Veterinary Pharmacology & Therapeutics

Jim E. Riviere
Mark G. Papich

Ninth Edition

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PREFACE

Welcome to the ninth edition of *Veterinary Pharmacology and Therapeutics*, the first edition of which was authored some 6 decades ago by Dr. L. Meyer Jones, a father of American veterinary pharmacology. As with previous editions, this book remains dedicated to veterinary medical students enrolled in professional schools and colleges of veterinary medicine. However, this book also has a broader audience in that veterinary medicine interns and residents, graduate students in comparative biomedical sciences, laboratory animal specialists, and researchers using animals have adopted this as the standard source for information available on comparative pharmacology.

The present edition is both an outgrowth of, and extension to, the eighth edition edited by H. Richard Adams. The major changes are focused on integrating topics covered in the traditional drug-specific chapters to several new chapters covering their applications in areas such as minor species or racing animals. The chapters on treatment of clinical problems are also greatly expanded to integrate the basic concepts discussed in earlier sections of the book with management of clinical diseases. This allows a discussion of pharmacological concepts from a different perspective than basic pharmacology, because drugs that are used throughout veterinary medicine in applications under different clinical scenarios often need further explanation. To accomplish our goals, experts in the clinical specialty areas and pharmacologists with expertise in specific areas have contributed tremendously to this edition of the textbook. A number of "traditional chapters" were completely revamped and revised by new contributors and other previous chapters were updated. We have attempted to provide an international perspective to this new edition by adding international authors and including drugs that have been used all over the world.

Veterinary pharmacology is in the process of great change and advancement. For many years, veterinary pharmacology was simply an extension of human pharmacology as common human medications were extrapolated for use in animal diseases. However, in the new millennium, there has been a greater emphasis by the pharmaceutical companies toward developing animal-specific drugs for their unique indications. Many of these include treatment aimed at quality of life issues in companion animals. As in previous editions, many human drugs—used off-label in animals—also are discussed, with an emphasis on the importance of interspecies differences. Sophisticated therapeutic approaches are being developed and utilized on a routine basis. New drug entities are being used and a more precise utilization of existing medications is employed in clinical practice. Antimicrobial and antiparasitic drugs must be

used in a more intelligent and prudent fashion to avoid development of resistance that can impact both animals and human public health. Human food safety concerns regarding drugs used in food-producing animals have taken on increased concern. All these developments lead to both growth and a broadening of this discipline, which is central to the practice of veterinary medicine.

One of the most important applications of this textbook will be as a supplement and reference source for instructors teaching veterinary pharmacology to professional veterinary students, graduate students, and veterinary technicians. To accommodate this use, the chapters have been organized logically in an order and format that will support the teaching of veterinary pharmacology to students. Whenever possible, helpful tables, diagrams, and charts are provided to facilitate learning. Teaching veterinary pharmacology to students has changed tremendously since the early editions of this textbook. Because of the tremendous explosion in the number of drugs available, it is no longer possible to cover every drug and every indication in a veterinary course. Therefore, this book is intended to be a supplement to a veterinary pharmacology course for the student to have access to more in-depth and comprehensive information than can be presented in course lectures.

In addition to the many authors that have contributed to this edition of *Veterinary Pharmacology and Therapeutics,* we owe a special thanks to the previous editor, and consulting editor for this edition, H. Richard Adams. We are proud to carry on as editors with the hope of continuing the excellence and quality that was a characteristic of the editions that he edited. We are also appreciative of the support of the publishers at Wiley-Blackwell. Among these individuals, special thanks go to Dede Andersen, Antonia Seymour, Jill McDonald, and Nancy Simmerman. We also thank Luann Kublin and especially Jeneal Leone, administrative assistants at CCTRP-NCSU, for their help in processing these chapters.

Jim E. Riviere
Mark G. Papich

Veterinary Pharmacology and Therapeutics

Ninth Edition

SECTION

1

Principles of Pharmacology

CHAPTER

1

VETERINARY PHARMACOLOGY: AN INTRODUCTION TO THE DISCIPLINE

JIM E. RIVIERE AND MARK G. PAPICH

Pharmacology is the science that broadly deals with the physical and chemical properties, actions, absorption, and fate of chemical substances termed *drugs* that modify biological function. It is a discipline that touches most areas of human and veterinary medicine and closely interfaces with pharmaceutical science and toxicology.

HISTORY OF PHARMACOLOGY

As long as humans and their animals have suffered from disease, chemical substances have played a role in their treatment. Substances obtained from plants and animals or their products were used according to precise prescriptions through antiquity. The mechanism attributed to why these substances worked are deeply rooted in the beliefs and mythologies of each culture, as were the rituals involved in their preparation.

The early history of pharmacology parallels human efforts to compile records of ailments and their remedies. The earliest recorded compilation of drugs, the *Pen Tsao*, consisted of a list of herbal remedies compiled in the reign of Chinese Emperor Shennung in 2700 B.C. Classic examples of medicinal use of chemicals, herbs, and other natural substances are found in the recorded papyri of ancient Egypt. The *Kahun papyrus,* written about 2000 B.C., lists prescriptions for treating uterine disease in women and specifically addresses veterinary medical concerns. The *Ebers papyrus,* written in 1150 B.C. is a collection of folklore covering 15 centuries of history. It is composed of over 800 prescriptions for salves, plasters, pills, suppositories, and other dosage forms used to treat specific ailments.

The ancient Greek philosopher-physicians of 500 B.C. taught that health was maintained by a balance of "humors," which were affected by temperature, humidity, acidity, and sweetness, rather than to the direct actions of gods or demons. Disease was treated by returning these humors to a proper balance. Hippocrates (460–370 B.C.) was an ancient Greek physician of the Age of Pericles. He is referred to as the "father of medicine" in recognition of his lasting contributions to the field as the founder of the Hippocratic school of medicine. He was a firm believer in the healing powers of nature, conducted systematic observations of his patients' symptoms, and began moving the practice of medicine from an art to a systematic clinical science. The first true *material medica*, a compilation of therapeutic substances and their uses, was compiled in 77 A.D. by Aristotle's student Dioscorides, while serving as a surgeon in Nero's Roman Legion traveling throughout the

Mediterranean. This served as the basis for the later works of Galen (131–201) that emerged as the authoritative material medica for the next 1,400 years! In fact, some pharmaceutical preparations consisting of primarily herbal or vegetable matter are still referred to as galenical preparations. As the Dark Ages descended upon Europe, such scholarship transferred to Byzantium, where in fact a veterinary compilation for farm animal treatments, *Publius Vegetius,* was compiled in the 5th century.

It took until the Renaissance to awaken the spirit of discovery in Europe. The Swiss physician Theophrastus Bombastus von Hohenheim (1492–1541), known as Paracelsus, introduced the clinical use of laudanum (opium) and a number of tinctures (extracts) of various plants, some of which are still in use today. He is remembered for using drugs for specific and directed purposes, and for the famous dictum "All substances are poisons; there is none which is not a poison. The proper dose separates a poison from a remedy." As these practices took root, official compilations of medicinal substances, their preparation, use, and dosages, started to appear in Europe. These publications, termed *pharmacopeia*, provided a unifying framework upon which the pharmaceutical sciences emerged. The first printed pharmacopeia, titled the *Dispensatorium* was published by Valerius Cordus in 1547 in Nuremberg, Germany. Local publications emerged in different European cities, with two pharmacopeias published in London in 1618. The *Edinburgh Pharmacopoeia* published in 1689 became the most influential during this period. It took until the mid-19th century before truly national pharmacopeias took hold, with the first *United States Pharmacopeia* published in 1820. The first *United States Pharmacopeia* has been given the title USP-0; the current edition of the *United States Pharmacopeia* is titled USP-30. There was also a British pharmacopeia published in 1864 and the *British Pharmacopeia* continues to be published today.

The history of pharmacology parallels the development of modern medicine and the realization that specific natural products and substances may cure specific diseases. The 16th and 17th centuries were marked by great explorations and the beginning of medical experimentation. In 1656, Sir Christopher Wren made the first intravenous injection of opium in a dog. The bark of the cinchona tree was brought by Jesuits from South America for use of treatment of malaria. In 1783, the English physician William Withering reported on his experience in the use of extracts from the foxglove plant to treat patients with "dropsy," a form of edema most likely caused by congestive heart failure.

In the early 1800s the French physiologist-pharmacologist Megendie, working with the pharmacist Pelletier, studied the effects of intravenous injections of ipecac, morphine, strychnine, and other substances on animals. Megendie was the first to prove that chemicals can be absorbed into the vascular system to exert a systemic effect. A prolific scientist, he also published a formulary that survived through eight editions from 1821–1836. The Spanish physician Orfila published the results of many experiments in a book entitled *Toxicologie Generale* in 1813. A student of Megendie, the famous physiologist Claude Bernard, and others showed in the mid-1800s that the active ingredient of foxglove botanical preparations was digitalis, and its action was on the heart. We continue to use digoxin today for the treatment of congestive heart failure in humans and animals. The important aspect of these early studies was that they used the experimental paradigm for demonstrating chemical activity, establishing both the philosophy and methods upon which the discipline of modern pharmacology is based.

The term *Pharmakologie* was applied to the study of material medica by Dale in London as early as 1692; however, it is generally regarded that the biochemist Rudolph Buchheim in the Baltic city of Dorpat established the first true experimental laboratory dedicated to pharmacology in the mid-18th century. He published some 118 contributions on a variety of drugs and their actions, and argued for pharmacology to be a separate discipline distinct from material medica, pharmacy, and chemistry. His work included in 1849 a textbook *Beiträge zur Ärzneimittellehre,* which classified drugs based on their pharmacological action in living tissue. He deleted traditional remedies if he could not demonstrate their action in his laboratory. This is the beginning of what we now know as *evidence-based pharmacology,* which requires that a chemical be termed a drug only if a specific action in living tissues can be demonstrated.

His student, Oswald Schmiedeberg, became a Professor of Pharmacology at the University of Strasbourg in 1872 and took upon himself the goal of making pharmacology an independent scientific discipline based upon precise experimental methodology that ultimately displaced material medica in medical school curriculums throughout Europe by the end of the 19th century and by the early 20th century in America. He studied the correlation between the chemical structure of substances and their

effectiveness as narcotics. He published some 200 publications as well as an authoritative textbook in 1883 that went through seven editions. This text classified drugs by their actions and separated experimental pharmacology from therapeutics. In addition he founded and edited the first pharmacology journal *Archiv für experimentelle Pathologie und Pharmakologie* in 1875, which in 2007 published volume 375 as *Naunym-Schmiedeberg's Archives of Pharmacology.* His more than 150 students spread the discipline of pharmacology throughout Europe and America.

One of his students, Dr. John Abel, held the first full-time professorship in pharmacology at the University of Michigan and is considered by some to be the father of American pharmacology. Professor Abel then moved to Johns Hopkins Medical School where he continued his basic pharmacological research and founded the *Journal of Biological Chemistry* as well as the *Journal of Pharmacology and Experimental Therapeutics.* He was instrumental in founding the *American Society of Pharmacology and Experimental Therapeutics* in 1908.

From these origins, the various disciplines of pharmacology grew, the common factor being the focus in experimental methods to discover and confirm drug actions. Today, the basic philosophy remains unchanged, although modern techniques are grounded in analytical chemistry, mathematical models, and the emerging science of genomics.

VETERINARY PHARMACOLOGY

The development of veterinary pharmacology generally paralleled that of human pharmacology. However, there is archeological evidence of an Indian military hospital for horses and elephants from 5000 B.C., at which time there also existed an extensive medical education program at the Hindu university at Takkasila. The formal discipline of veterinary pharmacology has its origins in the establishment of veterinary colleges and hospitals in France, Austria, Germany, and the Netherlands in the 1760s as a response to epidemics of diseases such as rinderpest that decimated animal populations throughout Western Europe. The Royal College of Veterinary Surgeons was established in London in 1791 followed in 1823 by the Royal (Dick) School of Veterinary Studies in Edinburgh. The earliest veterinary colleges were established in the United States in 1852 in Philadelphia and in Boston in 1854; however, both were short-lived. Modern existing North American veterinary schools founded in the late 1800s, and which continue in operation, include those in Iowa, Ohio, Ontario, Pennsylvania, and New York.

In these early colleges, teaching of pharmacology in veterinary schools was essentially material medica, and remained closely aligned with parallel efforts occurring in medical schools, especially when colleges were colocated on the same campuses. This was evident in the European schools, with a separation really occurring in the 20th century. However, this linkage was not absolute. An early mid-19th century veterinary textbook *The Veterinarian's Vade Mecum* was published by John Gamgee in England. It was essentially a material medica and did not reflect the biological-based classification system for substances used by Professor Buchheim in the same period. The first American professor of therapeutics at the School of Veterinary Medicine at Iowa State was a physician, D. Fairchild. Similarly, a textbook of veterinary pharmacology *Veterinary Material Medica and Therapeutics* published by the School of Veterinary Medicine at Harvard was authored by Kenelm Winslow, a veterinarian and physician. This book, an 8th Edition of which was published in 1919, began to follow the modern thrust described earlier of relating drug actions to biological effects on tissues. It seems veterinary medicine's 21st-century preoccupation with the "one-medicine" concept has deep historical roots.

The important event, which fully shifted veterinary pharmacology from one focused on material medica to the actual science of pharmacology, was the publication by Professor L. Meyer Jones in 1954 of the 1st Edition of the textbook you are now reading. From this point forward, veterinary pharmacology positions have existed in Colleges of Veterinary Medicine throughout the world, the structure of which are often a reflection of local university history, priorities, and academic structure.

Organized veterinary pharmacology occurred rather simultaneously in Europe and the Americas. The American Academy of Veterinary Pharmacology and Therapeutics (AAVPT) was founded in 1977 and the European Association for Veterinary Pharmacology and Toxicology (EAVPT) in 1978. These two organizations, together with the British Association for Veterinary Clinical Pharmacology and Therapeutics, launched the *Journal of Veterinary Pharmacology and Therapeutics* (JVPT) in 1978. Its founder, Dr. Andrew Yoxall, hoped that the journal would improve coordination and communication among pharmacologists and veterinary clinicians, and designed it for the publication of topics relating both to the clinical

aspects of veterinary pharmacology, and to the fundamental pharmacological topics of veterinary relevance. Now in its 30th year of publication, and also cosponsored by both the American College of Veterinary Clinical Pharmacology (ACVCP) and the Chapter of Veterinary Pharmacology of the Australian College of Veterinary Scientists, this journal remains the primary outlet for publication of veterinary-related science-based pharmacology investigations.

The discipline of clinical pharmacology is more directly related to applying pharmacological principles—particularly pharmacokinetics—to clinical patients. Fellows of the AAVPT formed the AVMA-recognized board certified specialty—the American College of Veterinary Clinical Pharmacology (ACVCP)—in 1991. The establishment of the ACVCP paralleled the establishment of the American Board of Clinical Pharmacology (ABCP)—the human medical counterpart—in the same year with the cooperation of the American College of Clinical Pharmacology.

REGULATIONS

A different perspective of the development of veterinary pharmacology over the last century is the development of regulatory bodies to insure that safe, effective, and pure drugs reach commerce. As discussed above, *material medica* and *pharmacopeia* were in large part the force that held pharmacology together as a discipline for centuries. Since 1820, the *United States Pharmacopeia (USP),* a private, not-for-profit organization, has endeavored to establish standards for strength, quality, purity, packaging, and labeling for all manufacturers of pharmaceutical substances in the United States. It took until 1990, under the pressure of Dr. Lloyd Davis, one of the founding fathers of AAVPT and ACVCP, to have USP specifically develop Committees to develop USP standards and information for veterinary drugs. Until this time, veterinary drugs whose manufacturers desired the "USP Label" processed drugs through committees that were largely populated by experts in human pharmaceutical sciences and medicine.

In the 20th century, due to the proliferation of charlatans and fraud in manufacture and distribution of so-called "pure" medicinal products, coupled with serious human health calamities due to nonregulated drugs reaching the market, Congress in 1927 established the Food, Drug and Insecticide Administration, which later became known as the Food and Drug Administration (FDA). In 1938, the pivotal Federal Food, Drug and Cosmetic Act was passed giving FDA the authority to regulate animal drugs by requiring evidence of product safety before distribution. In 1959, a veterinary medical branch was developed as a division and the Food Additive Amendments Act was passed, which gave FDA authority over animal food additives and drug residues in animal-derived foods. A Bureau of Veterinary Medicine, with Dr. M. Clarkson as its first director, was established in 1965 to handle the increasing regulatory responsibilities of animal drugs. Today, the FDA Center for Veterinary Medicine, directed by Dr. Bernadette Dunham, is the primary regulatory body for veterinary drugs in the United States. The interested reader should consult Chapters 54 and 55 of the present text for a more in-depth discussion of the current state of veterinary regulatory authority.

WHAT IS VETERINARY PHARMACOLOGY?

As can be appreciated from the breadth of material covered by the present textbook, veterinary pharmacology covers all aspects of using chemical and biological substances to treat diseases of animals. The basic principles of drug action are identical across veterinary and human pharmacology. Thus the principles of absorption, distribution, metabolism, and elimination covered here are the same as in any human pharmacology text, except for a focus on crucial species differences in anatomy, physiology, or metabolism that would alter these processes. The topics of pharmacodynamics, pharmacogenomics, and pharmacokinetics are also species-independent in basic concepts. These topics encompass what truly should be termed *comparative pharmacology*.

The subspecialties of veterinary pharmacology cover all those seen in human pharmacology, the classification of which can be seen from the division of the present text. These include classifying drugs as acting on the nervous, inflammatory, cardiovascular, renal, endocrine, reproductive, ocular, gastrointestinal, respiratory, and dermal systems as well as those used in chemotherapy of microbial, parasitic, and neoplastic diseases. Because of the potential exposure and heavy parasite load of both companion and production animals, antiparasitic drugs will get deeper coverage than seen in a human pharmacology text. There are a number of specialty areas that also reflect unique aspects of veterinary medicine, including aquatic and avian species, as well as aspects of regulations related to using drugs in food-producing animals with the result-

ing production of chemical residues and potential human food safety issues. This is simply not an issue in human medicine.

The discipline is often simply divided into basic and clinical pharmacology, the distinction being whether studies are conducted in healthy or diseased animals, studying experimental models or natural disease states, or involve laboratory or clinical studies in an actual veterinary clinical situation. However, the common denominator that separates a veterinary pharmacologist from his/her human pharmacology colleagues is dealing with species differences in both disposition and action of drugs.

Comparative pharmacology is the true common theme that courses through the blood of all veterinary pharmacologists, be they basic or clinical in orientation. How does a drug behave in the species being treated? Is the disease pathophysiology similar across species? Do dosages need to be adjusted? Are microbial susceptibilities for pathogens different? Is a drug absorbed, eliminated, or metabolized differently in this species or breed? Can the dosage form developed for a dog be used in an equine patient? Are there unique individual variations in the population due to pharmacogenomic variability that would alter a drug's effect in this patient? Are there unique species-specific toxicological effects for the drug in this patient? Is there a potential for drug-drug, drug-diet, or drug-environment interactions? Will this animal or its products be consumed by humans as food, and thus are potential residues from drug therapy a concern? All of these questions are addressed in the chapters that follow in this textbook.

The focus of veterinary pharmacology is to provide a rational basis for the use of drugs in a clinical setting in different animal species. These principles are fully discussed in the remainder of this text. The practicing veterinarian should appreciate every day that when a drug is given to a patient in his/her care, an experiment in clinical pharmacology is being conducted. The astute and successful practitioner will use principles of pharmacology to assure that the correct drug and dosage regimen is selected for the diagnosis in hand, that proper clinical outcomes will be assessed for both assuring efficacy and avoiding adverse effects, and finally that if a food-producing animal is being treated, proper caution is taken to insure the safety of animal-derived products to the human consumer.

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CHAPTER

2

ABSORPTION, DISTRIBUTION, METABOLISM, AND ELIMINATION

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The four key physiological processes that govern the time course of drug fate in the body are absorption, distribution, metabolism, and elimination, the so-called *ADME processes*. Pharmacokinetics, the study of the time course of drug concentrations in the body, provides a means of quantitating ADME parameters. When applied to a clinical situation, pharmacokinetics provides the practitioner with a useful tool to design optimally beneficial drug dosage schedules for each individual patient. In the research and premarketing phase of drug development, it is an essential component in establishing effective yet safe dosage forms and regimens. An understanding of pharmacokinetic principles allows more rational therapeutic decisions to be made. In food animals, pharmacokinetics provides the conceptual underpinnings for understanding and utilizing the withdrawal time to prevent violative drug residues from persisting in the edible tissues of food-producing animals. A working knowledge of this discipline provides the framework upon which many aspects of pharmacology can be integrated into a rational plan for drug usage.

AN OVERVIEW OF DRUG DISPOSITION

To fully appreciate the ADME processes governing the fate of drugs in animals, the various steps involved must be defined and ultimately quantitated. The processes relevant to a discussion of the absorption and disposition of a drug administered by the intravenous (IV), intramuscular (IM), subcutaneous (SC), oral (PO), or topical (TOP) routes are illustrated in Figure 2.1. The normal reference point for pharmacokinetic discussion and analysis is the concentra-

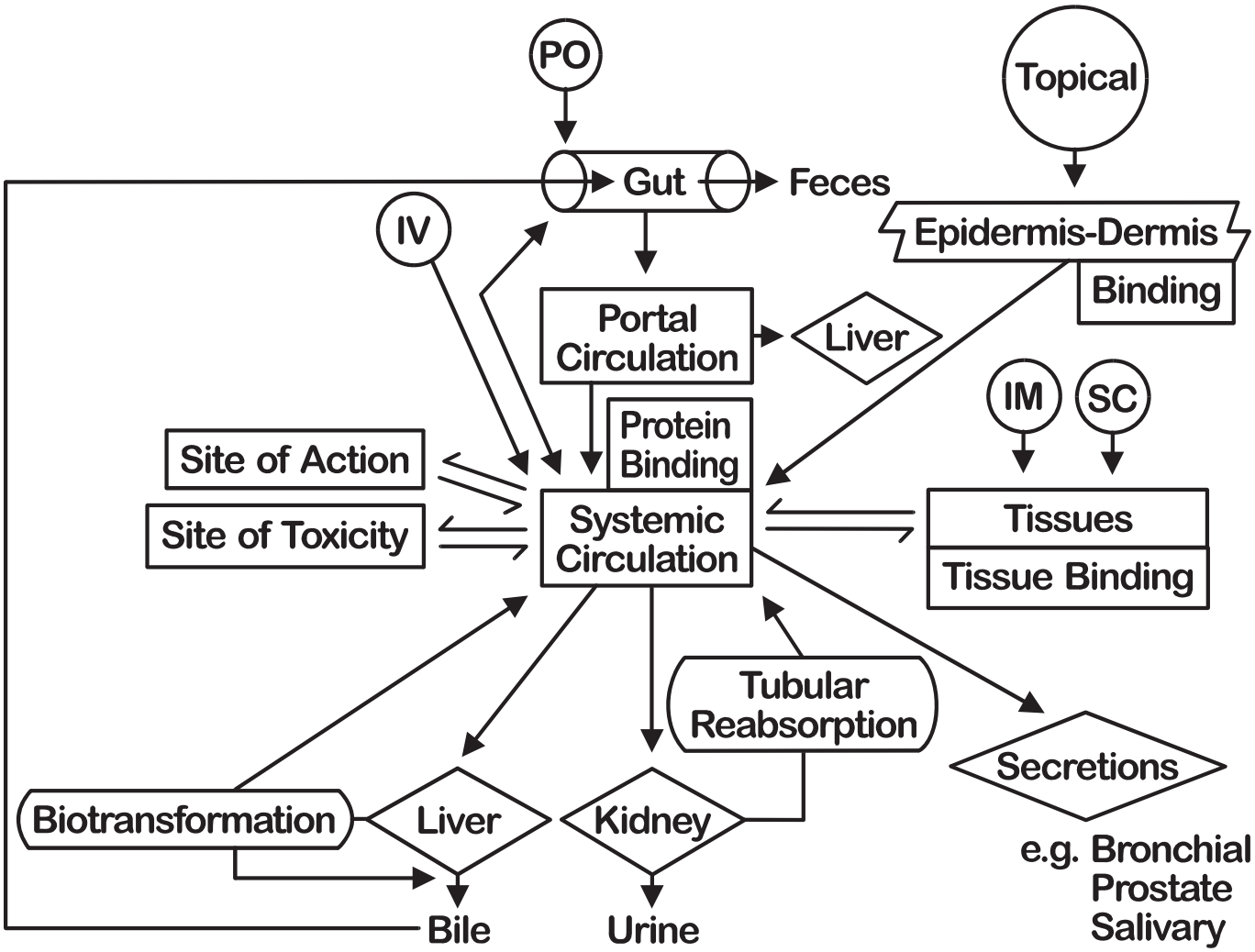

FIG. 2.1 Basic schema by which drug is absorbed, distributed, metabolized, and excreted from the body. These processes are those that form the basis for developing pharmacokinetic models.

tion of free, non–protein-bound drug dissolved in the serum (or plasma), because this is the body fluid that carries the drug throughout the body and from which samples for drug analysis can be readily and repeatedly collected. For the majority of drugs studied, concentrations in the systemic circulation are in equilibrium with the extracellular fluid of well-perfused tissues; thus, serum or plasma drug concentrations generally reflect extracellular fluid drug concentrations.

A fundamental axiom of using pharmacokinetics to predict drug effect is that the drug must be present at its site of action in a tissue at a sufficient concentration for a specific period of time to produce a pharmacologic effect. Since tissue concentrations of drugs are reflected by extracellular fluid and thus serum drug concentrations, a pharmacokinetic analysis of the disposition of drug in the scheme outlined in Figure 2.1 is useful to assess the activity of a drug in the in vivo setting.

This conceptualization is especially important in veterinary medicine where species differences in any of the ADME processes may significantly affect the extent and/or time course of drug absorption and disposition in the body. By dividing the overall process of drug fate into specific phases, this relatively complex situation can be more easily handled. It is the purpose of this chapter to overview the physiological basis of absorption, distribution, metabolism, (biotransformation) and elimination. This will provide a basis for the chapter on pharmacoki-