The fourth edition of this text is dedicated to the pioneering individuals instrumental in developing the specialty of veterinary anesthesiology and to the practitioners and scientists who continue to advance veterinary anesthesia and the evolving field of pain management. Every veterinarian, technician, and staff member who daily champions the humaneness of patient care in the academic, research, or clinical environment is to be appreciated. We owe much to members of the veterinary profession, as well as to those in allied medical fields, who have focused their life’s work on discovering better and safer methods of achieving anesthesia and pain alleviation in the animals that we are privileged to attend and heal.

We dedicate our efforts in bringing this edition to publication to our parents for imparting the values of hard work, loyalty, and patience; to our teachers and colleagues for the belief that scientific knowledge gives us the best chance to know what is real; to our wives for their undying devotion and support of family; and to our children and students for making everything joyful and worthwhile.

William J. Tranquilli
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Kurt A. Grimm
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Since the initial publication of *Veterinary Anesthesia* in 1973, the science and art of anesthesia and pain management have matured immeasurably. Today, a comprehensive book covering the entire field is beyond the capabilities of any one individual or area of study. As such, and as Founding Diplomates of the American College of Veterinary Anesthesiologists, it has been gratifying to see numerous authors, more than 65 in all, young and old alike, from a wide array of backgrounds and clinical specialties make contributions to this, the fourth edition and newly titled *Lumb and Jones’ Veterinary Anesthesia and Analgesia*.

We are indebted to Drs. Tranquilli, Thurmon, and Grimm for assuming editorship of this challenging endeavor. We believe that the fourth edition will continue to serve students, academic colleagues, and practitioners alike as the world’s most comprehensive source of information regarding the science and art of anesthesia and pain control in the numerous species that make up the animal world.

William V. Lumb
E. Wynn Jones
Preface

The first edition of *Veterinary Anesthesia* was published in 1973, followed by the second edition in 1984, and the third edition in 1996. The publishing of this, the fourth edition, in 2007 marks this text’s thirty-fourth anniversary.

Many changes have occurred in veterinary medicine and anesthesia during this time, with each succeeding edition of this text attempting to update and document these advances. In recent years, the ever-increasing emphasis on the treatment of animal pain has placed veterinary anesthesiology and pain management in a central role in the delivery of humane veterinary care. Accordingly, several chapters focusing on recent advancements in animal pain management have been included in this revision and, most noticeably, are reflected in the new title, *Lumb and Jones’ Veterinary Anesthesia and Analgesia*. Where possible, we have endeavored to conserve as much of the previous editions’ text as possible so as to continue to provide information on older anesthetic drugs and techniques that might still be employed by veterinarians in various regions of the world. Nevertheless, given the volume of space required to discuss much of the new knowledge and contemporary issues pertinent to veterinary anesthesia and analgesia, retention of much of the previous editions’ text was simply not possible. Fortunately, this information, much of which is of historical interest, will forever be available from earlier editions. It should be noted that some chapters’ text has been retained from previous editions and, as such, the current authors of these chapters (if not the same) wish to acknowledge the continued valuable contributions of earlier authors to this edition, as well. As in previous editions, the fourth edition provides evidence of numerous advances in our scientific and clinical knowledge pertinent to the provision of anesthesia and analgesia in a multitude of animal species.

This Lumb and Jones’ edition has more than 65 contributing authors, offering a wide array of scientific training and clinical experience. As would be expected, many contributors are anesthesiologists, but a number of new authors are specialized in other clinical areas, including clinical pharmacology, surgery, medicine, critical care, cardiology, neurology, urology, ophthalmology, dentistry, radiology, physical rehabilitation, and lab animal medicine. It is hoped that this increased diversity in authorship expertise will provide a comprehensive perspective to the management of anesthesia and pain in patients suffering from an array of clinical conditions and disease. All of the contributing authors have been encouraged to share their personal experiences in an effort to enhance the clinical utility of the information provided. The editors are indebted to the authors for the many hours devoted to the preparation of their individual chapters. Many of these authors have dedicated their careers to the field of veterinary anesthesiology and the humane treatment of animals. In so doing, these individuals have made numerous and, in some instances, monumental contributions to the advancement of veterinary medicine. Included among these individuals are Drs. W. Lumb, E. W. Jones, C. E. Short, W. W. Muir, W. N. McDonell, E. P. Steffey, R. T. Skarda, S. M. Hartsfield, S. C. Haskins, and P. A. Flecknell. Most recently, this dedication was best exemplified by Dr. Roman Skarda’s insistence on his continued contribution to the fourth edition while battling debilitating and painful disease before his eventual passing. These individuals cannot help but provide inspiration to all who have contributed their time and expertise to the completion of this book and to all who benefit from its reading.

Similar to previous editions, this revision can be viewed both as a textbook and as a comprehensive source of scientific knowledge relevant to the clinical management of anesthesia and provision of analgesic therapy. Individuals requiring information on the immobilization and anesthesia of wild, zoo, and laboratory animals also will find chapters devoted to these unique circumstances. In addition to chapters on cardiovascular, respiratory, nervous system, and acid-base physiology, the pharmacology of various classes of drugs employed in the delivery of anesthesia and analgesia has been reviewed and updated. Chapters on anesthetic equipment, monitoring, mechanical ventilation, and regional analgesic techniques are provided. Chapters covering acupuncture, physical rehabilitation, and palliative analgesia of companion animals have been added. Chapters continue to be devoted to the anesthesia of specific species and classes of animals including dogs, cats, horses, swine, ruminants, lab animals, zoo animals, free ranging terrestrial and aquatic mammals, birds, reptiles, amphibians, and fish. Several chapters discussing the unique anesthesia and pain management requirements of companion animals with specific diseases have again been included, as have chapters on specific surgical patients and procedures. New chapters on dental, cancer, orthopedic, and equine colic patients have been included in this edition. As in the third edition, chapters have been organized into sections to aid readers in locating specific information rapidly.

In closing, the editors extend their thanks to all of the anesthesiology faculty and staff at the University of Illinois for their hard work and understanding. Without their support, time would not have been available for the editorial assignments required by such a task.

The editors are also deeply indebted to and thank Erin Gardner and the staff at Blackwell Publishing for their untiring support and encouragement.

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Section I
GENERAL TOPICS
Chapter 1

History and Overview of Veterinary Anesthesia

John C. Thurmon and Charles E. Short

Introduction

The earliest recorded attempts to induce anesthesia appeared to have been performed in humans. Drugs and techniques used included opiates, alcohol, and asphyxiation by compression of the carotid arteries to induce unconsciousness, thus alleviating the pain of surgery. In 1540, Paracelsus produced ether and reported it to have a soporific effect in birds. Despite this discovery, no further progress was made until chemistry was developed and carbon dioxide and several other gases, including oxygen, were discovered.

In 1800, Sir Humphrey Davy suggested that nitrous oxide might have anesthetic properties. Approximately 20 years later, H. H. Hickman (1824) demonstrated that pain associated with surgery in dogs could be alleviated by inhalation of a mixture of nitrous oxide and carbon dioxide. He reasoned that the latter increased the rate and depth of breathing, thus enhancing the effects of nitrous oxide. More recent studies have shown that unconsciousness can be induced in 30 to 40 s in piglets breathing carbon dioxide (50%) alone in oxygen (50%).

It was not until 1842 that ether was used for human anesthesia. Two years later, a dentist, Horace Wells (1844), discovered the anesthetic properties of nitrous oxide. Although this finding was neglected for several years, nitrous oxide was reintroduced in humans in 1862. C. T. Jackson, a Boston physician, was the first to employ ether extensively in animals.

Chloroform was discovered by Liebig in 1831, but it was not until 1847 that it was first used to induce anesthesia in animals by Flourens and in people by J. Y. Simpson of Edinburgh, Scotland. With the introduction of chloroform, reports began to appear in the veterinary literature of its use in animals. Dadd routinely used general anesthesia in animals and was the first in the United States to advocate humane treatment of animals and the application of scientific principles (i.e., anesthesia) in veterinary surgery.

In 1875, Ore published the first monograph on intravenous anesthesia using chloral hydrate; 3 years later, Humbert described its use in horses. Pirogoff was the first to attempt rectal anesthesia with chloral hydrate in 1847. The rectal administration of chloral hydrate was used later in veterinary practice. Intraperitoneal injection was first used in 1892 in France. Thus, the various routes of administration of general anesthetics to animals were established by the end of the 19th century.

After the initial isolation of cocaine by Albert Niemann of Germany in 1860, Anrep, in 1878, suggested the possibility of using cocaine as a local anesthetic. In 1884, Kohler used cocaine for local anesthesia of the eye, and Halsted described cocaine nerve-block anesthesia a year later. Its use was popularized by Sir Frederick Hobday, an English veterinarian. Thereafter, G. L. Corning was credited for inducing cocaine spinal anesthesia in dogs in 1885. From his description, however, it would appear that he induced epidural anesthesia. In 1898, August Bier of Germany induced true spinal anesthesia in animals and then in himself and an assistant.

While local infiltration was popularized by Reclus (1890) and Schleich (1892), conduction anesthesia was first introduced by Halsted and Hall in New York in 1884. These techniques increased in popularity with the discovery of local anesthetics less toxic than cocaine. These developments enabled Cuille and Sendrail (1901) of France to induce subarachnoid anesthesia in horses, cattle, and dogs. Cathelin (1901) reported epidural anesthesia in dogs, but it remained for Retzgen, Benesch, and Brook to apply this technique in large animal species in the 1920s. Although paralumbar anesthesia was employed in humans by Sellheim in 1909, it was not until the 1940s that Farquharson and Formston applied this technique in cattle. Despite these promising developments with local analgesic techniques in the latter half of the 19th century, and perhaps owing to unfavorable results, general anesthesia was not readily adopted by the veterinary profession until well into the 20th century. It is sad to say, but a “heavy hand,” without analgesia/anesthesia, was the stock in trade of many practicing veterinarians.

In small domestic animals, ether and chloroform were commonly administered in the early part of the 20th century. However, general anesthesia became more widely accepted after discovery of the barbiturates in the late 1920s and, in particular, with the development of pentobarbital in 1930. Barbiturate anesthesia received an additional boost with the introduction of the thiobarbiturates and particularly with thiopental in 1934. Because of rough, prolonged recovery, the acceptance of general
anesthesia in large animals was delayed until phenothiazine derivatives were introduced by Charpentier in France in 1950.

General anesthesia of large farm animals was further advanced by the discovery of fluorinated hydrocarbons and the development of large animal anesthetic equipment for their safe administration. Discovery of newer drugs (e.g., tranquilizers, opioids, α2-adrenergic agonists, dissociatives, muscle relaxants, and inhalant anesthetics) has further advanced the utility of veterinary anesthesia in large and small animal species.5

Organized Veterinary Anesthesia in North America

During the late 1960s and early 1970s, a small group of physician anesthesiologists made it possible for a number of future diplomates of the American College of Veterinary Anesthesiologists (ACVA) to participate in their programs and to learn about the development of new anesthetic drugs and techniques. Among these physicians were Robert Dripps, University of Pennsylvania; Arthur Keats, Baylor University; Mort Shulman and Max Sadolv, University of Illinois; and Edmond I. Eger, University of California Medical College. During this same period, E. W. Jones (Oklahoma State University) and William Lumb (Colorado State University) were making significant contributions to the field of veterinary anesthesia while at their respective institutions. Jerry Gillespie was also making a unique contribution through his work on respiratory function of anesthetized horses.

Even though there were a number of interested faculty within veterinary colleges and research laboratories, not until 1970 was a major thrust directed at organizing veterinarians. Initially, a society of veterinary anesthesia was perceived. Later this society became the American Society of Veterinary Anesthesia (ASVA). Membership in the ASVA was open to all individuals working in the veterinary profession who had an interest in veterinary anesthesia. In 1970, the first organizational meeting was held in conjunction with the American Veterinary Medical Association (AVMA) to coordinate the efforts/interest of all those wishing to organize and develop the specialty of veterinary anesthesia. Their primary goal was to improve anesthetic techniques and to disseminate knowledge whenever and wherever possible. Charles Short was elected the first president of the new society. The ASVA was designed expressly to promote dissemination of information on veterinary anesthesia irrespective of individual training or background. Of major interest was the selection of individuals to speak at the ASVA and other scientific and educational meetings (e.g., the AVMA, the American Animal Hospital Association [AAHA], and the American Association of Equine Practitioners [AAEP]). As the ASVA developed, publication of articles on anesthesia seemed in order. Bruce Heath accepted editorial responsibilities of articles submitted for the ASVA journal. In 1971, John Thurmon chaired the Ad Hoc Committee to establish the American College of Veterinary Anesthesiologists. The AVMA had established guidelines for the selection of founding-charter diplomates of specialty organizations. The Ad Hoc Committee requirements for charter diploma status included 10 years of active service in the specialty, significant publications, intensive training, and being the head of an anesthesiology program or spending a major portion of one’s professional time in anesthesia or a closely related subject area. Seven members of the ASVA were found to meet these qualifications. This group would later become the founding diplomates of the ACVA.

Between 1970 and 1975, the constitution and bylaws were drafted and formalized. In 1975, the AVMA Council on Education recommended preliminary approval of the ACVA. This was confirmed by the AVMA House of Delegates in that same year. Thus, the ACVA was officially established in North America. Of importance throughout this process were the insight and efforts of Drs. Lumb and Jones, after which this text is named. They greatly assisted in the establishment of the ACVA because of their sincere interest in the sound principles of veterinary anesthesia. During this period, several didactic texts were published on animal anesthesia that helped to establish anesthesia as a stand-alone discipline and specialty within veterinary medicine. The first edition of this text, Lamb and Jones’ Veterinary Anesthesia, was published in 1973; Clinical Veterinary Anesthesia, edited by Charles Short, was published in 1974; and Textbook of Veterinary Anesthesia, edited by Larry Soma, was published in 1971.

During the late 1970s, many of the founding diplomates began to establish residency training programs in their respective veterinary colleges. From 1975 to 1980, the ACVA developed continuing education programs, programs in self-improvement, and programs for testing and certification of new diplomates. Along with residency training programs, new faculty positions were created for training veterinary anesthesiologists in a number of colleges of veterinary medicine across North America. In 1980, the ACVA sought and was granted full accreditation by the AVMA, an effort headed by Eugene Steffey, then president of the ACVA.

During the past 3 decades, a number of other organizations around the world have promoted and contributed greatly to the standing of veterinary anesthesia. They include the Association of Veterinary Anaesthetists of Great Britain and Ireland (AVA), as well as the Veterinary Anesthesia and Surgery Association in Japan. These associations were instrumental in organizing the first International Congress of Veterinary Anesthesiology with its stated objective of globally advancing the field of veterinary anesthesia. The first International Congress of Veterinary Anesthesiology was held in Cambridge, England, in 1982, followed by congresses in Sacramento, California, in 1985; in Brisbane, Australia, in 1988; in Utrecht, the Netherlands, in 1991; in Guelph, Canada, in 1994; in Thessaloniki, Greece, in 1997; in Bern, Switzerland, in 2000; in Knoxville, Tennessee, in 2003; and in Santos, Brazil, in 2006.

Concurrently, organized veterinary anesthesia was being advanced in Europe. Veterinary anesthesiologists in the United Kingdom established the Association of Veterinary Anaesthetists and awarded the Diploma of Veterinary Anaesthesia to those with specialty training. Later, interests in board specialization became evident in the United Kingdom and many European countries, resulting in the establishment of the European College of Veterinary Anesthesiologists (ECVA). Currently, a number of veteri-
nary anesthesiologists are boarded by both the ACVA and the ECVA. For further information concerning the early history of anesthesia, the reader is referred to a number of sources.6–9

The establishment of the ACVA and the ECVA in recent decades has advanced veterinary anesthesia on a worldwide stage primarily through the increased availability of scientific meetings and literature. Both the ACVA and the ECVA have, as their official scientific publication, the *Journal of Veterinary Anaesthesia and Analgesia*.

**Definitions**

The term *anesthesia*, derived from the Greek term *anaisthæsia*, meaning “insensibility,” is used to describe the loss of sensation to the entire or any part of the body. Anesthesia is induced by drugs that depress the activity of nervous tissue locally, regionally, or within the central nervous system (CNS). From a pharmacological viewpoint, there has been a significant redefining of the term *general anesthesia*.10 Both central nervous stimulants and depressants can be useful general anesthetics.11 Several terms are used in describing the effects of anesthetic drugs:

1. **Analgesia** refers to freedom from or absence of pain.
2. **Tranquilization** results in behavioral change wherein anxiety is relieved and the patient becomes relaxed but remains aware of its surroundings. In this state, it may appear to be indifferent to minor pain.
3. **Sedation** is a state characterized by central depression accompanied by drowsiness. The patient is generally unaware of its surroundings but responsive to painful manipulation.
4. **Narcosis** is a drug-induced state of deep sleep from which the patient cannot be easily aroused. Narcosis may or may not be accompanied by analgesia.
5. **Hypnosis** is a condition of artificially induced sleep, or a trance resembling sleep, resulting from moderate depression of the CNS from which the patient is readily aroused.
6. **Local analgesia** (anesthesia) is a loss of sensation in circumscribed body area.
7. **Regional analgesia** (anesthesia) is insensitivity in a larger, though limited, body area (e.g., paralumbar nerve blockade).
8. **General anesthesia** is drug-induced unconsciousness that is characterized by controlled but reversible depression of the CNS and analgesia. In this state, the patient is not arousable by noxious stimulation. Sensory, motor, and autonomic reflex functions are attenuated.
9. **Surgical anesthesia** is the state/plane of general anesthesia that provides unconsciousness, muscular relaxation, and analgesia sufficient for painless surgery.
10. **Balanced anesthesia** is induced by multiple drugs. Drugs are targeted to specifically attenuate individual components of the anesthetic state; that is, consciousness, analgesia, muscle relaxation, and alteration of autonomic reflexes.
11. **Dissociative anesthesia** is induced by drugs (e.g., ketamine) that dissociate the thalamocortical and limbic systems. This form of anesthesia is characterized by a cataleptoid state in which the eyes remain open and swallowing reflexes remain intact. Skeletal muscle hypertonus persists unless a strong sedative, peripheral or central muscle relaxant, or other concurrent medications are administered.

**Reasons for Administering Anesthesia**

First and foremost, anesthetics alleviate pain and induce muscle relaxation, essential for safe surgery.12 Other important uses include restraint, safe transportation of wild and exotic animals, various diagnostic and therapeutic procedures, euthanasia, and the humane slaughter of food animals.

**Types of Anesthesia**

The diverse uses for anesthesia (as it relates to immobilization, muscle relaxation, and analgesia) and the requirements peculiar to species, age, and disease state necessitate the use of a variety of drugs, drug combinations, and methods. Anesthesia is often classified according to the type of drug and/or method/route of drug administration:

1. **Inhalation**: Anesthetic gases or vapors are inhaled in combination with oxygen.
2. **Injectable**: Anesthetic solutions are injected intravenously, intramuscularly, and subcutaneously. Other injectable routes include intrathoracic and intraperitoneal. These latter two routes are not generally recommended.
3. **Oral or rectal**: These routes are ordinarily used for liquid anesthetics or suppositories.
4. **Local and conduction**: Anesthetic drug is applied topically, injected locally into or around the surgical site (field block), or injected around a large nerve trunk supplying a specific region (conduction or regional nerve block). In the latter instance, the injection may be perineural (nerve block) or into the epidural or subarachnoid space (true spinal analgesia).
5. **Electronarcosis, electroanesthesia, or electrosleep**: Electrical currents are passed through the cerebrum to induce deep narcosis. Even though there have been successful studies, this form of anesthesia has never gained popularity and is rarely used in veterinary practice. Electronarcosis should not be confused with the inhumane practice of electroimmobilization.
6. **Transcutaneous electrical nerve stimulation (TENS, TNS, or TES)**: Local analgesia is induced by low-intensity, high-frequency electric stimulation of the skin through surface electrodes.
7. **Hypnosis**: A non–drug-induced trancelike state sometimes employed in rabbits and birds.
8. **Acupuncture**: An ancient Chinese system of therapy using long, fine needles to induce analgesia.
9. **Hypothermia**: Body temperature is decreased, either locally or generally, to supplement insensitivity and decrease anesthetic drug requirement and reduce metabolic needs. It is primarily used in neonates or in patients undergoing cardiovascular surgery.
References

Pharmacology

Anesthesia is, of necessity, a reversible process. Knowledge of the factors underlying production of anesthesia, and those that may modify it, is essential to the success of the procedure. The dose of anesthetic and the techniques for its administration are based on the average normal healthy animal. Because of the many phenomena that modify the effect of an anesthetic, it is unlikely that any given animal will be exactly average.

Marked variations in response to a standard dose of anesthetic result from the interplay of many factors, especially those related to the central nervous system (CNS) status (excited or depressed) and metabolic activity of the animal, existing disease or pathology, and the uptake and distribution of the anesthetic.

Biological Variation

Since elimination of anesthetics depends on the species and the metabolic processes within the animal, conditions affecting the metabolic rate exert a marked influence on anesthetic effect. Small animals have a higher basal metabolic rate per unit of surface area than large animals; therefore, in general, the smaller the animal, the larger is the dose per unit of body weight necessary for anesthesia. Animals with large quantities of fat, which is a relatively inactive nonmetabolizing tissue, have a lower basal metabolic rate per unit of body weight and usually require less anesthetic than lean muscular animals in good condition. Animals in poorer condition may also require less anesthetic. Dogs kept on a low food intake causing weight losses of 10% to 20% showed a marked increase in duration of anesthesia after a single anesthetic injection. In newborns, the basal metabolic rate is low. It gradually increases to its highest point at puberty through early adulthood and then gradually declines. Response to barbiturates varies in dogs of differing ages. Very young animals and older adult animals are most sensitive, whereas dogs in the age range of 3 to 12 months are least sensitive. These age variations are also related to changes in liver enzyme activity. Changes in metabolism with age are not as clear-cut as originally thought. This probably reflects that neither gross weight nor surface area are reliable measures of the active tissue mass of the body. In humans, at least, data on fat-free body weight indicate little change between young and aged adults. The basal metabolic rate of males is approximately 7% higher than that of females. In females, a rise occurs during pregnancy, owing to the metabolic activity of the fetuses. Conflicting evidence regarding sex differences in susceptibility to anesthetics has been reported. For example, pregnant rats were most susceptible, nonpregnant females less, and male rats least susceptible to anesthetic effect. In contrast, Kennedy could find no sex variance in the response of mice to barbiturate anesthesia. Female rats have been shown to be more sensitive to muscle relaxants than males of a similar age. Apparently, hormones may cause minor differences in an individual’s response to an anesthetic.

Pharmacogenetic Differences

Variation in the dose response to drugs because of genetic-related factors can be found in the literature. As examples, the heritable difference in the ability of rabbits to hydrolyze atropine and cocaine, genetic variations in response to pentobarbital in mice, and strain sensitivity to nitrous oxide and to non-oxygen-dependent reductive biotransformation of halothane in rats have all been reported. In a few people, plasma cholinesterase has been found to be completely absent or replaced by an inactive variant with resultant prolonged action of succinylcholine. Some breeds of swine are susceptible to malignant hyperthermia. Metabolic rate increases with activity; hence, active animals require relatively larger doses of anesthetic agents. Mice
have been shown to be most sensitive to pentobarbital in the early morning. A seasonal response to morphine has been recorded in rabbits, and circadian rhythms have been shown to modify minimum alveolar concentrations for halothane and other inhalant anesthetics by 5% to 10% in rats.\(^7\)

**Pharmacokinetics**

General anesthesia is produced by the action of an anesthetic on the brain and spinal cord. The agent must therefore achieve access to the central nervous tissue. Although Van Dyke and Chenoweth\(^12\) demonstrated that significant quantities of some inhalation anesthetics are metabolized within the body, for practical purposes they are primarily exhaled. Small amounts are eliminated in feces and urine or diffused through the skin and mucous membranes. Thus, providing respiration and circulation are maintained, inhalants are readily eliminated from the body. In contrast, injectable agents depend on redistribution within the body, biotransformation, principally in the liver, and excretion via the kidneys. With injectable anesthetics, there is less control over the elimination process; for this reason, some consider them to be more dangerous than inhalant anesthetics.

Anesthetics are commonly administered by intravenous injection and occasionally by intramuscular, intrathoracic, intraperitoneal, subcutaneous, and even oral or rectal routes. Intravenous administration bypasses the absorption phase of the drug with the consequences that onset and intensity of action are less variable, titration of dose according to response is facilitated, and the risk of toxicity lessens quickly with the progressive decline of drug concentration in the plasma.\(^13\)

The body may be considered to have multiple compartments (Table 2.1), which are differentiated by blood supply and tissue-blood partition coefficients. After initial intravenous injection, mixing and dilution rapidly occur, and an initial blood concentration of the drug is established. Blood thus becomes the medium by which the drug is delivered to and removed from its site of action. Factors affecting drug concentration and/or availability in the plasma also affect its concentration and availability at the site of action. Binding of drugs to plasma protein, in which form they cannot readily penetrate cellular membranes, and the removal of drugs by tissues that store, metabolize, and excrete them are both important factors that lower the effective concentration of drugs at their site of action.\(^13,14\) Binding is a reversible fusion of small molecules, such as barbiturates, with protein or other macromolecules, thereby limiting penetration of cellular membranes by molecular size, ionization, and limited lipid solubility. Protein binding varies with the properties of the drug, its concentration, and plasma pH and protein concentration. The fraction of bound drug increases with decreasing drug concentration and vice versa, and is modified by the presence of other drugs that compete for available binding sites. The rate of clearance of drug from the blood, the drug’s distribution to the tissues, and availability of drug to produce its desired effects thus may all be modified by the drug concentration, plasma pH and protein, state of body hydration, and minimally by the presence of other drugs.\(^14\)

After initial dilution within the vascular system, the drug is distributed to the various tissue compartments according to their perfusion, their capacity for the drug (volume of tissue \(\times\) tissue-blood partition coefficient), and the partial pressure gradient of drug between blood and tissue. The vessel-rich group of tissues achieves equilibrium with the blood more quickly than do other tissue groups (Table 2.2).\(^14\) Although fat and muscle groups have similar tissue blood flows per unit of tissue, the higher solubility of most anesthetics (e.g., thiobarbiturates) in fat than in muscle accounts for the greater time required to achieve equilibrium for fat than for muscle. Changes in tissue blood flow, solubility, and blood-tissue partial pressure gradients thus influence uptake and distribution of intravenous anesthetics. Since the plasma concentration of an intravenous anesthetic falls rapidly (Fig. 2.1),\(^15\) and its partial pressure is quickly exceeded by that in the vessel-rich tissues, anesthetic reenters the blood from these tissues to be redistributed to tissues that have greater time constants. This redistribution reduces anesthetic concentration in the brain, anesthesia lightens, and anesthetic accumulates in muscle, fat, and vessel-poor tissues.

The ultimate effect of any general anesthetic is contingent upon its ability to cross the blood-brain barrier. This barrier, like the placenta, has permeability characteristics of cellular membranes and therefore limits the penetration of nonlipophilic, ionized, or protein-bound drugs. Penetration of these barriers is, in fact, so slow that little or no drug of the aforementioned types enters the brain or fetus after a single intravenous bolus dose. The barriers are not, however, absolute, and slow penetration does occur, becoming significant when the level of drug is maintained over a prolonged period.\(^13\) The high lipid solubility of thiopental relative to pentobarbital accounts for the more rapid onset of, and recovery from, anesthesia induced by the former.\(^16\)

Within moments of tissue uptake and redistribution, elimination of the drug begins. The circulation distributes drug to vessel-rich organs able to biotransform and/or excrete it. The liver is the primary site of biotransformation, whereas the kidney is primarily responsible for excretion. Other organs may occasionally be involved, such as in the elimination of morphine via the gastrointestinal tract.\(^13\) Biotransformation increases the rate of disappearance of the drug from active sites and converts most hypnotics

<table>
<thead>
<tr>
<th>Group</th>
<th>Region</th>
<th>Mass (kg)</th>
<th>% Cardiac Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel rich</td>
<td>Brain</td>
<td>1.4</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Liver (splanchnic)</td>
<td>2.6</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Heart</td>
<td>0.3</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
<td>0.3</td>
<td>23</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Muscle</td>
<td>31.0</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Skin</td>
<td>3.6</td>
<td>8</td>
</tr>
<tr>
<td>Fat</td>
<td>Adipose tissue</td>
<td>12.5</td>
<td>6</td>
</tr>
<tr>
<td>Vessel poor</td>
<td>Residual tissue</td>
<td>11.3</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>63.0</td>
<td>100</td>
</tr>
</tbody>
</table>

From Bard.\(^73\) Data on adipose tissue and residual tissue have been added.
and anesthetics from lipophilic nonpolar compounds to polar water-soluble derivatives capable of excretion by the kidneys. Without such conversion, elimination of lipophilic nonvolatile drugs is markedly prolonged owing to reabsorption, after glomerular filtration, into the systemic circulation via the tubular epithelium. Although the metabolites produced by biotransformation are usually less active, in the case of prodrugs (e.g., chloral hydrate) toxic compounds may be produced.\textsuperscript{17} The biotransformation rate is determined by the drug concentration at the site of metabolism (e.g., plasma concentration and hepatic blood flow) and by the intrinsic rate of the process. The latter is determined by such factors as enzymatic activity and cofactor availability (e.g., genetics, presence of other drugs, nutrition, or hypoxia).\textsuperscript{13} Most drug metabolism follows first-order kinetics (a constant fraction is metabolized in a given period). In the event that the concentration exceeds the capacity of the biotransformation process (saturation), elimination assumes zero-order kinetics, where a constant amount of drug is eliminated,\textsuperscript{13} and the pharmacological effect is disproportionately prolonged with increasing or multiple doses.\textsuperscript{16} Species variations in biotransformation may also be encountered; for example, the duration and effects of lidocaine in humans, dogs, guinea pigs, and rats differ, and the glucuronide conjugation of drugs, such as morphine, salicylic acid, and propofol, in cats markedly differs from dogs.

Factors Modifying Pharmacokinetics

It is thus apparent that many factors of common occurrence, such as rate of administration and concentration of anesthetic, physical status, muscular development, adiposity, respiratory and circulatory status, drug permeability coefficients, prior and/or concurrent drug administration, fear, recent feeding, and solubility of inhalant anesthetics in bags and hoses may all modify the up-

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Blood Flow (L/min)</th>
<th>Tissue Volume (L)</th>
<th>Thiopental Tissue-Blood Partition Coefficient</th>
<th>Capacity\textsuperscript{a}</th>
<th>Time Constant (min)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel-rich</td>
<td>4.5</td>
<td>6</td>
<td>1.5</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Muscle group</td>
<td>1.1</td>
<td>33</td>
<td>1.5</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>Fat group</td>
<td>0.32</td>
<td>14.5</td>
<td>11.0</td>
<td>160</td>
<td>500</td>
</tr>
<tr>
<td>Vessel-poor</td>
<td>0.075</td>
<td>12.5</td>
<td>1.5</td>
<td>19</td>
<td>250</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Tissue volume × tissue-blood partition coefficient.

\textsuperscript{b} Capacity/blood flow.

From Saidman.\textsuperscript{14}
take, distribution, and elimination of anesthetics. Concentration and rate of injection of a given dose affect anesthetic action, particularly with rapid-acting anesthetics. The more dilute the drug or slower the injection, the less is the effect produced.

Modification of cardiac output, ventilation, ventilation-perfusion ratios, and/or alveolar-capillary diffusion from any cause will influence both the uptake and elimination of inhalant drugs, most especially those of greater solubility. Some common examples causing these modifications include diaphragmatic hernia, pulmonary edema, pulmonary emphysema or atelectasis, and recumbency in large animals.

Permeation of the blood-brain barrier by narcotics and narcotic antagonists is contingent on partition coefficients, ionization, and protein binding, and is therefore influenced by hypocarbia and hypercarbia. For example, during hypocarbia (alkalemia), higher serum morphine concentrations, higher drug distribution in the lipid phase, and increased ratio of free base-acid salt of morphine facilitate penetration of morphine into the canine brain, despite decreased cerebral blood flow.\(^{19}\)

Variation in distribution of blood to the vessel-rich and vessel-poor tissues, to fat, to muscle, and to the alveoli themselves will modify the pattern of induction and recovery. In shock, the proportion of the cardiac output flowing to the brain is increased, and the potential for redistribution is reduced. Owing to reduced blood volume, dilution of the drug is also diminished, as is hepatic and renal blood flow. The reduction in blood volume diminishes both biotransformation and renal excretion. Induction is thus rapid, the dose required is reduced, and recovery is delayed. Even removal of 2% of the body weight in blood tremendously prolongs dogs’ recovery time from thiopental anesthesia.\(^{2}\) It may thus be concluded that significant hemorrhage, such as might accompany a surgical bleed, will significantly increase sleeping time.

When fear, struggling, or fever occur, increases in cardiac output and decreases in circulation time prolong the time necessary for equilibration of inhalant anesthetic concentration between alveoli and pulmonary capillaries. Muscle and skin blood flow is increased, induction of inhalant anesthesia is delayed, and more anesthetic is required. It is well known that animals showing a period of excitement during induction of inhalant anesthesia always require more anesthetic. This causes a tendency toward overdosing, with its attendant dangers. For this reason, preanesthetic sedation is often advantageous.

Hounds such as the whippet, greyhound, Afghan, borzoi, wolfhound, and saluki have a low fat-to-body mass ratio, a low muscle-to-body mass ratio, and consequent increased blood levels of unbound drug when anesthetized with a barbiturate. Anesthesia with a barbiturate alone is thus characterized by increased sleep times, rougher recoveries, and occasional fatalities. Thin-type muscled or emaciated patients may have similar characteristics.\(^{20}\)

According to Dukes,\(^{21}\) a large meal of meat may increase the metabolic rate of dogs as much as 90% above the basal level (specific dynamic effect). Carbohydrate and fat also produce this elevation, though to a lesser extent. It is usually 12 to 18 h after the last meal before the basal metabolic rate is attained in carnivorous animals. In contrast, birds are more susceptible to starvation. A 6-h preanesthetic fast may induce hypoglycemia and marked sensitivity to depressant drugs in small birds.\(^{22}\) Certainly it is important to consider that starvation induces low plasma glucose, mobilizes liver glycogen stores, and reduces circulating fatty acids, all of which may alter drug detoxification rates.\(^{7}\) In addition to altering the metabolic rate, feeding increases chylomicrons in the blood. It has been shown that thiobarbiturates localize in these, which shortens the anesthesia time.\(^{23}\) Feeding also increases blood flow to the abdominal viscera and influences overall anesthetic distribution.

With the exception of the gastrointestinal tract, nitrogen is the major gas constituent of closed internal body spaces. Owing to the high blood-gas partition coefficient of nitrous oxide relative to nitrogen and the gases of the intestinal tract, administration of nitrous oxide transfers this gas to internal gas spaces of the body. The volume or pressure of the gases within these spaces may thus increase. Volume increases in highly compliant spaces (e.g., intestinal, peritoneal, and thoracic) and pressure changes in non-compliant spaces (e.g., sinuses and middle ear).\(^{15}\) In the intestinal loops of dogs anesthetized with halothane-oxygen and 75% nitrous oxide, the intestinal gas volume was shown to increase 1.8 times in 2 h and 2.5 times in 4 h, respectively. In experimental pneumothorax in dogs, the increase was more rapid: A 200-mL pneumothorax was doubled in 10 min, tripled in 45 min, and quadrupled in 2 h. In pneumoencephalograms in dogs, the inhalation of 75% nitrous oxide increased cisternal pressure by 60 torr in 10 min.\(^{15}\) Consequently, the use of nitrous oxide is contraindicated in patients with pneumothorax, in those undergoing pneumoencephalograms, and in patients with intestinal obstructions requiring prolonged anesthesia.

Most noninhaled drugs are weak acids (barbiturates) or weak bases (narcotics, narcotic antagonists, and muscle relaxants). Once the drug is injected, equilibrium between ionized and non-ionized forms of drug depends on the pH of the blood or tissues and the dissociation constant (\(pK_a\)) of the drug. A difference in pH between tissue and blood may thus cause a drug concentration difference. Plasma acidosis, for instance, increases intracellular barbiturate but decreases intracellular narcotic concentration.\(^{14}\)

Drug availability at the site of action or of elimination is also modified by the degree of protein binding. Protein binding is diminished by uremia, hypoproteinemia, and minimally by administration of drugs competing for the binding sites. It may also be impaired by a change in pH or in the nature of the protein secondary to disease, or by dehydration. Decreased binding may make more drug available for specific action, with consequent increased sensitivity to a normal dose.\(^{14}\)

Preanesthetic administration of opioid analgesics generally lowers the metabolic rate, whereas atropine administration causes a slight rise. When they are administered in combination, however, the metabolic rate is usually decreased. Generally speaking, tranquilizers can be expected to lower the metabolic rate.

It has been known for decades that administration of various drugs and pesticides can either stimulate or inhibit hepatic microsomal drug-metabolizing enzymes (enzyme induction and enzyme inhibition). More than 200 drugs are recognized as enzyme
A nephrotoxic vinyl ether (compound A). Concentrations of compound A in the anesthetic circuit rarely reach nephrotoxic concentrations even during low-flow anesthesia unless the carbon dioxide–absorbant material has become desiccated.

Inhalant anesthetics are variably metabolized to inorganic fluorides and hexafluoroisopropanol by cytochrome P-450, which, although produced in less than toxic concentrations (<50 µm/L), are potentially toxic to both the liver and the kidney. The potential for such toxicity during anesthesia is enhanced by hypoxia. Hepatic microsomal enzymes may also be inhibited, with delay of biotransformation. Known inhibitors include organophosphorus insecticides, pesticide synergists of the methylene-dioxyphenyl type, guanidine, carbon tetrachloride, chloramphenicol, tetracyclines, and certain inhalation anesthetics. Inhibition has been illustrated by the prolonged plasma half-lives of barbiturates, narcotics, and local anesthetics during halothane anesthesia and by prolonged barbiturate anesthesia after a prior course of barbiturates, narcotics, and local anesthetics during halothane anesthesia.

### Table 2.3. Examples of drugs capable of producing microsomal enzyme induction.

<table>
<thead>
<tr>
<th>Hypnotics</th>
<th>Antihistaminics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturates</td>
<td>Diphenylhydramine (Benadryl)</td>
</tr>
<tr>
<td>Glutethimide</td>
<td>Cortisone</td>
</tr>
<tr>
<td>(Doriden)</td>
<td>Prednisone</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Norethynodrel (Enovid)</td>
</tr>
<tr>
<td>Chloral hydrate</td>
<td>Methyltestosterone</td>
</tr>
<tr>
<td>Tranquilizers</td>
<td>Anesthetics</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Diethyl ether</td>
</tr>
<tr>
<td>(Thorazine)</td>
<td>Halothane (Fluothane)</td>
</tr>
<tr>
<td>Promazine</td>
<td>Insecticides</td>
</tr>
<tr>
<td>(Sparine)</td>
<td>DDT</td>
</tr>
<tr>
<td>Meprobamate</td>
<td>Chlordane</td>
</tr>
<tr>
<td>(Equanil)</td>
<td></td>
</tr>
<tr>
<td>Chlor Diazepoxide (Librium)</td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td></td>
</tr>
<tr>
<td>Diphenylhydantoin (Dilantin)</td>
<td></td>
</tr>
<tr>
<td>Methylphenylethylhydantoin (Mesantoin)</td>
<td></td>
</tr>
</tbody>
</table>

From Brown.17

Inducers (Table 2.3). Enzyme levels are maximally enhanced after approximately 5 days of administration of the inducing agent.24 The nature of the induction varies with the type of drug, its dose, and the patient’s age, thyroid function, and genetics, to name a few factors.24,25 Enzyme induction with accelerated biotransformation reduces the pharmacological activity of drugs normally eliminated by biotransformation, such as certain barbiturates, tranquilizers, hypnotics, and anti-inflammatory drugs. Because inhalation anesthetics undergo minimal biotransformation, their elimination is influenced by enzyme induction less. Although this occurrence has little or no effect on the conduct of clinical anesthesia, it is of significance relative to viscerotoxicity. Inhalant anesthetics are variably metabolized to inorganic fluoride and hexafluoroisopropanol by cytochrome P-450, which, although produced in less than toxic concentrations (<50 µm/L), are potentially toxic to both the liver and the kidney.25 The potential for such toxicity during anesthesia is enhanced by hypoxia. Toxicity associated with biotransformation is also enhanced by reduced liver antioxidants, such as glutathione or vitamin E. In all instances, toxicity of the organohalogens depends primarily on formation of reactive intermediates, especially those produced by non-oxygen-dependent (reductive) biotransformation, and is contingent on the extent and type of biotransformation, the metabolic and environmental drug pathways resulting from induction.24 The extent to which such induced metabolic effects influence clinical animal anesthesia is unknown. Inhalant anesthetics (halothane, isoflurane, sevoflurane, and desflurane) are also known to form carbon monoxide and increase anesthetic circuit temperatures when they come in contact with soda lime or Barlyme.26-28 The production of carbon monoxide is highest with desflurane and isoflurane and almost nonexistent with halothane and sevoflurane, although sevoflurane causes the greatest increases in anesthetic circuit temperature and can be degraded to a nephrotoxic vinyl ether (compound A).29,30 Concentrations of compound A in the anesthetic circuit rarely reach nephrotoxic concentrations even during low-flow anesthesia unless the carbon dioxide–absorbant material has become desiccated.30

### Table 2.4. Interactions at tissue receptor sites.

<table>
<thead>
<tr>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>Chloroform</td>
<td>Arrhythmias due to sensitization</td>
</tr>
<tr>
<td>Levarterenol</td>
<td>Halothane</td>
<td>of the heart to catecholamines by Drug 2</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>Thiamylal</td>
<td></td>
</tr>
</tbody>
</table>

From Abbitt.74

**Hepatic microsomal enzymes may also be inhibited, with delay of biotransformation.** Known inhibitors include organophosphorus insecticides, pesticide synergists of the methylene-dioxyphenyl type, guanidine, carbon tetrachloride, chloramphenicol, tetracyclines, and certain inhalation anesthetics. Inhibition has been illustrated by the prolonged plasma half-lives of barbiturates, narcotics, and local anesthetics during halothane anesthesia and by prolonged barbiturate anesthesia after a prior course of barbiturates, narcotics, and local anesthetics during halothane anesthesia. Relevant drug interactions may also result from protein binding and interaction at receptor sites. To prevent or treat bacterial infections associated with surgery, antibiotics are often administered prior to, during, or immediately after general anesthesia. In many instances, little consideration is given to altered responses that may occur from the interaction between antibiotics and drugs commonly used in the operating room. For example, a variety of antibiotics have been shown to cause neuromuscular blockade, the most notable of which are the aminoglycosides (Table 2.4).32,33

The effect of disease on the metabolic rate usually varies with its duration. In the early febrile stage, the rate may be increased;
however, as the disease progresses, toxemia may reduce the rate to low levels. Fever increases the metabolic rate in accordance with van’t Hoff’s law, which states that for each degree Fahrenheit the temperature rises, the metabolic rate increases by 7%. When animals suffer from toxemia or liver disease, liver functions are often impaired and the ability of the animal to detoxify anesthetics is depressed. Shock lowers the metabolic rate and, because of suppressed cardiovascular function, impairs uptake and distribution of anesthetic agents.

Hepatocellular disease causes reduced protein (primarily albumin) production with consequent limitation of protein binding, increased pharmacological activity of drugs, and unexpected sensitivity to such drugs as thiopental and propofol. Production of specific protein, such as pseudocholinesterase, may also be impaired, with consequent increased duration of action of succinylcholine. Hepatic disease may delay drug biotransformation because of enzyme inhibition or decreased hepatic blood flow. Significant amounts of some drugs (e.g., morphine, chloramphenicol, and digitoxin) and/or their metabolites (polar, molecular weight > 300) are likely to be excreted in the bile. Drugs dependent on hepatic elimination must therefore be administered with caution and modified by dose in the presence of hepatic disease.

Distribution and elimination of anesthetic and related drugs can also be impaired by renal disease with increased potential toxicity. Protein binding of organic acids is reduced in uremic patients, causing increased pharmacological activity (sensitivity); examples include pentobarbital, phenylbutazone, and cardiac glycosides. The increase in free-drug fraction in plasma of patients with renal disease correlates with the degree of hypoalbuminemia. Renal disease may also limit excretion and thereby prolong activity of muscle relaxants, such as pancuronium.

The degree by which renal disease actually influences drug protein binding, and therefore overall drug activity and/or excretion, may be modified by fluid therapy (dilution or increased glomerular filtration) and by changes in plasma pH.

Hyperthyroidism is accompanied by an elevated metabolic rate and may increase anesthetic requirement, whereas hypothyroidism is generally accompanied by a lowering of the metabolic rate and a reduced anesthetic requirement. Leukemia in some forms increases the metabolic rate, as does long-term severe pain, and thus these pathologies may likewise increase overall anesthetic requirement.

Irradiation may affect (a) potency, onset, duration of action, and brain levels of injectable anesthetics, and (b) activity of the hepatic microsomal enzyme system. Earlier onset of drug action can apparently be caused by radiation-induced modification of the blood-brain barrier. In adult animals, drug action is prolonged, which may be caused by (a) sensitization with a region-specific increase in brain serotonin and/or (b) partial inhibition of hepatic oxidase. Prenatal irradiation may impair the hepatic microsomal enzyme system. The anesthetic effects of barbiturates (thiopental and pentobarbital) decrease immediately after irradiation (1 to 3 h). Later, as irradiation sickness develops (days 10 to 15), sensitivity to anesthetics increases.

Cellular Effects and Teratogenicity

Interest in mutagenic, carcinogenic, and teratogenic effects of anesthetics peaked after an increase in spontaneous abortions among anesthetists was noted in 1970. It is assumed that this increased abortion rate was caused by chronic exposure to trace concentrations of anesthetics. Exposure to such anesthetic concentrations in the first trimester of pregnancy should be avoided. Exposure of rats to nitrous oxide on day 9 of gestation has been shown to cause fetal resorption and skeletal and soft tissue anomalies. Others have also demonstrated that inhalation anesthetics are teratogenic in animals, especially chicks. Corresponding teratogenesis in humans has not been conclusively proved.

Epidemiological studies have suggested an increased incidence of cancer among women, but not men, who work in operating rooms. Commonly used anesthetics, with the exception of fluoroene, have not been shown to be potential carcinogens by in vitro tests. Both general and local anesthetics can inhibit cell division. Anesthetics also affect such immune phenomena as cellular adherence, phagocytosis, lymphocyte transformation, chemotaxis, and the killing of tumor cells.

Assessment of Anesthetic Actions

General anesthesia has simply been defined as complete unconsciousness. When inducing this state, however, anesthetists require all the following components in patients: unconsciousness, insensitivity to pain, muscle relaxation, and absence of reflex response. The degree to which these are required for specific procedures varies. Anesthetists must therefore select the most suitable drugs and be able to assess the degree to which the varying effects are induced. Anesthesia depth is often difficult to assess, and several experimental measures, including minimum alveolar concentration (MAC) and minimum inhibitory concentration (MIC), have been developed for assessing and comparing anesthetic activity (Table 2.5). Anesthetic drugs that induce adequate anesthesia in one species and operation may be insufficient at similar doses in another species. Signs characterizing a continuum of progressive increases in CNS depression and analgesia may not occur with some drugs and drug combinations. For example, the dissociatives do not induce the typical ocular signs of increasing CNS depression, and higher doses of propofol do not produce more insensitivity to pain commensurate with increased CNS depression. Consequently, veterinarians using modern anesthetic drugs must be familiar with their specific characteristics in order to use them effectively and safely.

Historically, the progressive changes produced by the administration of anesthetic drugs have been classified into four stages. Recognizing the signs characteristic of these stages following administration of most anesthetics enables anesthetists to determine whether the required CNS depression has been achieved or whether it is insufficient or too much.

Stages of General Anesthesia

For descriptive purposes, the levels of CNS depression induced by anesthetics have been divided into four stages depending on neuromuscular signs exhibited by patients (Table 2.6). It should