GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS

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SECTION I

GENERAL PRINCIPLES

INTRODUCTION

Leslie Z. Benet

In its entirety, *pharmacology* embraces the knowledge of the history, source, physical and chemical properties, compounding, biochemical and physiological effects, mechanisms of action, absorption, distribution, biotransformation and excretion, and therapeutic and other uses of drugs. Since a *drug* is broadly defined as any chemical agent that affects processes of living, the subject of pharmacology is obviously quite extensive.

For the clinician and the student of health sciences, however, the scope of pharmacology is less expansive than indicated by the above definitions. The clinician is interested primarily in drugs that are useful in the prevention, diagnosis, and treatment of human disease. Study of the pharmacology of these drugs can be reasonably limited to aspects that provide the basis for their rational clinical use. Secondarily, the clinician also is concerned with chemical agents that are not used in therapy but are commonly responsible for household and industrial poisoning as well as environmental pollution. Study of these substances is justifiably restricted to the general principles of prevention, recognition, and treatment of such toxicity or pollution. Finally, all health professionals share in the responsibility to help resolve the continuing sociological problem of the abuse of drugs.

The basic pharmacological concepts summarized in this section apply to the characterization, evaluation, and comparison of all drugs. A clear understanding and appreciation of these principles is essential for the subsequent study of the individual drugs. The relationship between the dose of a drug given to a patient and the utility of that drug in treating the patient's disease is described by two basic areas of pharmacology: *pharmacokinetics* and *pharmacodynamics.* Operationally, these terms may be defined as what the body does to the drug (pharmacokinetics) and what the drug does to the body (pharmacodynamics).

Pharmacokinetics (Chapter 1) deals with the *absorption, distribution, biotransformation,* and *excretion* of drugs. These factors, coupled with dosage, determine the concentration of a drug at its sites of action and, hence, the intensity of its effects as a function of time. Many basic principles of biochemistry and enzymology and the physical and chemical principles that govern the active and passive transfer and the distribution of substances, both small molecules and protein drugs, across biological membranes are readily applied to the understanding of this important aspect of pharmacology.

The study of the biochemical and physiological *effects* of drugs and their *mechanisms of action* is termed *pharmacodynamics* (Chapter 2). Pharmacodynamics borrows freely from both the subject matter and the experimental techniques of physiology, biochemistry, cellular and molecular biology, microbiology, immunology, genetics, and pathology. It is unique mainly in that attention is focused on the characteristics of drugs. As the name implies, the subject is a dynamic one. The student who attempts merely to memorize the pharmacodynamic properties of drugs is forgoing one of the best opportunities for correlating the entire field of preclinical medicine. For example, the actions and effects of the saluretic agents can be fully understood only in terms of the basic principles of renal phys-

iology and of the pathogenesis of edema. Conversely, great insight into normal and abnormal renal physiology can be gained by the study of the pharmacokinetics and pharmacodynamics of the saluretic agents.

The clinician is understandably interested mainly in the effects of drugs in human beings. This emphasis on *clinical pharmacology* is justified, since the effects of drugs often are characterized by significant interspecies variation, and since they may be modified further by disease. In addition, some drug effects, such as those on mood and behavior, can be adequately studied only in human beings. However, technical, legal, and ethical considerations limit pharmacological evaluation in human subjects, and the choice of drugs must be based in part on their pharmacological evaluation in animals. Consequently, some knowledge of animal pharmacology and comparative pharmacology is helpful in deciding the extent to which claims for a drug based upon studies in animals can be reasonably extrapolated to patients.

Pharmacotherapeutics (Chapter 3) deals with the use of drugs in the prevention and treatment of disease. Many drugs stimulate or depress biochemical or physiological function in human beings in a sufficiently reproducible manner to provide relief of symptoms or, ideally, to alter favorably the course of disease. Conversely, chemotherapeutic agents are useful in therapy because they have only minimal effects on human beings but can destroy or eliminate pathogenic cells or organisms.

Whether a drug is useful for therapy is crucially dependent upon its ability to produce its desired effects only with tolerable undesired effects. Thus, from the standpoint of the clinician interested in the therapeutic uses of a drug, the selectivity of its effects is one of its most important characteristics. Drug therapy is rationally based upon the correlation of the actions and effects of drugs with the physiological, biochemical, microbiological, immunological, and behavioral aspects of disease. In addition, disease may modify the pharmacokinetic properties of a drug by alteration of its absorption into the systemic circulation and/or its disposition.

Toxicology (Chapter 4) is the aspect of pharmacology that deals with the adverse effects of drugs. It is concerned not only with drugs used in therapy but also with the many other chemicals that may be responsible for household, environmental, or industrial intoxication. The adverse effects of the pharmacological agents employed in therapy are properly considered an integral part of their total pharmacology. The toxic effects of other chemicals is such an extensive subject that clinicians must usually confine their attention to the general principles applicable to the prevention, recognition, and treatment of drug poisonings of any cause.

Traditionally, most drugs were small chemicals with molecular weights in the hundreds, as well as a few that were natural human or animal hormones. Within the past decade, through advances in molecular and cellular biology, a number of protein and peptide drugs have been approved for clinical use. These therapies are designed to interact with a particular receptor or enzyme to ameliorate disease. Today we now consider the possibility of the drug directly replacing a diseased receptor (or gene) or of administering agents that allow patients to make their own therapeutic protein through gene-based therapy (Chapter 5). The emergence of gene therapy is based on the assumption that the best treatment for genetic diseases will be therapy that is directed to the mutant gene itself. This requires a direct assault on mutant genes to replace or supplement defective genetic material with normal, functional genes. Pharmacokinetics of these new gene-based therapies, particularly delivery of the "drug" to its site of action or function, is a major hurdle for this new therapeutic modality. Gene therapy requires unique methods, many of which are gene-based themselves through enhanced uptake of DNA expression vectors, to deliver a gene to its target cell.