RESPIRATORY THERAPY PHARMACOLOGY

SECOND EDITION

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Preface to the Second Edition

DESPITE A NUMBER of changes and several new chapters, the second edition of *Respiratory Therapy Pharmacology* has the same purposes as the first edition: to provide a clear, organized introduction to respiratory care pharmacology for the beginning student and a summary of drug classes for the practitioner.

In keeping with the evolution of the field of respiratory therapy, the second edition incorporates a substantial amount of new material. The first chapter, on general pharmacologic principles, has been reorganized to provide a more coherent framework for the various concepts needed in the subsequent discussion of particular drug classes. In chapter 3, the presentation of the autonomic nervous system has been expanded to include the parasympathetic agents. Chapters on the bronchoactive drugs (Chaps. 4 to 8) have been updated, with mucus-controlling and surface-active agents combined into a single chapter (Chap. 6), and with cold and cough medications added as a new section. The discussion of antibiotics in respiratory care has been generalized to include a brief characterization of major antibiotic and antimicrobial groups, including antituberculous agents; aerosolized antibiotics are presented in more detail. Chapters 11, 12 and 13 are new and are intended to provide an overview of drugs affecting the CNS (depressants and stimulants), cardiovascular agents, and the diuretic group, respectively. Because these classes of drugs are not *directly* targeted at air-

way smooth muscle or secretions, the emphasis is on their mode of action and effects rather than on details of clinical use and administration.

The approach to respiratory care pharmacology used in the text is unchanged: assumptions of previous knowledge are minimized, with relevant background physiology described for each pharmacologic class of drugs before clinical applications are discussed.

The intent of the bibliography following each chapter is to list helpful sources of additional information or to reference cited research results. No attempt is made to provide an exhaustive bibliography of the latest research in a given area.

It is hoped that the text will be received in the spirit in which it is offered: as a helpful means for understanding respiratory care pharmacology.

Preface to the First Edition

RESPIRATORY THERAPY PHARMACOLOGY represents one area of drug application, which can be summarized as the area of bronchoactive drugs. Respiratory therapy pharmacology is even more specific than general pharmacology, which is itself an applied field of study resting on more fundamental sciences such as chemistry and biology. Generally, the specific drugs utilized in respiratory care are delivered by aerosol, another distinguishing characteristic. The group of bronchoactive drugs is intended to provide pharmacologic care of the airway, either through control of bronchial smooth muscle, or through control of secretions. Seven categories of drugs used directly by respiratory therapy are currently included in the bronchoactive group, offering a diversely challenging field of study. In each category of drugs considered in the text, a brief review of the underlying pharmacology and physiology is first offered, and then specific drugs are identified for review. A general introductory consideration of basic pharmacologic principles and the autonomic nervous system is included, as well as drug dosage calculations, with practice problems and answers. Several drug categories (neuromuscular blockers, prostaglandins) not directly used by respiratory therapists are also discussed.

The material considered ranges from the factual and simple to the theoretical and complex, in the hope of providing useful information for all levels of personnel engaged in respiratory care. Limitation of scope to res-

piratory therapy drugs and drugs directly related to respiratory care is deliberate, in the belief that the field has evolved to the point of requiring in-depth treatment of well-defined subjects, rather than a comprehensive review of all topics within one text.

Acknowledgments

It is said that the revision of a text is more difficult than the initial writing. If so, acknowledgment of the help of others is even more necessary. The efforts of good friends and past teachers, William Grosse, Ph.D., and John Holbrook, Ph.D., are deeply appreciated. John Holbrook has given generously of his time and has co-authored chapter 11, on CNS depressants and stimulants. John Youtsey, Ph.D., Chairman of the Department of Respiratory Therapy at Georgia State University, has provided an atmosphere conducive to completing the task of writing a new edition. Sincere appreciation is also given to William Biggers and Paul Brown, for assistance with art work. Elizabeth Davis and Leigh Walling have patiently provided expert typing of the text. The greatest indebtedness is to the students in respiratory care pharmacology, whose need for knowledge was the ultimate motivation for writing this book.

"If I have seen further, it is by standing on the shoulders of giants."
—Isaac Newton, letter to Robert Hooke, Feb. 5, 1675

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General Principles of Pharmacology

The study of respiratory therapy pharmacology represents a specialty area and as such presupposes a background of general pharmacologic principles, as well as the more fundamental knowledge of chemistry, biology, biochemistry, anatomy, and human physiology. Those principles, definitions and concepts which are most useful for general clinical practice or, especially, for understanding drugs given directly by respiratory care personnel, are reviewed below.

BASIC TERMINOLOGY

Drugs: The many complex functions of the human organism are regulated by chemical agents such as hormones, kinins, and catecholamines. Chemicals interact with the organism to alter its function, thus illuminating the life processes, and at times providing methods of diagnosis, treatment, or prevention of disease. Such chemicals are called drugs. Most simply and universally, a drug is any chemical which alters the organism's functions or processes. Examples include oxygen, alcohol, LSD, and vitamins.

Pharmacology: Pharmacology is the study of the interactions of drugs (chemicals) with the organism. This is the most general statement of the field and includes more particular, specialized aspects, such as dos-

age forms; preparation and dispensation (pharmacy); absorption, distribution, breakdown, and elimination of drugs in the body (pharmacokinetics); as well as the drug effect and interaction within the body (pharmacodynamics). Other areas of specialized knowledge include the harmful effects of drugs (toxicology), the art of treating disease with drugs (therapeutics), and the sources of drugs (pharmacognosy).

Another specialty area of general pharmacology is pharmacogenetics, or the study of the interrelationship of genetic differences and drug effects. Respiratory care personnel may often encounter a practical example of pharmacogenetics with succinylcholine, a neuromuscular blocking agent. Normally, this drug produces a rapid but short paralysis of skeletal muscles, but in approximately one in 3,000 individuals, it causes prolonged paralysis. Succinylcholine is normally metabolized by a plasma enzyme, which is a serum cholinesterase. The abnormal response is caused by a genetically based abnormal or missing serum cholinesterase, and individuals with this genetic difference require supported ventilation until the paralysis-induced apnea ends and the succinylcholine is eliminated.

LEGISLATION AFFECTING DRUGS

1906—The first Food and Drugs Act was passed by Congress; the *United States Pharmacopeia* (USP) and the *National Formulary* (NF) were given official status.

1914—The Harrison Narcotic Act was passed to control the importation, sale, and distribution of opium and its derivatives, as well as other narcotic analgesics.

1938—The Food, Drug and Cosmetic Act became law. This is the current Federal Food, Drug and Cosmetic Act to protect the public health and to protect physicians from irresponsible drug manufacturers. This act is enforced by the Food and Drug Administration (FDA) of the Department of Health and Human Services.

1952—The Durham-Humphrey Amendment defined the drugs that may be sold by the pharmacist only on prescription.

1962—The Kefauver-Harris Law was passed as an amendment to the Food, Drug and Cosmetic Act of 1938. This act requires proof of safety and efficacy of all drugs introduced since 1938. Drugs in use prior to that time have not been reviewed but are under study.

May 1, 1971—The Controlled Substances Act became effective. This act lists requirements for the control, sale, and dispensation of narcotics and dangerous drugs. Five schedules of controlled substances have been defined; these schedules generally define drugs in order of decreasing

potential for abuse, increasing medical use, and decreasing physical dependence. Examples of each schedule follow:

Schedule 1—heroin, marijuana, LSD, peyote, and mescaline.

Schedule 2—opium, morphine, codeine, cocaine, amphetamines.

Schedule 3—glutethimide (Doriden), paregoric, and barbiturates, with some exceptions.

Schedule 4—phenobarbital, barbital, chloral hydrate, meprobamate (Equanil, Miltown), and paraldehyde.

Schedule 5—narcotics containing nonnarcotics in mixture form, such as cough preparations or Lomotil.

NAMING DRUGS

Because a drug is a chemical, is officially regulated in the United States, and is sold as a competitive product by various manufacturers, a drug has a variety of descriptive names rather than a single name.

A drug that becomes officially approved for general clinical use in the United States will have at least five different names: a chemical name, code name, official name, generic name, and brand name.

Chemical name: The name indicating the drug's chemical structure.

Code name: A name assigned by a manufacturer to an experimental chemical which shows potential as a drug. An example is aerosol SCH 1000, which is the code name for ipratropium bromide, an experimental parasympatholytic bronchodilator (see Chap. 5).

Generic name: The name assigned to a chemical by the United States Adopted Name (USAN) Council when the chemical appears to have therapeutic use and the manufacturer wishes to market the drug. Instead of a numerical or alphanumerical code, as in the code name, this name often is loosely based on the drug's chemical structure. For example, isoproterenol has an isopropyl group attached to the terminal nitrogen on the amino side chain, whereas metaproterenol has the same chemical structure as isoproterenol except that a dihydroxy attachment on the catechol nucleus is now in the meta position (carbon-3,5 instead of carbon-3,4). The term "generic" as applied to drug names is a misnomer, since generic implies a class or family of agents, such as sympathomimetics, or even catecholamines, rather than a single drug. The generic name is also known as the nonproprietary name, in contrast to the brand name.

Official name: In the event that an experimental drug becomes fully approved for general use and is admitted to the USP—NF, the generic name becomes the official name. Since an officially approved drug may be marketed by many manufacturers under different names, it is rec-

ommended that clinicians use the official name, which is nonproprietary, and not a brand name.

Trade name: This is the brand name given by a particular manufacturer; it is also known as the proprietary name. For example, the generic drug isoproterenol is marketed by Winthrop as Isuprel and by Abbott Laboratories as Norisodrine. Note that dosage strengths may vary with different manufacturers.

An example of the different names for the same drug is provided by beclomethasone dipropionate, an aerosolized corticosteroid used to treat asthmatics:

Chemical name: 9α-chloro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate

Official name: beclomethasone dipropionate

Generic name: beclomethasone dipropionate

Trade name: Vanceril (Schering), Beclovent (Glaxo)

SOURCES OF DRUG INFORMATION

The two official volumes giving drug standards in the United States are:

United States Pharmacopeia (USP)—first published in 1820 as a private medical effort; given official status in 1906 with the first congressional Food and Drugs Act. The *Pharmacopeia* specifies standards for such drugs as oxygen, indicated by the USP label. The *Pharmacopeia* undergoes revision every 5 years.

The National Formulary (NF)—first published in 1888, with the same legal status as the USP. It is published by the American Pharmaceutical Association and continuously revised. In 1980, which was the date for revision of the USP, the USP and NF were combined into a single volume.

Other sources of drug information are:

AMA Drug Evaluations—gives information and results on new drugs which are not yet officially included in the USP.

Physicians' Desk Reference (PDR)—prepared by manufacturers of drugs, and therefore potentially lacking the objectivity of the preceding sources, this annual volume does provide useful information, including descriptive color charts for drug identification, names of manufacturers, and general drug actions.

Hospital Formulary—published by the American Society of Hospital Pharmacists, and very informative. It contains monographs and commentaries on classes of drugs (antibiotics, steroids, etc.).

An in-depth discussion of general pharmacologic principles and modes of drug action can be found in:

Aviado D.M.: *Krantz & Carr's Pharmacologic Principles of Medical Practice,* ed. 8. Baltimore, Williams & Wilkins Co., 1972.

Goodman A.G., Goodman L.S., Gilman A. (eds.): *Goodman and Gilman's The Pharmacological Basis of Therapeutics,* ed. 6. New York, Macmillan, 1980.

SOURCES OF DRUGS

Although the sources of drugs is not a crucial area of expertise for the respiratory care clinician, it can be one of the most interesting. Recognition of naturally occurring drugs dates back to Egyptian papyrus records, to the ancient Chinese, and to the Central American civilizations. Natural sources of drugs are known today in remote regions of modern America such as Appalachia.

The prototype of cromolyn sodium was khellin, found in the Eastern Mediterranean plant *Ammi visnaga,* and the plant was used in ancient times as a muscle relaxant. Today its synthetic derivative is used as an antiasthmatic agent. Similar stories can be told for curare, derived from large vines and used by South American Indians to coat their arrow tips for lethal effect; for digitalis obtained from the foxglove plant *(Digitalis purpurea),* reputedly used by the Mayans for relief of angina and definitely referred to by 13th-century Welsh physicians; and of course for the notorious poppy seed, source of the opium alkaloids and immortalized in *Confessions of an English Opium Eater.*

Today the most common source of drugs is chemical synthesis, but plants, minerals, and animals have often contributed the prototype of the active ingredient. Examples of each source are given below:

Animal—thyroid hormone, insulin, pancreatic dornase.

Plant—khellin *(Ammi visnaga),* atropine (*belladonna* alkaloid), digitalis (foxglove), reserpine *(Rauwolfia serpentina),* volatile oils of eucalyptus, pine, anise.

Mineral—copper sulfate, magnesium sulfate (Epsom salts), mineral oil (liquid hydrocarbons).

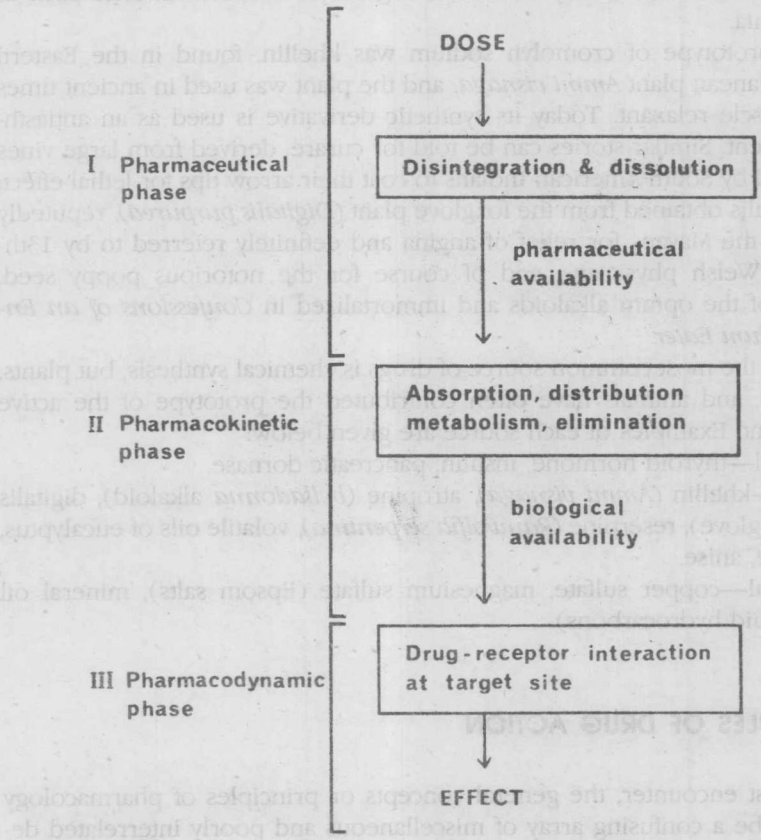
PRINCIPLES OF DRUG ACTION

On first encounter, the general concepts or principles of pharmacology seem to be a confusing array of miscellaneous and poorly interrelated details. However, a conceptual framework suggested by Ariens and Simonis in

1974 is very useful for organizing some of these details in a way that is more easily remembered and perhaps better understood.

Ariens and Simonis identified three basic phases of drug action from the initial administration of a dose through the drug's ultimate effect on the body: the pharmaceutical phase, the pharmacokinetic phase, and the pharmacodynamic phase. Figure 1–1 illustrates the sequential nature of these three phases. The advantage of such a conceptualization is that it provides an organizational framework within which can be fit such details as dosage forms, routes of administration, rate of uptake, plasma half-life, and membrane transport.

Fig 1–1. The major phases of drug action in sequence, from dosage administration to effect in the body. (Based on Ariens E.J., Simonis A.M.: Drug action: Target tissue, dose-response relationships, and receptors, in Teorell T., Dedrick R.L., Condliffe P.G. (eds.): *Pharmacology and Pharmacokinetics.* New York, Plenum Press, 1974.)



THE PHARMACEUTICAL PHASE

A necessary condition for any drug action in the body is that the drug become available for absorption. The drug form (tablet, liquid, etc.) greatly influences the disintegration and dissolution of the active substance. The route of administration is a second major determinant of drug availability to the body. The form in which a drug is supplied and the route of administration are obviously related, and both are selected on the basis of other factors, such as amount of drug, susceptibility of the drug to degradation, and location of the target site in the body.

The *dosage form of a drug* is defined as the product or unit in which the drug is received, e.g., tablet, capsule, injectible liquid, or ointment.

The route of administration depends on the following factors:

1. Whether systemic or only local effect is needed.
2. The desired rate of onset and duration of action of the drug.
3. The stability of the drug in gastric and/or intestinal fluids.
4. Whether or not the patient is able to swallow, retain, and absorb drugs given orally.
5. Convenience versus safety of various routes.
6. The amount of the drug: large amounts can be administered orally or intravenously (IV), smaller amounts intramuscularly (IM) or subcutaneously (SC).

Oral Route

The oral route is generally the safest, most convenient and most economical delivery route for drugs intended to have systemic effect.

Dosage forms for the oral route include:

1. Tablets—solid dosage forms prepared by molding or compressing the drug in dies.
2. Capsules—contain medication within a soluble shell of gelatin, methylcellulose, or calcium alginate.
3. Pills—globular or ovoid dosage forms prepared from a cohesive, plastic mass.
4. Powders—mixtures of dry, powered drugs. (Powders may be used externally also, such as dusting powders, powders for douche solutions, etc.).
5. Solutions—homogeneous mixtures of a solvent and a solute. A common solvent is water.