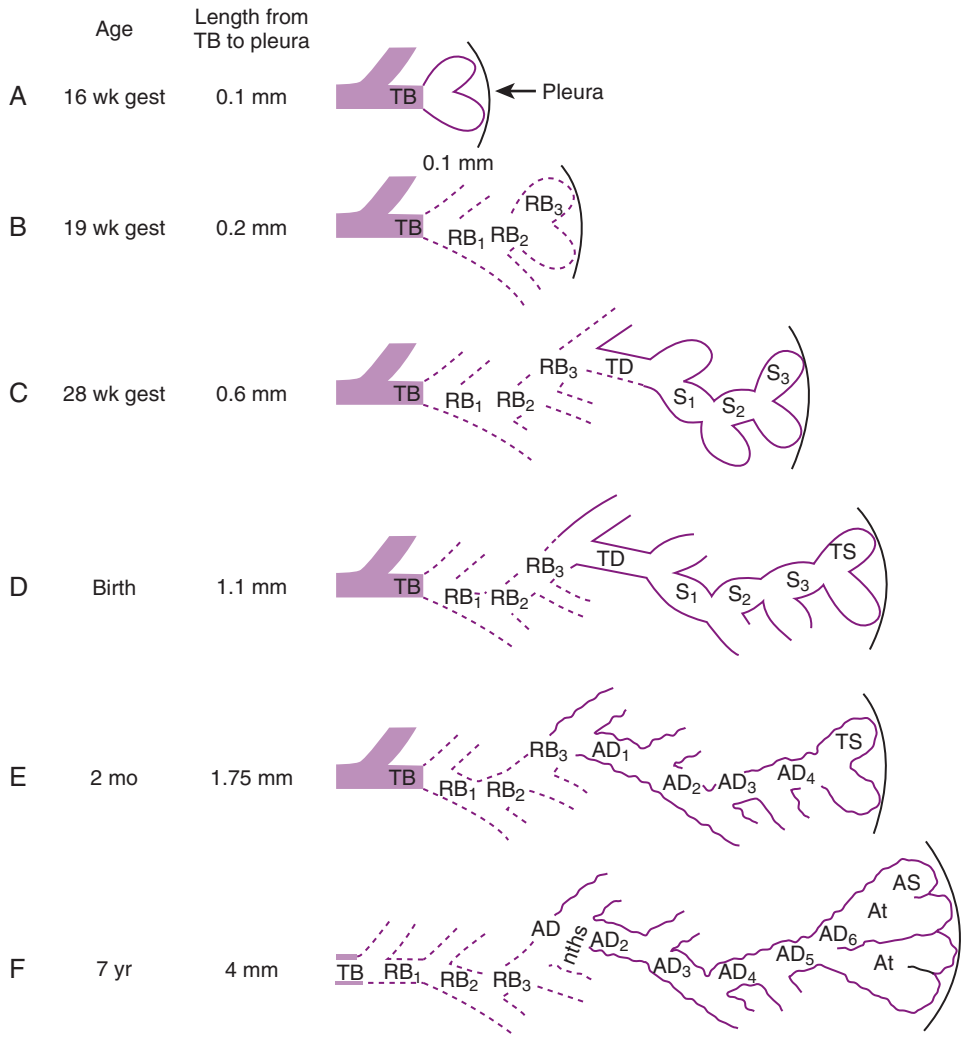

FIG 3-2 Development of the Acinus in Human Lungs at Various Ages. *TB,* Terminal bronchiole; *RB,* respiratory bronchiole; *TD,* transitional duct; *S,* saccule; *TS,* terminal saccule; *AD,* alveolar duct; *At,* atrium; *AS,* alveolar sac. (From Hislop A, Reid L. Development of the acinus in the human lung. *Thorax.* 197429:90.)

remaining two-thirds comes from fetal urinary outputs. Congenital diaphragmatic hernia is characterized by unilateral pulmonary hypoplasia secondary to ipsilateral herniation of abdominal viscera displaced into the thoracic cavity. 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 with accumulating lung fluid and results in an accelerated growth of the otherwise hypoplastic lung (DiFiore et al. 1994). (See also the "Pulmonary Hypoplasia" section.)

The lung fluid contains components of surfactant from the osmiophilic lamellar bodies produced in and expelled from the cuboidal Type II alveolar pneumocytes during the last trimester of pregnancy. Lamellar bodies start to appear in the type II pneumocytes at about 24 to 26 weeks' gestation but occasionally as early as 20 weeks' gestation (Spear et al. 1969; Lauweryns 1970). In mature lungs, lamellar bodies, which contain pulmonary surfactant, are expelled from the type II pneumocytes onto the alveolar surface, spread and form a thin alveolar lining layer, and reduce surface tension at the air-liquid interface and stabilize air spaces. The presence of functioning pulmonary surfactant is essential to keeping pulmonary alveoli of different sizes open side by side during the respiratory cycle (see "Surface Activity" and "Pulmonary Surfactant" below). 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 insufficient pulmonary surfactant production and their inactivation by plasma proteins exudating onto the alveolar surface.

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 to prevent premature contractions 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 central nervous system development, prenatal glucocorticoid therapy has been used widely since the 1980s to induce lung maturation and surfactant synthesis in mothers at risk of premature delivery with great success for the survival of prematurely born infants (Avery 1984; Avery et al. 1986).

Prenatal Development of Breathing

Respiratory rhythmogenesis occurs long before parturition. Dawes and colleagues (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 full-term 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 1992; Rigatto et al. 1988). 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} >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).

Prenatal fetal gas exchange takes place between the maternal (uterine arterial) capillary blood and cotyledonay vasculatures in the fetal side of the placenta. Arteriolized umbilical venous blood returns to the right side of the fetal heart via the ductus venosus and inferior vena cava. The mean value of well-oxygenated umbilical venous PO_2 (functionally somewhat analogous to arteriolized pulmonary venous blood in normal adult circulation) in the near-term eucapneic gravida is reported to be 29 mm Hg (range, 25 to 33), whereas preductal (carotid) PO_2 ranges between 20 and 25 mm Hg; the average postductal umbilical arterial PO_2 (analoguous to desaturated pulmonary arterial blood) is 22 mm Hg in eucapneic gravida at elective caesarian section (Peng et al. 1972). More recent studies have reported median umbilical arterial (postductal) PO_2 of 17 mm Hg and a PCO_2 of 52 mm Hg (Helwig et al. 1996).

NEONATAL RESPIRATORY ADAPTATION

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, Faridy, and Pagtakhan 1975; Baier et al. 1990; Rigatto 1992). Indeed, the clamping of the umbilical cord and increasing arterial oxygen tensions with air breathing and resultant relative "hyperoxia" from the normally low fetal PO_2 (but not transient hypoxia during labor and delivery) initiate and maintain rhythmic breathing at birth. The current concept regarding the mechanism of continuous neonatal breathing is summarized in Box 3-1.

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 (Karlberg et al. 1962) (Fig. 3-3). 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 to 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 ($\dot{Q}_P$ or simply Q) increases markedly, thus allowing gas exchange between alveolar air and pulmonary capillaries to increase. Changes in PO_2, PCO_2, 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 alveolar-ventilation/pulmonary-perfusion ($\dot{V}_A/\dot{Q}_{PP}$, $\dot{V}_A/\dot{Q}$, or simply V/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 adequate supply of pulmonary surfactant.

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).

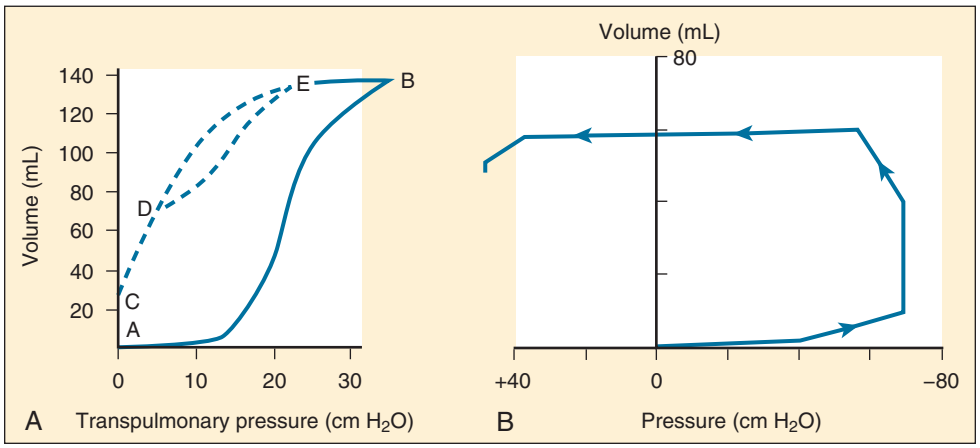

FIG 3-3 **A,** Typical pressure-volume curve of expansion of a gas-free lung. *A-B,* Initial expansion. In the example, approximately 30 cm H_2O pressure will be necessary to overcome surface forces. *C,* Deflation to zero pressure with gas trapping. *D-E,* Subsequent breaths with a further increase 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.* 1962;51:121.)

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

	Pa_{O_2} (mm Hg)	Sa_{O_2} (%)	Pa_{CO_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.

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, and is 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, Bryan, and Levinson 1972).

During the early postnatal period, the lung volume of infants is disproportionately small in relation to body size (Table 3-2). 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) because the elastic fibers do not develop until the postnatal period (Mansell, Bryan, and Levinson 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 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

TABLE 3-2 Normal Values for Lung Functions in Persons of Various Ages

	AGE								
	1 wk	1 yr	3 yr	5 yr	8 yr	12 yr	Male 15 yr	Male 21 yr	Female 21 yr
Height (cm)	48	75	96	109	130	150	170	174	162
Weight (kg)	3.3	10	15	18	26	39	57	73	57
FRC (mL)	75*	(263)	(532)	660	1174	1855	2800	3030	2350
FRC/weight (mL/kg)	(25)	(26)	(37)	(36)	(46)	(48)	(49)	(42)	(41)
VC (mL)	100†	(475)	(910)	1100	1855	2830	4300	4620	3380
V_E (mL/min)	550	(1775)	(2460)	(2600)	(3240)	(4150)	5030	6000	5030
V_T (mL)	17	(78)	(112)	(130)	(180)	(260)	360	500	420
f (frequency)	30	(24)	(22)	(20)	(18)	16	14	12	12
V_A (mL/min)	385	(1245)	(1760)	(1800)	(2195)	(2790)	3070	4140	3530
V_D (mL)	75	21	37	49	75	105	141	150	126
C_1 (mL/cm H_2O)	5	(16)	(32)	44	71	91	130	163	130
Peak flow rates (L/min)	10	136			231	325	437	457	365
R (cm H_2O/L/sec)	29‡	(13)	(10)	8	6	5	3	2	2
DLCO (mL/mm Hg/min)§				11	15	20	27	28	24
Cardiac output (L/min)	(0.9)	1.9	2.7	3.2	4.4	5.7	(7.0)	(7.6)	(7.2)
Lung weight (g)	49	120	166	211	290	470	640	730	

Parentheses, Interpolated values.
*Supine.
†Crying vital capacity.
‡Nose breathing.
§Single-breath technique.
Data from Bucci G, Cook CD, Barrie H. Studies of respiratory physiology in children. V. Total lung diffusion, diffusing capacity of pulmonary membrane, and pulmonary capillary blood volume in normal subjects from 7 to 40 years of age. *J Pediatr.* 1961;58:820; Comroe JH Jr et al. *The lung.* Chicago: Year Book; 1962; Cook CD et al. Studies of respiratory physiology in the newborn infant. I. Observations on the normal premature and full-term infants. *J Clin Invest.* 1955;34:975; Cook CD et al. Studies of respiratory physiology in the newborn infant. VI. Measurements of mechanics of respiration. *J Clin Invest.* 1957;36:440; Cook CD, Hamann JF. Relation of lung volumes to height in healthy persons between the ages of 5 and 38 years. *J Pediatr.* 1961;59:710; Koch G. Alveolar ventilation, diffusing capacity and the A-a PO_2 difference in the newborn infant, *Respir Physiol* 4:168, 1968; Long EC, Hull WE: Respiratory volume-flow in the crying newborn infant. *Pediatrics.* 1961;27:373; and Murray AB, Cook CD. Measurement of peak expiratory flow rates in 220 normal children from 4.5 to 18.5 years of age. *J Pediatr.* 1963;62:186.

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, such as laryngotracheobronchitis [subglottic croup] and 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.

CONTROL OF BREATHING

The mechanism that regulates and maintains pulmonary gas exchange is remarkably efficient. In a normal person, the level of P_{ACO_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 (Cherniack and Pack 1988) (Fig. 3-4). 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 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

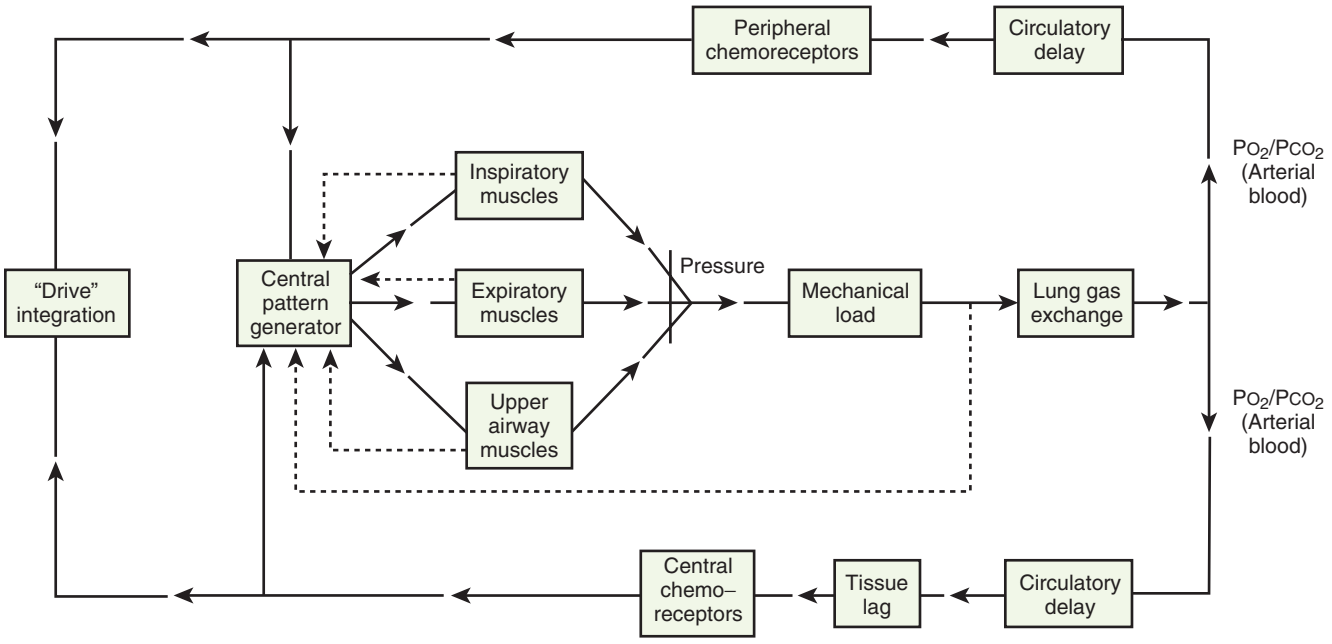

FIG 3-4 Block Diagram of Multi-Input, Multi-Output System That Controls Ventilation.

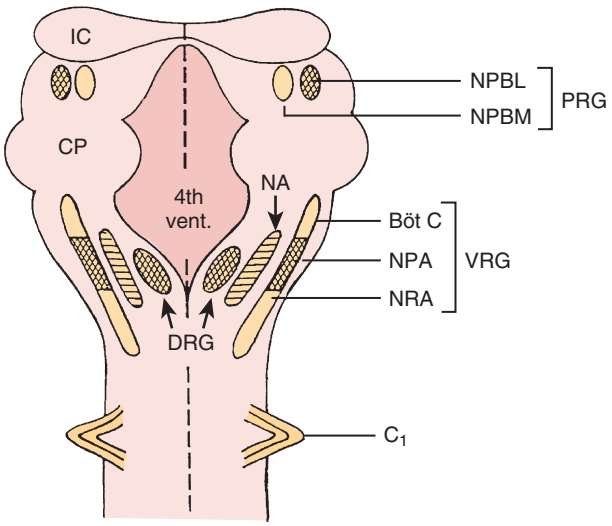

FIG 3-5 Schematic Representation of the Respiratory Neurons on the Dorsal Surface of the Brainstem. Cross-hatched areas contain predominantly inspiratory neurons, blank areas contain predominantly expiratory neurons, and dashed areas contain both inspiratory and expiratory neurons. *Böt C,* Bötzinger complex; *CI,* 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, ed. *Physiological and pharmacological basis of anesthesia.* Philadelphia: Williams & Wilkins; 1995.)

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 (von Euler 1986; Tabatabai and Behnia 1995; Berger 2000) (Fig. 3-5).

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 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 (see 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, Lipski, and Kubin 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, Lipski, and Kubin 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, Erure, and Suzuki 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; Merrill, Lipski, and Kubin 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; Merrill, Lipski, and Kubin 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) (Cohen 1979; Mitchell and Berger 1981) (see Fig. 3-5). 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, Tsubone, and Sant'Ambrogio 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) 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, Bryan, and Bryan 1974).

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, Jeffrey, and Sant'Ambrogio 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

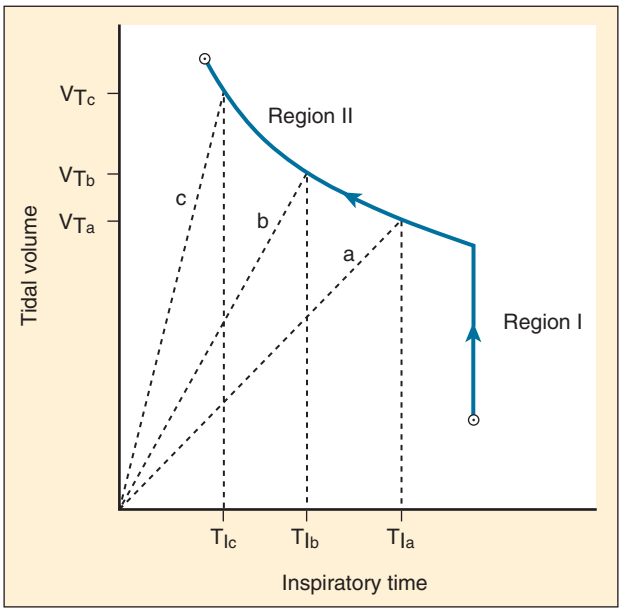

FIG 3-6 Relationship Between Tidal Volume (V_T) and Inspiratory Time (T_I) as Ventilation Is Increased in Response to Respiratory Stimuli. Note that in region I, Vt increases without changes in T_I. In region II, as the ventilatory drive increases (from a to b to c), inspiratory time on the *x*-axis also decreases (from TIa to TIb to TIc) so as to limit the increase in tidal volume on the *y*-axis (from VTa to VTb to VTc). 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: WB Saunders; 1994.)

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 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) 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.

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 PCO_2, pH, and PO_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 PCO_2 or pH (Pappenheimer et al. 1965). Because 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.

Peripheral Chemoreceptors

The carotid bodies, located near the bifurcation of the common carotid artery, react rapidly to changes in Pa_{O_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

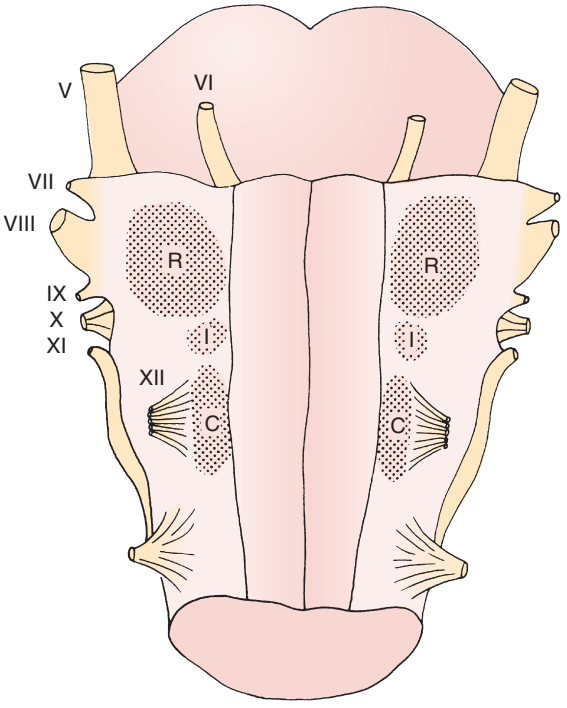

FIG 3-7 View of the Ventral Surface of the Medulla Shows the Chemosensitive Zones. The rostral (*R*) and caudal (*C*) zones are chemosensitive. The intermediate (*I*) zone is not chemosensitive but may have a function in the overall central chemosensory response. The roman numerals indicate the cranial nerves. (From Berger AJ, Hornbein TF: Control of respiration. In: Patton HD et al., eds. *Textbook of physiology,* 21st ed. Philadelphia: WB Saunders; 1989.)

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. A variety of neurochemicals have been found in the carotid body, including acetylcholine, dopamine, substance P, enkephalins, and vasoactive intestinal peptide. The exact functions of these cell types and the mechanisms of chemotransduction and the specific roles of these neurochemicals have not been well established (Berger 2000).

The carotid bodies are perfused with extremely high levels of blood flow and respond rapidly to an oscillating Pa_{O_2} rather than a constant Pa_{O_2} at the same mean values (Dutton et al. 1964; Fenner, Jansson, and Avery 1968). This mechanism may be partly responsible for hyperventilation during exercise.

The primary role of peripheral chemoreceptors is their response to changes in arterial PO_2. Moderate to severe hypoxemia (Pa_{O_2} less than 60 mm Hg) results in a significant increase in ventilation in all age groups, except newborn, particularly premature, infants, whose ventilation is decreased by hypoxemia (Dripps and Comroe 1947; Rigatto, Brady, and de la Tone Verduzco 1975). Peripheral chemoreceptors are also partly responsible for hyperventilation in hypotensive patients. Respiratory stimulation is absent in certain states of tissue hypoxia, such as moderate to severe anemia and carbon monoxide poisoning; despite a decrease in oxygen content, Pa_{O_2} in the carotid bodies is maintained near normal levels, so the chemoreceptors are not stimulated.

In acute hypoxemia, the ventilatory response via the peripheral chemoreceptors is partially opposed by hypocapnia, which depresses the medullary chemoreceptors. When a hypoxemic environment persists for a few days—for example, during an ascent to high altitude—ventilation increases further as cerebrospinal fluid bicarbonate decreases and pH returns to normal (Severinghaus et al. 1963). However, later studies demonstrated that the return of cerebrospinal fluid pH to normal is incomplete, and a secondary increase in ventilation precedes the decrease in pH, indicating that some other mechanisms are involved (Bureau and Bouverot 1975; Foster, Dempsey, and Chosy 1975). In chronic hypoxemia that lasts for a number of years, the carotid bodies initially exhibit some adaptation to hypoxemia and then gradually lose their hypoxic response. In people native to high altitudes, the blunted response of carotid chemoreceptors to hypoxemia takes 10 to 15 years to develop and is sustained thereafter (Sorensen and Severinghaus 1968; Lahiri et al. 1978). In cyanotic heart diseases, the hypoxic response is lost much sooner but returns after surgical correction of the right-to-left shunts (Edelman et al. 1970).

In patients who have chronic respiratory insufficiency with hypercapnia, hypoxemic stimulation of the peripheral chemoreceptors provides the primary impulse to the respiratory center. If these patients are given excessive levels of oxygen, the stimulus of hypoxemia is removed, and ventilation decreases or ceases. P_{CO_2} further increases, patients become comatose (CO_2 narcosis), and death may follow unless ventilation is supported. Rather than oxygen therapy, such patients need their effective ventilation increased artificially with or without added inspired oxygen.

Response to Carbon Dioxide

The graphic demonstration of relations between the alveolar or arterial PCO_2 and the minute ventilation ($\dot{V}E/PCO_2$) is commonly known as the CO_2 response curve (Fig. 3-8). This curve normally reflects the response of the chemoreceptors and respiratory center to carbon

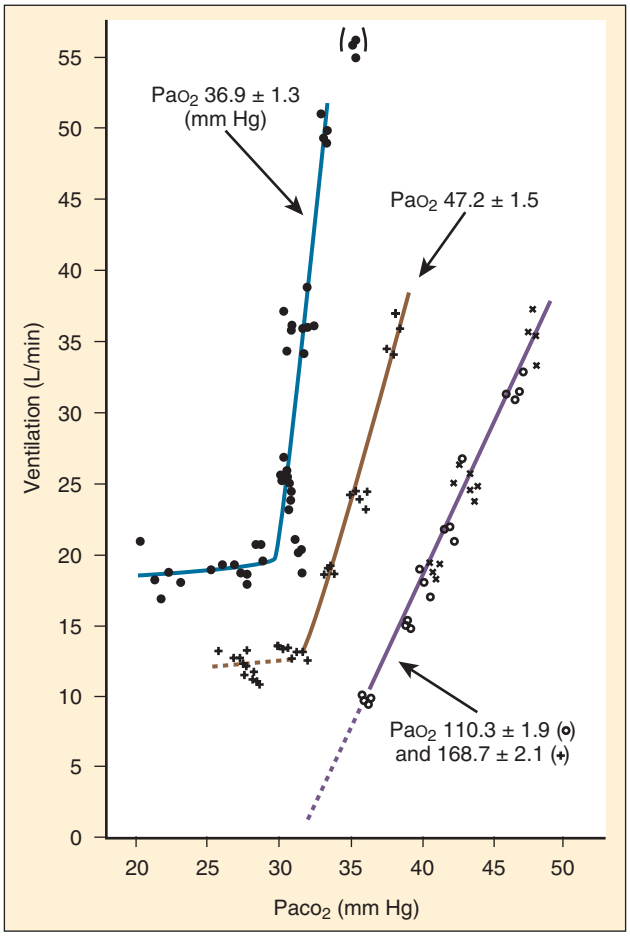

FIG 3-8 Effect of Acute Hypoxemia on the Ventilatory Response to Steady-State Pa_{O_2} in One Subject. Inspired oxygen was adjusted in each experiment to keep Pa_{O_2} constant at the level as indicated. (From Nielsen M, Smith H. Studies on the regulation of respiration in acute hypoxia. *Acta Physiol Scand.* 1951;24:293.)

dioxide. The CO_2 response curve is a useful means for evaluation of the chemical control of breathing, provided that the mechanical properties of the respiratory system, including the neuromuscular transmission, respiratory muscles, thorax, and lungs, are intact. In normal persons, ventilation increases more or less linearly as the inspired concentration of carbon dioxide increases up to 9% to 10%, above which ventilation starts to decrease (Dripps and Comroe 1947). Under hypoxemic conditions, the CO_2 response is potentiated, primarily via carotid body stimulation, resulting in a shift to the left of the CO_2 response curve (Nielsen and Smith 1951) (see Fig. 3-8). On the other hand, anesthetics, opioids, and barbiturates in general depress the medullary chemoreceptors and, by decreasing the slope, shift the CO_2 response curve progressively to the right as the anesthetic concentration increases (Munson et al. 1966) (Fig. 3-9).

A shift to the right of the CO_2 response curve in an awake human may be caused by decreased chemoreceptor sensitivity to CO_2, as seen in patients whose carotid bodies had been destroyed (Wade et al. 1970). It may also be caused by lung disease and resultant mechanical failure to increase ventilation despite intact neuronal response to carbon dioxide. In patients with various central nervous system dysfunctions, the CO_2 response may be partially or completely lost (central congenital hypoventilation syndrome) (Severinghaus and Mitchell 1962). In the awake state, these patients have chronic hypoventilation

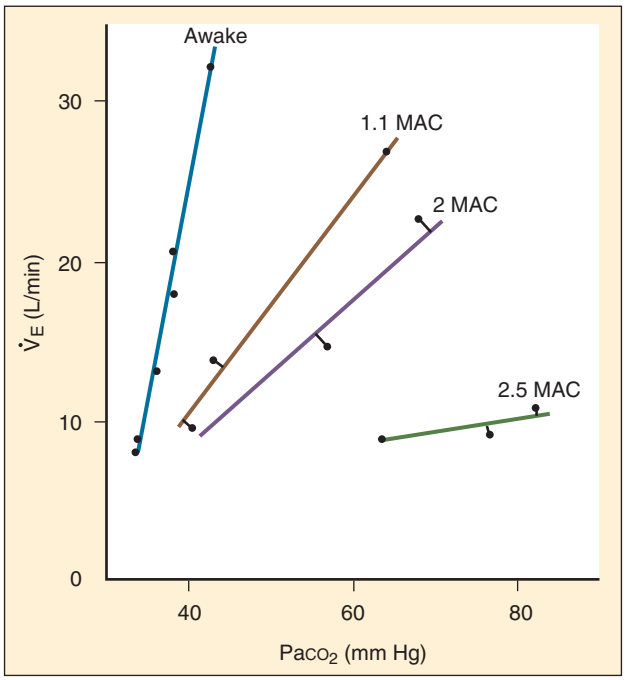

FIG 3-9 CO_2 Response Curve with Halothane. Family of steady-state CO_2 response curves in one subject awake and at three levels of halothane anesthesia. Note progressive decrease in ventilatory response to Pa_{O_2} with increasing anesthetic depth (MAC; ventilatory response in awake state was measured in response to end-tidal P_{CO_2}). (Courtesy Dr. Edwin S. Munson; data from Munson ES, et al. The effects of halothane, fluroxene, and cyclopropane on ventilation: A comparative study in man. *Anesthesiology.* 1966;27:716.)

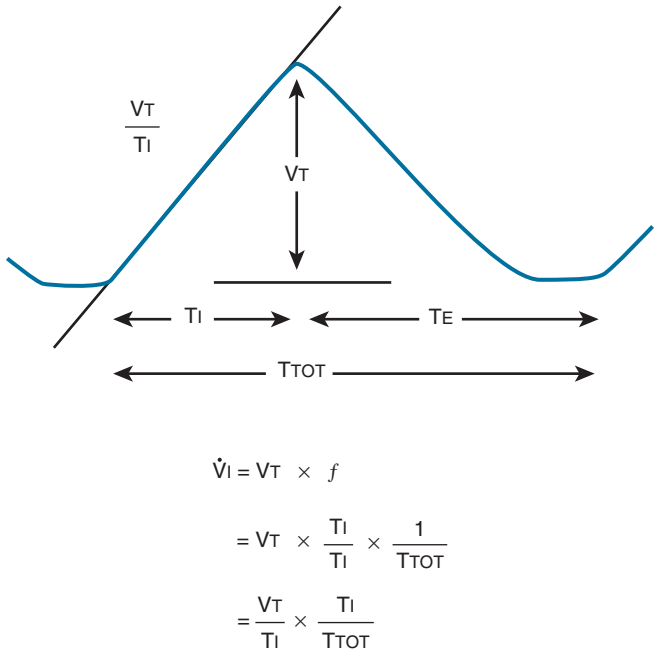

FIG 3-10 Schematic Drawing of Tidal Volume and Timing Components on Time-Volume Axes. *VT,* Tidal volume; *TI,* inspiratory time; *TE,* expiratory time; *TTOT,* total time for respiratory cycle; *f,* respiratory frequency; *VT/TI,* mean inspiratory flow rate; *TI/TTOT,* respiratory duty cycle.

but can breathe on command. During sleep, they further hypoventilate or become apneic to the point of CO_2 narcosis and death unless mechanically ventilated or implanted with a phrenic pacemaker (Glenn et al. 1973).

It has been difficult to separate the neuronal component from the mechanical failure of the lungs and thorax, because the two factors often coexist in patients with chronic lung diseases (Guz et al. 1970). Whitelaw and colleagues (1975) demonstrated that occlusion pressure at 0.1 second ($P_{0.1}$, or the negative mouth pressure generated by inspiratory effort against airway occlusion at FRC) correlates well with neuronal (phrenic) discharges but is uninfluenced by mechanical properties of the lungs and thorax. The occlusion pressure is a useful means for the clinical evaluation of the ventilatory drive.

As mentioned previously, hypoxemia potentiates the chemical drive and increases the slope of the CO_2 response curve ($\dot{V}E/PCO_2$). Such a change has been interpreted as "a synergistic (or multiplicative) effect" of the stimulus, whereas a parallel shift of the curve has been considered as "an additive effect." This analysis may be useful for descriptive purposes, but it is misleading. Because ventilation is the product of tidal volume and frequency ($\dot{V}E = V_T \times f$), an additive effect on its components could result in a change in the slope of the CO_2 response curve. Obviously, the responses of tidal volume and frequency to CO_2 should be examined separately to understand the effect of various respiratory stimulants and depressants.

Milic-Emili and Grunstein (1975) proposed that ventilatory response to CO_2 be analyzed in terms of the mean inspiratory flow (VT/TI, where VT is tidal volume and TI is the inspiratory time) and in terms of the ratio of inspiratory time to total ventilatory cycle duration or respiratory duty cycle (TI/TTOT) (Fig. 3-10). Because the tidal volume is equal to VT/TI × T_I and respiratory frequency (*f*) is 1/TTOT, ventilation can be expressed as follows:

$$\dot{V}E = VT \times f = VT/TI \times TI/TTOT$$

The advantage of analyzing the ventilatory response in this fashion is that VT/TI is an index of inspiratory drive, which is independent of the timing element. The tidal volume, on the other hand, is time dependent, because it is (VT/TI) × TI. The second parameter, TI/TTOT, is a dimensionless index of effective respiratory timing (respiratory duty cycle) that is determined by the vagal afferent or central inspiratory off-switch mechanism or by both (Bradley et al. 1975). From this equation, it is apparent that in respiratory disease or under anesthesia, changes in pulmonary ventilation may result from a change in VT/TI, TI/TTOT, or both. A reduction in TI/TTOT indicates that the relative duration of inspiration decreased or that expiration increased. Such a reduction in the TI/TTOT ratio may result from changes in central or peripheral mechanisms. In contrast, a reduction in VT/TI may indicate a decrease in the medullary inspiratory drive or neuromuscular transmission or an increase in inspiratory impedance (i.e., increased flow resistance, decreased compliance, or both). By relating the mouth occlusion pressure to VT/TI, it becomes clinically possible to determine whether changes in the mechanics of the respiratory system contribute to the reduction in VT/TI (Milic-Emili 1977).

Analysis of inspiratory and expiratory durations provides useful information on the mechanism of anesthetic effects on ventilation. Fig. 3-11 illustrates the effect of pentobarbital, which depresses minute ventilation, and diethyl ether, which "stimulates" ventilation in newborn rabbits. With both anesthetics, the mean inspiratory flow (VT/TI) did not change, but VT decreased because TI was shortened. With pentobarbital, however, TE was prolonged disproportionately, and TI/TTOT and frequency decreased; consequently, minute ventilation was decreased. With ether, on the other hand, ventilation increased

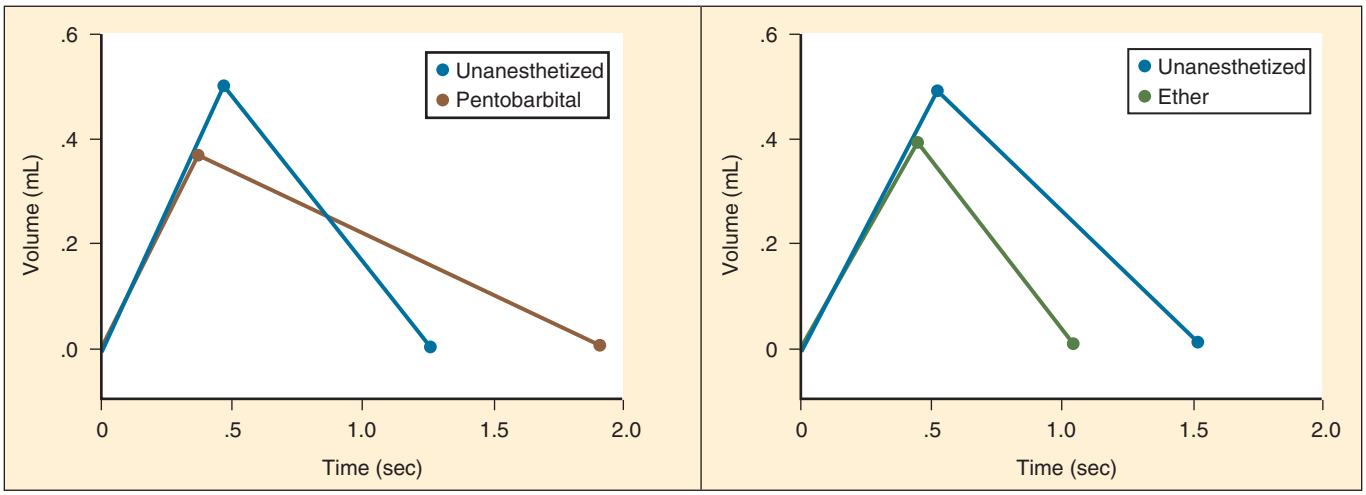

FIG 3-11 Schematic Summary of Changes in the Average Respiratory Cycle in a Group of Newborn Rabbits Before and After Sodium Pentobarbital Anesthesia *(Left)* and Before and During Ether Anesthesia *(Right).* Measurements obtained during spontaneous room air breathing. Zero on the time axis indicates onset of inspiration. Mean inspiratory flow is represented by the slope of the ascending limb of the spirograms. (Modified from Milic-Emili J. Recent advances in the evaluation of respiratory drive. *Int Anesthesiol Clin.* 1977;15:75.)

as the result of disproportionate decrease in Te and consequent increases in TI/TTOT and frequency (Milic-Emili 1977).

Control of Breathing in Neonates and Infants

Response to Hypoxemia in Infants

During the first 2 to 3 weeks of age, both full-term and premature infants in a warm environment respond to hypoxemia (15% oxygen) with a transient increase in ventilation followed by sustained ventilatory depression (Brady and Ceruti 1966; Rigatto and Brady 1972a, 1972b; Rigatto et al. 1975) (Fig. 3-12). In infants born at 32 to 37 weeks' gestation, the initial period of transient hyperpnea is abolished in a cool environment, indicating the importance of maintaining a neutral thermal environment (Cross and Oppe 1952; Ceruti 1966; Perlstein, Edward, and Sutherland 1970). When 100% oxygen is given, a transient decrease in ventilation is followed by sustained hyperventilation. This ventilatory response to oxygen is similar to that of the fetus and is different from that of the adult, in whom a sustained decrease in ventilation is followed by little or no increase in ventilation (Dripps and Comroe 1947). By 3 weeks after birth, hypoxemia induces sustained hyperventilation, as it does in older children and adults.

The biphasic depression in ventilation has been attributed to central depression rather than to depression of peripheral chemoreceptors (Albersheim et al. 1976). In newborn monkeys, however, tracheal occlusion pressure, an index of central neural drive, and diaphragmatic electromyographic output were increased above the control level during both the hyperpneic and the hypopneic phases in response to hypoxic gas mixture (LaFramboise et al. 1981; LaFramboise and Woodrum 1985). These findings imply that the biphasic ventilatory response to hypoxemia results from changes in the mechanics of the respiratory system (thoracic stiffness or airway obstruction), rather than from neuronal depression, as has been assumed (Jansen and Chernick 1983). Premature infants continue to show a biphasic response to hypoxemia even at 25 days after birth (Rigatto 1986). Thus, in terms of a proper response to hypoxemic challenge, maturation of the respiratory system may be related to postconceptional rather than postnatal age.

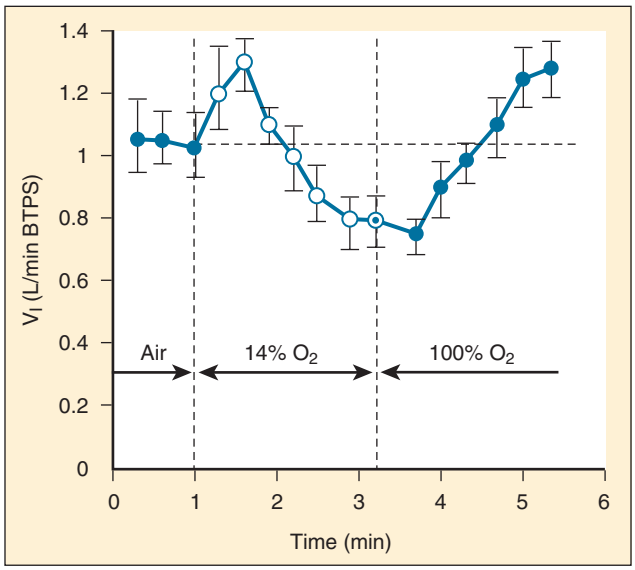

FIG 3-12 Effect on Ventilation of 14% Oxygen (Hypoxia) from Room Air and Then to 100% Oxygen (Hyperoxia) in Three Newborn Infants. Ventilation (mean ± SEM) is plotted against time. During acute hypoxia there was a transient increase in ventilation followed by depression. Hyperoxia increased ventilation. (Modified from Lahiri S, et al. Regulation of breathing in newborns, *J Appl Physiol.* 1978;44:673.)

Response to Carbon Dioxide in Infants

Newborn infants respond to hypercapnia by increasing ventilation but less so than do older infants. The slope of the CO_2 response curve increases appreciably with gestational age, as well as with postnatal age, independent of postconceptional age (Rigatto, Brady, and de la Tone Verduzco 1975; Rigatto et al. 1975, 1982; Frantz et al. 1976). This increase in slope may represent an increase in chemosensitivity, but it may also result from more effective mechanics of the respiratory system. In adults, the CO_2 response curve both increases in slope and