GOODMAN and GILMAN's

The Pharmacological Basis of Therapeutics

EIGHTH EDITION

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In this textbook, reference to proprietary names of drugs is ordinarily made only in chapter sections dealing with preparations. Such names are given in SMALL-CAP TYPE, usually immediately following the official or nonproprietary titles. Proprietary names of drugs also appear in the Index.

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CHAPTER

4 PRINCIPLES OF THERAPEUTICS

Alan S. Nies

THERAPY AS A SCIENCE

Over a century ago Claude Bernard formalized criteria for gathering valid information in experimental medicine. However, application of these criteria to therapeutics and to the process of making decisions about therapeutics has, until recently, been slow and inconsistent. At a time when the diagnostic aspects of medicine had become scientifically sophisticated, therapeutic decisions were often made on the basis of impressions and traditions. Historically, the absence of accurate data on the effects of drugs in man was due in large part to ethical standards of human experimentation. "Experimentation" in human beings was precluded, and it was not generally conceded that every treatment by any physician should be designed and in some sense recorded as an experiment.

Although there must always be ethical concern about experimentation in man, principles have been defined, and there are no longer ethical restraints on the gathering of either experimental or observational data on the efficacy and toxicity of drugs in adults. Furthermore, it should now be considered absolutely unethical to use the *art* as opposed to the *science* of therapeutics on any patient who directly (the adult or child) or indirectly (the fetus) receives drugs for therapeutic purposes. Observational (nonexperimental) techniques that can greatly add to our knowledge of the effects of drugs can be applied to all populations (Sheiner and Benet, 1985; Whiting *et al.*, 1986). The fact that such observational techniques have largely been applied in a nonsystematic fashion has led us to rely on a relative paucity of information about many drugs. Therapeutics must now be dominated by objective evaluation of an adequate base of factual knowledge.

Conceptual Barriers to Therapeutics as a Science. The most important barrier that inhibited the development of therapeutics as a science seems to have been the belief that multiple variables in diseases and in the effects of drugs are uncontrollable. If this were true, the scientific method would not be applicable to the study of pharmacotherapy. In fact, therapeutics is the aspect of patient care that is most amenable to the acquisition of useful data, since it involves an intervention and provides an opportunity to observe a response. It is now appreciated that clinical phenomena can be defined, described, and quantified with some precision. The approach to complex clinical data has been artfully discussed by Feinstein (1983).

Another barrier to the realization of therapeutics as a science was overreliance on traditional diagnostic labels for disease. This encouraged the physician to think of a disease as static rather than dynamic, to view patients with the same "label" as a homogeneous rather than a heterogeneous population, and to consider a disease as an entity even when information about pathogenesis was not available. If diseases are not considered to be dynamic, "standard" therapies in "standard" doses will be the order of the day; decisions will be reflexive. Needed instead is an attitude that makes the physician responsible for recognition of and compensation for changes that occur in pathophysiology as the underlying process evolves. For example, the term *myocardial infarction* refers to localized destruction of myocardial cells caused by interruption of the blood supply; however, decisions about therapy must take into account a variety of autonomic, hemodynamic, and electrophysiological variables that change as a function of time, size, and location of the infarction. Failure to take all such variables into

account while planning a therapeutic maneuver may result in ineffective therapy in some patients while exposing others to avoidable toxicity. If groups of patients are in reality heterogeneous and receive alternative treatments, true differences in efficacy or toxicity between therapies may go unrecognized. A diagnosis or label of a disease or syndrome usually indicates a spectrum of possible causes and outcomes. Therapeutic experiments that fail to match groups for the known variables that affect prognosis yield uninterpretable data.

A third conceptual barrier was the incorrect notion that data derived empirically are useless because they are not generated by application of the scientific method. Empiricism is often defined as the practice of medicine founded on mere experience, without the aid of science or a knowledge of principles. The connotations of this definition are misleading; empirical observations need not be scientifically unsound. In fact, concepts of therapeutics have been greatly advanced by the clinical observer who makes careful and controlled observations on the outcome of a therapeutic intervention. The results, even when the mechanisms of disease and their interactions with the effects of drugs are not understood, are nevertheless often crucial to appropriate therapeutic decisions. Frequently, the initial suggestion that a drug may be efficacious in one condition arises from careful, empirical observations that are made while the drug is being used for another purpose. Examples of valid empirical observations that have resulted in new uses of drugs include the use of penicillamine to treat arthritis, lidocaine to treat cardiac arrhythmias, and propranolol and clonidine to treat hypertension. Conversely, empiricism, when not coupled with appropriate observational methods and statistical techniques, often results in findings that are inadequate or invalid.

Clinical Trials. Application of the scientific method to experimental therapeutics is exemplified by a well-designed and well-executed clinical trial. Clinical trials form the basis for therapeutic decisions by all physicians, and it is therefore essential that they be able to evaluate the results and conclusions of such trials critically. To maximize the likelihood that useful information will result from the experiment, the objectives of the study must be defined, homogeneous populations of patients must be selected, appropriate control groups must be found, meaningful and sensitive indices of drug effects must be chosen for observation, and the observations must be converted into data and then into valid conclusions (Feinstein, 1977). The *sine qua non* of any clinical trial is its controls. Many different types of controls may be used, and the term *controlled study* is not synonymous with *randomized double-blind technique*. Selection of a proper control group is as critical to the eventual utility of an experiment as the selection of the experimental group. Although the randomized, double-blind controlled trial is the most effective design for distributing bias and unknown variables between the "treatment" and the "control" groups, it is not necessarily the optimal design for all studies. It may be impossible to use this design to study disorders that occur rarely, disorders in patients who cannot, by regulation or ethics or both, be studied (*e.g.*, children, women of childbearing age, fetuses, or some patients with psychiatric diseases), or disorders with a uniformly fatal outcome (*e.g.*, rabies, where historical controls can be used).

There are several requirements in the design of clinical trials to test the relative effects of alternative therapies. (1) *Specific outcomes* of therapy that are clinically relevant and quantifiable must be measured. (2) The *accuracy of diagnosis* and the *severity of the disease* must be comparable in the groups being contrasted; otherwise, false-positive and false-negative errors may occur. (3) The *dosages* of the drugs must be chosen and individualized in a manner that allows relative efficacy to be compared at equivalent toxicities or allows relative toxicities to be compared at equivalent efficacies. (4) *Placebo effects*, which occur in a large percentage of patients, can confound many studies—particularly those that involve subjective responses; controls must take this into account. However, subjective assessments are important in determining whether a therapy improves the patient's well-being. In fact, quality of life can be assessed by the experimental subject and can be objectively tabulated and incorporated into evaluation of a therapy (Williams, 1987). (5) *Compliance* with the experimental regimens should be assessed before subjects are assigned to experimental or control groups. The drug-taking behavior

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