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

of the subjects should be reassessed during the course of the trial. Noncompliance, even if randomly distributed between both groups, may cause falsely low estimates of the true potential benefits or toxicity of a particular treatment. (6) *Sample size* should be estimated prior to beginning a clinical trial and must be taken into account in interpreting the results of the trial. Depending upon such factors as the overall prognosis of the disease and the anticipated improvement in outcome or toxicity from the new treatment, very large numbers of subjects may be needed; otherwise, the possibility of a false-negative result is high (*i.e.*, no statistically significant differences between the two treatments will be found, even though differences actually exist) (Young *et al.*, 1983; Simon, 1986). (7) *Ethical considerations* may be major determinants of the types of controls that can be used and must be evaluated explicitly (Rosner, 1987; Rothman, 1987). For example, in therapeutic trials that involve life-threatening diseases for which there is already an effective therapy, the use of a placebo is unethical, and new treatments must be compared with "standard" therapies.

The results of clinical trials of new therapeutic agents or of old agents for new indications may have severe limitations in terms of what can be expected of drugs when they are used in an office practice. The selection of the patients for experimental trials usually eliminates those with coexisting diseases, and such trials usually assess the effect of only one or two drugs, not the many that might be given to or taken by the same patient under the care of a physician. Clinical trials are usually performed with relatively small numbers of patients for periods of time that may be shorter than are necessary in practice, and compliance may be better controlled than it can be in practice. These factors lead to several inescapable conclusions:

1) Even if the result of a valid clinical trial of a drug is thoroughly understood, the physician can only develop a hypothesis about what the drug might do to a particular patient, and there can be no assurance that what occurred in other patients will be seen. In effect, the physician uses the results of a clinical trial to establish an experiment in each patient. The detection of anticipated and unanticipated effects and the determination of whether or not they are due to the drug(s) being used are important responsibilities of the physician during the supervision of a therapeutic regimen. If an effect of a drug is not seen in a clinical trial, it may still be revealed in the setting of clinical practice. About one half or more of both useful and adverse effects of drugs that were not recognized in the initial formal trials were subsequently discovered and reported by practicing physicians.

2) If an anticipated effect of a drug has not occurred in a patient, this does not mean that the effect cannot occur in that patient or in others. Many factors in the individual patient may contribute to lack of efficacy of a drug. They include, for example, misdiagnosis, poor compliance by the patient to the regimen, poor choice of dosage or dosage intervals, coincidental development of an undiagnosed separate illness that influences the outcome, the use of other agents that interact with primary drugs to nullify or alter their effects, undetected genetic or environmental variables that modify the disease or the pharmacological actions of the drug, or unknown therapy by another physician who is caring for the same patient. Of equal importance, even when a regimen appears to be efficacious and innocuous, a physician should not attribute all improvement to the therapeutic regimen chosen, nor should a physician assume that a deteriorating condition reflects only the natural course of the disease. Similarly, if an anticipated untoward or toxic effect is not seen in a particular patient, it can still occur in others. Physicians who use only their own experience with a drug to make decisions about its use unduly expose their patients to unjustifiable risk or unrealized efficacy. For example, simply because a doctor has not seen a case of chloramphenicol-induced aplastic anemia in his own practice does not mean that such a disaster may not occur; the drug should still be used for the proper indications.

3) Rational therapy is therapy based on the use of observations that have been evaluated critically. It is no less crucial to have a scientific approach to the treatment of an individual patient than to use this approach when investigating drugs in a research setting. In both instances, it is the patient who benefits. Such an approach can be formalized in the practice setting by performing randomized, controlled trials in individual patients who have stable clinical symptomatology. With this strategy a specific ther-

apy of uncertain efficacy can be compared with a placebo or alternative therapy in a double-blind design with well-defined end points that are tailored to the individual patient. The outcome of such a trial is immediately relevant to the particular patient, although it may not apply to all other patients (Guyatt *et al.*, 1986).

INDIVIDUALIZATION OF DRUG THERAPY

As has been implied above, therapy as a science does not apply simply to the evaluation and testing of new, investigational drugs in animals and man. It applies with equal importance to the treatment of each patient as an individual. Therapists of every type have long recognized and acknowledged that individual patients show wide variability in response to the same drug or treatment method. Progress has been made in identifying the sources of variability (Vesell, 1986). Important factors are presented in Figure 4–1; the basic principles that underlie these sources of variability have been presented in Chapters 1 and 2.

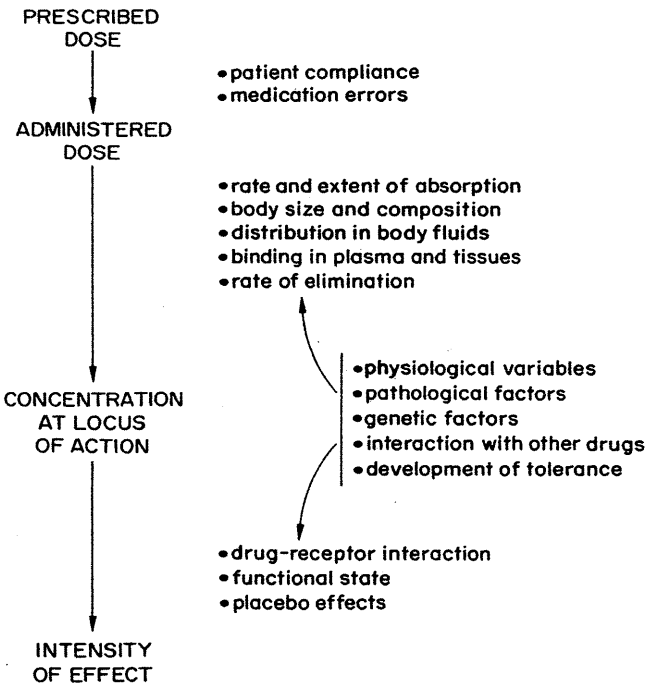

Figure 4–1. *Factors that determine the relationship between prescribed drug dosage and drug effect.* (Modified from Koch-Weser, 1972.)

The following discussion relates to the strategies that have been developed to deal with variability in the clinical setting. (*See also* Appendix II.)

PHARMACOKINETIC CONSIDERATIONS

Interpatient and intrapatient variation in disposition of a drug must be taken into account in choosing a drug regimen. For a given drug, there may be wide variation in its pharmacokinetic properties among individuals. For some drugs, this variability may account for one half or more of the total variation in eventual response. The relative importance of the many factors that contribute to these differences depends in part on the drug itself and on its usual route of elimination. Drugs that are excreted primarily unchanged by the kidney tend to have smaller differences in disposition among patients with similar renal function than do drugs that are inactivated by metabolism. Of drugs that are extensively metabolized, those with high metabolic clearance and large first-pass elimination have marked differences in bioavailability, whereas those with slower biotransformation tend to have the largest variation in elimination rates between individuals. Studies in identical and nonidentical twins have revealed that genotype is a very important determinant of differences in the rates of metabolism (Penno and Vesell, 1983). For many drugs, physiological and pathological variations in organ function are major determinants of their rate of disposition. For example, the clearance of digoxin and gentamicin is related to the rate of glomerular filtration, whereas that of lidocaine and propranolol is primarily dependent on the rate of hepatic blood flow. The effect of aging and diseases that involve the kidneys or liver is to impair elimination and to increase the variability in the disposition of drugs. In such settings, measurements of concentrations of drugs in biological fluids can be used to assist in the individualization of drug therapy (Spector *et al.*, 1988). Since old age and renal or hepatic diseases may also affect the responsiveness of target tissues (*e.g.*, the brain), the physician should be alert to the possibility of a shift in the range of therapeutic concentrations.

A test should not be performed simply because an assay is available. More assays of drugs are available than are generally useful. Determinations of concentrations of drug in blood, serum, or plasma are particularly useful when well-defined criteria are fulfilled. (1) There must be a demonstrated relationship between the concentration of the drug in plasma and the eventual therapeutic effect that is desired and/or the toxic effect that must be avoided. (2) There should be substantial interpatient variability in disposition of the drug (and small intrapatient variation). Otherwise, concentrations of drug in plasma could be predicted adequately from dose alone. (3) It should be difficult to monitor intended or unintended effects of the drug. Whenever clinical effects or minor toxicity are easily measured (*e.g.*, the effect of a drug on blood pressure), such assessments should be preferred in the decision to make any necessary adjustment of dosage of the drug. However, the effects of some drugs in certain settings are not easily monitored. For example, the effect of Li^+ on manic–depressive psychosis may be delayed and difficult to quantify. For some drugs, the initial manifestation of toxicity may be serious (*e.g.*, digitalis-induced arrhythmias or theophylline-induced seizures). The same concepts apply to a number of agents used for cancer chemotherapy. Other drugs (*e.g.*, antiarrhythmic agents) produce toxic effects that mimic symptoms or signs of the disease being treated. Many drugs are used for prophylaxis of an intermittent, potentially dangerous event; examples include anticonvulsants and antiarrhythmic agents. In each of these situations, titration of drug dosage may be aided by measurements of concentrations of the drug in blood. (4) The concentration of drug required to produce therapeutic effects should be close to the value that causes substantial toxicity (*see* below). If this circumstance does not apply, patients could simply be given the largest dose known to be necessary to treat a disorder, as is commonly done with penicillin. However, if there is an overlap in the concentration–response relationship for desirable and undesirable effects of the drug, as is true for theophylline, determinations of concentration of drug in plasma may allow the dose to be optimized. All four of the above-described criteria should be met if the measurement of drug concentrations is to be of significant value in the adjustment of dosage. Knowledge of concentrations of drugs in plasma or urine is also particularly useful for detection of therapeutic failures that are due to lack of patient compliance with a medical regimen or for identification of patients with unexpected extremes in the rate of drug disposition.

Assay of drugs to assist the physician in achieving a desired concentration of drug in blood or plasma (*i.e.*, "targeting" the dose) is an example of the use of an *intermediate end point of therapy*. An intermediate end point is defined as a specific goal of treatment that is used in place of the ultimate clinical goal, which may be difficult to assess. The concept of intermediate end points, including concentrations of drugs, as a guide to individualization of therapy can also be applied in other ways; one is to provide an indication for a change in the choice of drug therapy. Measurements of concentrations of drugs in plasma and/or measurements of one or more pharmacological effects of the drug can provide an indication of probable lack of efficacy. Other issues of importance with regard to the measurement and interpretation of drug concentrations are discussed in Chapter 1 and Appendix II.

PHARMACODYNAMIC CONSIDERATIONS

Considerable interindividual variation in the response to drugs remains after the concentration of the drug in plasma has been adjusted to a target value; for some drugs this pharmacodynamic variability accounts for much of the total variation in responsiveness between patients. As discussed in Chapter 2, the relationship between the concentration of a drug and the magnitude of the observed response may be complex, even when responses are measured in simplified systems *in vitro*, although typical sigmoidal concentration–effect curves are usually seen (Figure 2–6). When drugs are administered to patients, however, there is no single characteristic relationship between the drug concentration in plasma and the measured effect; the concentration–

effect curve may be concave upward, concave downward, linear, or sigmoid. Moreover, the concentration–effect relationship may be distorted if the response being measured is a composite of several effects, such as the change in blood pressure produced by a combination of cardiac, vascular, and reflex effects. However, such a composite concentration–effect curve can often be resolved into simpler curves for each of its components. These simplified concentration–effect relationships, regardless of their exact shape, can be viewed as having four characteristic variables: potency, slope, maximal efficacy, and individual variation. These are illustrated in Figure 4–2 for the common sigmoid log dose–effect curve.

Potency. The location of the concentration–effect curve along the *concentration axis* is an expression of the potency of a drug. Although often related to the dose of a drug required to produce an effect, potency is more properly related to the concentration of the drug in plasma in order to approximate more closely the situation in isolated systems *in vitro* and to avoid the complicating factors of pharmacokinetic variables. Although potency obviously affects drug dosage, potency *per se* is relatively unimportant in the clinical use of drugs as long as the required dose can be given conveniently. There is no justification for the view that more potent drugs are superior therapeutic agents. However, if the drug is to be administered by transdermal absorption, a highly potent drug is required, since the capacity of the skin to absorb drugs is limited.

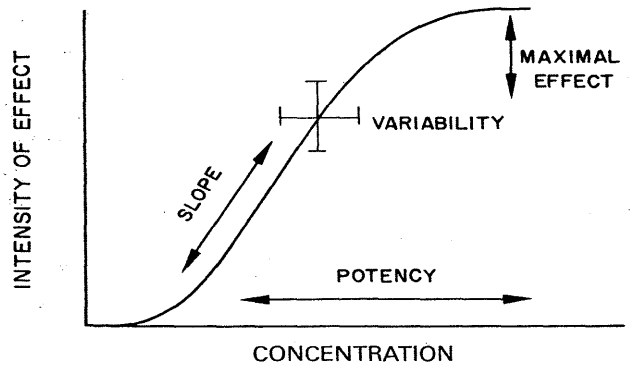

Figure 4–2. *The log dose-effect relationship.*

Representative log dose-effect curve, illustrating its four characterizing variables (*see* text for explanation).

Maximal Efficacy. The maximal effect that can be produced by a drug is its *maximal efficacy* or, simply, *efficacy*. As discussed in Chapter 2, maximal efficacy is determined by the properties of the drug and its receptor–effector system and is reflected in the plateau of the concentration–effect curve. In clinical use, however, a drug's dosage may be limited by undesired effects, and the true maximal efficacy of the drug may not be achievable. Efficacy of a drug is clearly a major characteristic—of much more clinical importance than is potency; furthermore, the two properties are not related and should not be confused. For instance, although some thiazide diuretics have similar or greater potency than the loop diuretic furosemide, the maximal efficacy of furosemide is considerably greater.

Slope. The slope of the concentration–effect curve reflects the mechanism of action of a drug, including the shape of the curve that describes drug binding to its receptor (*see* Chapter 2). The steepness of the curve dictates the range of doses that are useful for achieving a clinical effect. Aside from this fact, the slope of the concentration–effect curve has more theoretical than practical usefulness.

Biological Variability. Different individuals vary in the magnitude of their response to the same concentration of a single drug or to similar drugs when the appropriate correction has been made for differences in potency, maximal efficacy, and slope. In fact, a single individual may not always respond in the same way to the same concentration of drug. A concentration–effect curve applies only to a single individual at one time or to an average individual. The intersecting brackets in Figure 4–2 indicate that an effect of varying intensity will occur in different individuals at a specified concentration of a drug or that a range of concentrations is required to produce an effect of specified intensity in all of the patients.

Specific terms are used to refer to individuals who are unusually sensitive or resistant to a drug and to describe those in whom the drug produces a qualitatively different effect. The mechanisms of these unusual effects are described in general in this chapter and are discussed for individual drugs throughout this textbook. If a drug produces an effect at a very low dosage, the individual is said to be *hyperreactive*. (*Hypersensitivity* usually refers to effects associated with drug allergy, and *supersensitivity* is used to describe the increased sensitivity that results from denervation or long-term treatment with a receptor antagonist.) Individuals who are resistant to drug effect are said to be *hyporeactive*. *Tolerance* connotes hyporeactivity acquired as a result of exposure to the drug, and if tolerance develops rapidly, it is called *tachyphylaxis*. *Idiosyncrasy* is a term that describes an unusual effect of the drug, irrespective of intensity or dosage, that occurs in a small percentage of the population. However, because this term is often confused with drug allergy and because it conveys no useful information, it should probably be abandoned in favor of simple descriptions of the effect and terms that refer to the underlying mechanisms, which are often genetic or immunological.

Attempts have been made to define and measure individual "sensitivity" to drugs in the clinical setting, and progress has been made in understanding some of the determinants of sensitivity to drugs that act at specific receptors. For example, responsiveness to β-adrenergic receptor agonists may change because of disease (*e.g.*, thyrotoxicosis) or because of prior administration of either β-adrenergic agonists or antagonists that can cause changes in the concentration of the β-adrenergic receptor and/or coupling of the receptor to its effector systems (Bristow *et al.*, 1982; Stiles *et al.*, 1984). Resistance of tumors to the antineoplastic agent methotrexate may occur because of gene amplification and subsequent synthesis of large quantities of the receptor for the cytotoxic action of this drug, dihydrofolate reductase (Brown *et al.*, 1983). Receptors are not static components of the cell; they are in a dynamic state that is influenced by both endogenous and exogenous factors (*see* Chapters 2 and 5).

Concentration–Percent Curve. The concentration of a drug that produces a specified effect in a single patient is termed the *individual effective concentration*. This is a *quantal* response, since the defined effect is either present or absent. Individual effective concentrations are usually log-normally distributed, which means that a normal variation curve is the result of plotting the logarithms of the concentration against the frequency of patients achieving the defined effect (Figure 4–3A). A cumulative frequency distribution of individuals achieving the defined effect as a function of drug concentration is the *concentration–percent curve* or the *quantal concentration–effect curve*. This curve resembles the sigmoid shape of the graded concentration–effect curve discussed above (Figure 4–2), but the slope of the concentration–percent curve is an expression of the pharmacodynamic variability in the population rather than an expression of the concentration range from a threshold to a maximal effect in the individual patient.

The dose of a drug required to produce a specified effect in 50% of the population is the *median effective dose*, abbreviated as the ED_{50} (Figure 4–3B). In preclinical studies of drugs, the *median lethal dose*, as determined in experimental animals, is abbreviated as LD_{50}. The ratio of the LD_{50} to the ED_{50} is an indication of the *therapeutic index*, which is a statement of how *selective* the drug is in producing its desired effects. In clinical studies, the dose, or preferably the concentration, of a drug required to produce toxic effects can be compared to the concentration required for the therapeutic effects in the population in order to evaluate the clinical therapeutic index. However, since pharmacodynamic variation in the population may be marked, the concentration or dose of drug required to produce a therapeutic effect in most of the population will usually overlap the concentration required to produce toxicity in some of the population, even though the drug's therapeutic index may be large. Also, the concentration–percent curves for efficacy and toxicity need not be parallel, adding yet

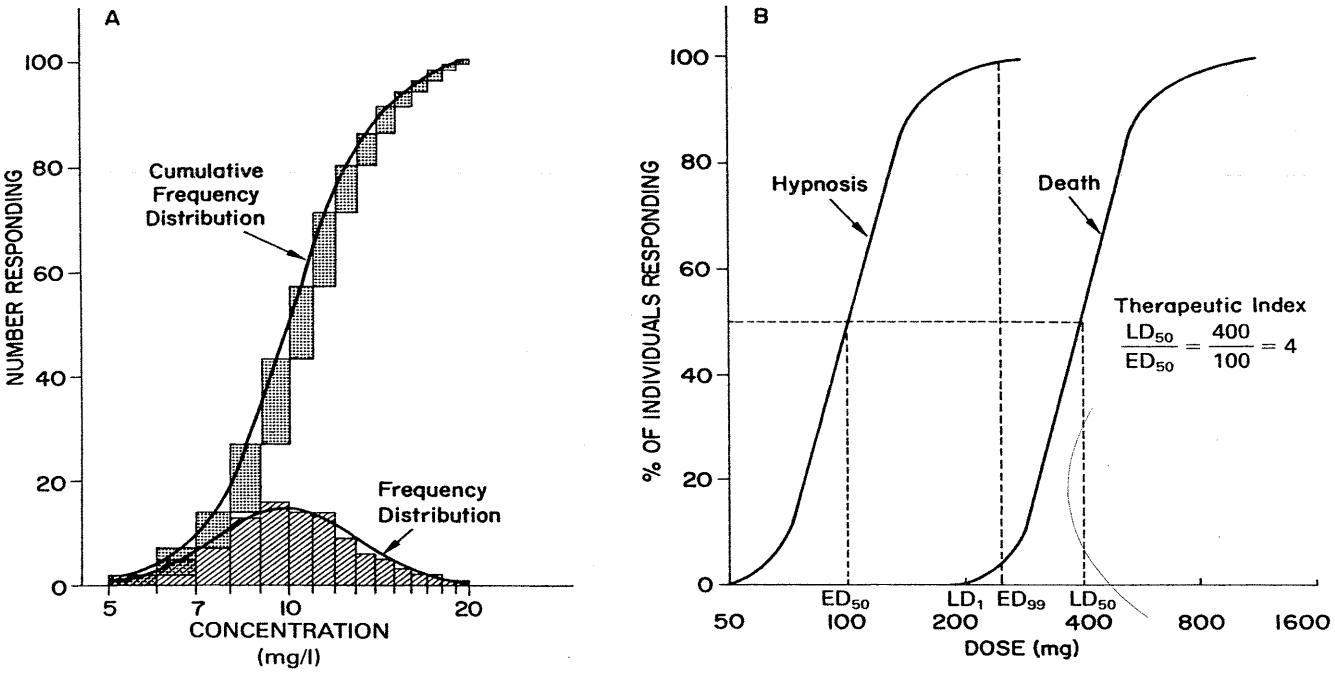

Figure 4–3. *Frequency distribution curves and quantal dose-effect curves.*

A. An experiment was performed on 100 subjects and the effective concentration to produce a quantal response was determined for each individual. The number of subjects who required each dose is plotted, giving a lognormal frequency distribution (bars with diagonal lines). The stippled bars demonstrate that the normal frequency distribution, when summated, yields the cumulative frequency distribution—a sigmoidal curve that is a quantal concentration–effect curve.

B. Quantal Dose-Effect Curves. Animals were injected with varying doses of a sedative–hypnotic, and the responses determined and plotted (*see* text for additional explanation).

another complexity to the determination of the therapeutic index in patients. Finally, *no drug produces a single effect*, and, depending on the effect being measured, the therapeutic index for a drug will vary. For example, much less codeine is required for cough suppression than for control of pain in 50% of the population, and thus the margin of safety, selectivity, or therapeutic index of codeine is much greater as an antitussive than as an analgesic.

Other Factors That Affect Therapeutic Outcome

The variation in pharmacokinetic and pharmacodynamic parameters that accounts for much of the need to individualize therapy has been discussed. Other factors, listed in Figure 4–1, should also be considered as potential determinants of success or failure of therapy. The following presentation serves as an introduction to these subjects, some of which are also discussed elsewhere in this textbook.

Drug–Drug Interactions. The use of several drugs is often essential to obtain a desired therapeutic objective or to treat coexisting diseases. Examples abound, and the choice of drugs to be employed concurrently can be based on sound pharmacological principles. In the treatment of hypertension, a single drug is effective in only a modest percentage of patients. In the treatment of heart failure, the concurrent use of a diuretic with a vasodilator and/or a cardiac glycoside is often essential to achieve an adequate cardiac output and to keep the patient free from edema. Multiple-drug therapy is the norm in cancer chemotherapy and for the treatment of certain infectious diseases. The goals in these cases are usually to improve efficacy and to delay the emergence of malignant cells or of microorganisms that are resistant to the effects of

available drugs. When physicians use several drugs concurrently, they face the problem of knowing whether a specific combination in a given patient has the potential to result in an interaction, and, if so, how to take advantage of the interaction if it leads to improvement in efficacy or how to avoid the consequences of an interaction if they are adverse.

A *potential drug interaction* refers to the possibility that one drug may alter the intensity of pharmacological effects of another drug given concurrently. The net result may be enhanced or diminished effects of one or both of the drugs or the appearance of a new effect that is not seen with either drug alone.

The frequency of significant beneficial or adverse drug interactions is unknown. Surveys that include data obtained *in vitro*, in animals, and in case reports tend to predict a frequency of interactions that is higher than actually occurs. While such reports have contributed to skepticism about the overall importance of drug interactions, there certainly are a number of potential interactions of clinical importance, and the physician must be alert to the possibility of their occurrence (McInnes and Brodie, 1988). Estimates of the incidence of clinical drug–drug interactions range from 3 to 5% in patients taking a few drugs to 20% in patients who are receiving 10 to 20 drugs. Because most hospitalized patients receive at least six drugs, the scope of the problem is clearly significant (Steel *et al.*, 1981). Recognition of beneficial effects and recognition and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed, a mental set to attribute unusual events to drugs rather than to disease, and adequate observation of the patient. Automated monitoring of prescription orders in the hospital or outpatient pharmacy may decrease the physician's need to memorize potential interactions. Nevertheless, knowledge of likely mechanisms of drug interactions is the only way the clinician can be prepared to analyze new findings systematically. It is incumbent upon the physician to be familiar with the basic principles of drug–drug interactions in planning a therapeutic regimen. Such reactions are discussed for individual drugs throughout this textbook. (*See also* Hansten, 1985; Rizack and Hillman, 1987; Tatro, 1988.)

Interactions may be either pharmacokinetic (alteration of the absorption, distribution, or disposition of one drug by another) or pharmacodynamic (*e.g.*, interactions between agonists and antagonists at drug receptors). The most important adverse drug–drug interactions occur with drugs that have easily recognizable toxicity and a low therapeutic index, such that relatively small changes in drug effect can have significant adverse consequences. Additionally, drug–drug interactions can be important if the disease being controlled with the drug is serious or potentially fatal if untreated and if therapeutic end points are clearly defined. Thus, major interactions have involved oral anticoagulants, oral hypoglycemics, antibiotics, antiepileptics, antiarrhythmics, and cardiac glycosides.

Pharmacokinetic Drug Interactions. Drugs may interact at any point during their absorption, distribution, metabolism, or excretion; the result may be an increase or decrease in the concentration of drug at the site of action. Since individuals vary in their rate of disposition of any given drug, the magnitude of an interaction that alters pharmacokinetic parameters is not always predictable, but can be very significant.

The delivery of drug into the circulation may be altered by physicochemical interactions that occur prior to absorption. For example, drugs may interact in an intravenous solution to produce an insoluble precipitate that may or may not be obvious. In the gut, drugs may chelate with metal ions or adsorb to medicinal resins. Thus, Ca^{2+} and other metallic cations contained in antacids are chelated by tetracycline, and the complex is not absorbed. Cholestyramine adsorbs and inhibits the absorption of thyroxine, cardiac glycosides, warfarin, corticosteroids, and probably other drugs. The rate and sometimes the extent of absorption can be affected by drugs that reduce gastric motility, but this is usually of little clinical consequence. Interactions within the gut may be indirect and complex. Antibiotics that alter the gastrointestinal flora can reduce the rate of bacterial synthesis of vitamin K such that the effect of oral anticoagulants, which compete with vitamin K, will be enhanced. If a drug is metabolized by the gastrointestinal microorganisms, antibiotic therapy may result in an increase in the absorption of the drug, as has been demonstrated for some patients receiving digoxin (Lindenbaum *et al.*, 1981).

Many drugs are extensively bound to plasma albumin (acidic drugs) or α_1-acid glycoprotein (basic drugs). In general, only unbound drug is free to exert an effect or to be distributed to the tissues. Thus, displacement of one drug from its binding site by another might be expected to result in a change in drug effects. Although such binding/displacement interactions occur, they are rarely of clinical significance. This is because the displaced drug distributes rapidly into the tissues; the larger the apparent volume of distribution of the drug, the less is the rise in the concentration of free drug in the plasma. Furthermore, following the displacement, more free drug is available for metabolism and excretion. Thus, the body's clearance processes eventually reduce the free drug concentration to that which existed prior to the drug-displacement interaction. As a result, the effect of such an interaction is usually small, transient, and frequently unrecognized. However, the relationship of free drug to the total (bound plus free) drug is changed, and the interpretation of plasma drug assays that measure total drug concentration must be altered.

A few drugs are actively transported to their site of action. For instance, the antihypertensive drugs guanethidine and guanadrel cause inhibition of sympathetic function after being transported into adrenergic neurons by the norepinephrine uptake mechanism. Inhibition of this neuronal uptake system by tricyclic antidepressants and some sympathomimetic amines will inhibit the sympathetic blockade and reduce the antihypertensive effects of guanethidine and guanadrel.

Interactions involving drug metabolism can increase or decrease the amount of drug available for action by inhibition or induction of metabolism, respectively. Inhibition of metabolism is usually more predictable than induction, which is influenced by genetic differences between patients. Examples of drugs that inhibit the metabolism of others include inhibitors of some isozymes of cytochrome P_{450} (cimetidine, amiodarone, phenylbutazone, isoniazid, sodium valproate, and erythromycin), xanthine oxidase (allopurinol), and monoamine oxidase (MAO) inhibitors. Drugs that accelerate the metabolism of other agents include barbiturates, rifampin, phenytoin, carbamazepine, chronic smoking, and certain chlorinated hydrocarbons. The effects of enzyme induction are most obvious when drugs are given orally, because all of the absorbed compound must pass through the liver prior to reaching the systemic circulation. Therefore, even for drugs that have a systemic clearance that is mainly dependent on hepatic blood flow (*e.g.*, propranolol), the amount of drug that escapes metabolism on the first pass will be influenced by enzyme induction. Examples of drugs that are affected by enzyme inducers are oral anticoagulants, quinidine, corticosteroids, low-dose estrogen contraceptives, theophylline, mexiletine, methadone, and some β-adrenergic blocking agents.

The ability of one drug to inhibit the renal excretion of another is dependent on an interaction at active transport sites. Many of the reported interactions occur at the anion transport site, where, for example, probenecid inhibits the excretion of penicillin to cause the desirable effects of elevated plasma concentrations of the antibiotic and a longer half-life. Similarly, the renal elimination of methotrexate is inhibited by probenecid, salicylates, and phenylbutazone, but in this case methotrexate toxicity may result from the interaction. Interactions at the transport site for basic drugs include the inhibition of excretion of procainamide by cimetidine and amiodarone. An interaction at an unknown tubular site causes inhibition of the excretion of digoxin by quinidine, verapamil, and amiodarone. Finally, the excretion of Li^+ can be affected by drugs that alter the ability of the proximal renal tubule to reabsorb Na^+. Thus, clearance of Li^+ is reduced and concentrations of Li^+ in plasma are increased by diuretics that cause volume depletion and by nonsteroidal antiinflammatory drugs that enhance proximal tubular reabsorption of Na^+.

Pharmacodynamic Interactions. There are numerous examples of drugs that interact at a common receptor site or that have additive or inhibitory effects due to actions at different sites in an organ. Such interactions are described throughout this textbook. Frequently overlooked is the multiplicity of effects of many drugs. Thus, phenothiazines are effective α-adrenergic antagonists; many antihistamines and tricyclic antidepressants are potent inhibitors of muscarinic receptors. These "minor" actions of drugs may be the cause of drug interactions.

Other interactions of an apparently pharmacodynamic nature are poorly understood or are mediated indirectly. Halogenated hydrocarbons, including many general anesthetics, sensitize the myocardium to the arrhythmogenic actions of catecholamines. This effect may result from an action on the pathway that leads from adrenergic receptor to effector, but the details are unclear. The striking interaction between meperidine and monoamine oxidase inhibitors to produce seizures and hyperpyrexia may be related to excessive amounts of an excitatory neurotransmitter, but the mechanism has not been elucidated.

One drug may alter the normal internal milieu, thereby augmenting or diminishing the effect of another agent. A well-known example of such an interaction is the enhancement of the toxic effects of digoxin as a result of diuretic-induced hypokalemia.

Summary. Drug–drug interactions are only one of the many factors discussed in this chapter that can alter the patient's response to therapy. The major task of the physician is to determine if an interaction

has occurred and the magnitude of its effect. When unexpected effects are seen, a drug interaction should be suspected. Careful drug histories are important because patients may take over-the-counter drugs, may take drugs prescribed by another physician, or may take drugs prescribed for another patient. Care must be exercised when major changes are made in a drug regimen, and drugs that are not necessary should be discontinued. When an interaction is discovered, the interacting drugs may often be used effectively with adjustment of dosage or other therapeutic modifications.

Fixed-Dose Combinations. The concomitant use of two or more drugs adds to the complexity of individualization of drug therapy. The dose of each drug should be adjusted to achieve optimal benefit. Thus, patient compliance is essential, yet more difficult to achieve. To obviate the latter problem many fixed-dose drug combinations are marketed. The use of such combinations is advantageous only if the ratio of the fixed doses corresponds to the needs of the individual patient.

In the United States, a fixed-dose combination of drugs must be approved by the Food and Drug Administration (FDA) before it can be marketed, even though the individual drugs are available for concurrent use. To be approved, certain conditions must be met. The two drugs must act to achieve a better therapeutic response than either drug alone (*e.g.*, many antihypertensive drug combinations); or one drug must act to reduce the incidence of adverse effects caused by the other (*e.g.*, a diuretic that promotes the urinary excretion of K^+ combined with a K^+-sparing diuretic).

Placebo Effects. The net effect of drug therapy is the sum of the pharmacological effects of the drug and the nonspecific placebo effects associated with the therapeutic effort. Although identified specifically with administration of an inert substance in the guise of medication, placebo effects are associated with the taking of any drug, active as well as inert.

Placebo effects result from the physician–patient relationship, the significance of the therapeutic effort to the patient, and the mental set imparted by the therapeutic setting and by the physician. They vary significantly in different individuals and in any one patient at different times. Placebo effects are commonly manifested as alterations of mood, other subjective effects, and objective effects that are under autonomic or voluntary control. They may be favorable or unfavorable relative to the therapeutic objectives. Exploited to advantage, placebo effects can significantly supplement pharmacological effects and can represent the difference between success and failure of therapy (Brody, 1982).

A placebo (in this context, better termed *dummy medication*) is an indispensable element of the controlled clinical trial. In contrast, a placebo has only a limited role in the routine practice of medicine. Although the inert medication may be an effective vehicle for a placebo effect, the physician–patient relationship is generally preferable. Relief or lack of relief of symptoms upon administration of a placebo is not a reliable basis for determining whether the symptoms have a "psychogenic" or "somatic" origin.

Tolerance. Tolerance may be acquired to the effects of many drugs, especially the opioids, various central nervous system (CNS) depressants, and organic nitrates. When this occurs, *cross-tolerance* may develop to the effects of pharmacologically related drugs, particularly those acting at the same receptor site, and drug dosage must be increased to maintain a given therapeutic effect. Since tolerance does not usually develop equally to all effects of a drug, the therapeutic index may decrease. However, there are also examples of the development of tolerance to the undesired effects of a drug and a resultant increase in its therapeutic index (*e.g.*, tolerance to sedation produced by phenobarbital when used as an anticonvulsant).

The mechanisms involved in the development of tolerance are only partially understood. In animals, tolerance often occurs as the result of induced synthesis of the hepatic microsomal enzymes involved in drug biotransformation; the possible significance of this *drug-disposition* or *pharmacokinetic tolerance* during chronic medication in man is an area of continuing investigation. The most important factor in the development of tolerance to the opioids, barbiturates, ethanol, and organic nitrates is some type of cellular adaptation referred to as *pharmaco-*

dynamic tolerance; multiple mechanisms are involved. Tachyphylaxis, such as that to histamine-releasing agents and to the sympathomimetic amines that act indirectly by releasing norepinephrine, has been attributed to depletion of available mediator, but other mechanisms may also contribute. The subject of tolerance is discussed in more detail in Chapter 22.

Genetic Factors. Genetic factors are the major determinants of the normal variability of drug effects and are responsible for a number of striking quantitative and qualitative differences in pharmacological activity (Vesell, 1986). Many of the genetically determined *quantitative* differences in drug response are due to polygenic influences on drug metabolism, which result in a more or less normal distribution of rates of drug clearance across the population. Recently, however, there has been an increasing number of drugs whose metabolic clearances segregate into distinct groups because the drug biotransformation is controlled by a single gene.

Metabolic processes that are under monogenic control include (1) N-acetyltransferase-catalyzed N-acetylation of isoniazid, procainamide, hydralazine, dapsone, sulfamethazine, sulfasalazine, and some potential carcinogenic amines (Horai and Ishizaki, 1987); (2) cytochrome P_{450}-catalyzed oxidation of several β-adrenergic receptor blocking agents, encainide, propafenone, tricyclic antidepressants, phenformin, and dextromethorphan (Clark, 1985; Gonzalez, *et al.*, 1988); (3) several methyltransferase-catalyzed methylations of thiopurines (mercaptopurine, thioguanine, and azathioprine), aliphatic thiol-containing drugs (captopril and penicillamine), catecholamines, and possibly histamine (Weinshilboum, 1988); and (4) plasma cholinesterase-catalyzed hydrolysis of succinylcholine. The quantitative differences in drug response in patients with these genetically determined differences in drug metabolism are due to greater or lesser amounts of active compound in the body, whether this be the parent drug or an active metabolite.

Genetically determined *qualitative* differences in drug effect occur when a known minor toxic property of a drug assumes an exaggerated importance due to a genetic defect in the ability to avoid the toxicity. For example, individuals who are deficient in glucose-6-phosphate dehydrogenase activity are unable to cope with the oxidative stress produced by some drugs, resulting in drug-induced hemolysis.

The objectives of *pharmacogenetics* include not only identification of differences in drug effects that have a genetic basis but also development of simple methods by which susceptible individuals can be recognized before the drug is administered.

APPROACH TO INDIVIDUALIZATION

After it has been determined that pharmacotherapy is necessary to modify the symptoms or outcome of a disease, the therapist is faced with two types of decisions: the first is qualitative (the initial choice of a specific drug) and the second quantitative (the initial dosage regimen). Optimal treatment will result only when the physician is aware of the sources of variation in response to drugs, and when the dosage regimen is designed on the basis of the best available data about the diagnosis, severity and stage of the disease, presence of concurrent diseases or drug treatment, and predefined goals of acceptable efficacy and limits of acceptable toxicity. If objectively assessable expectations of drug therapy are not set before therapy is initiated, therapy is likely to be ineffective and continued longer than necessary, unless an obvious adverse effect occurs.

In most clinical settings, the decision about the choice of drug is substantially influenced by the confidence the physician has in the accuracy of his diagnosis and estimates of the extent and severity of disease. Based on the best available information, the physician must decide on an initial drug from a group of reasonable alternatives. The extent of this evaluation is itself dependent on many factors, including a cost–benefit analysis of diagnostic tests, and this must be based on the availability and specificity of alternative therapies (Pauker and Kassirer, 1987). The initial dosage regimen is determined by estimation, if possible, of the pharmacokinetic properties of the drug in the individual patient. The estimate must be based on an appreciation of the variables that are most likely to affect the disposition of the particular drug. These variables have been discussed above (*see* Figure 4–1 and Appendix II). Subsequent adjustments may be aided in some instances by measurement of drug concentrations but must ultimately be

based on whether the regimen is efficacious, either without adverse effects or at an acceptable level of toxicity.

It has been stated above that every therapeutic plan is and should be treated as an experiment. As such, most of the considerations that were specified in the discussion of clinical trials must be applied to individual patients. Of utmost importance is the definition of specific goals of treatment and the means to assess whether these goals are being achieved. Whenever possible, the objective end point should be related as closely as possible to the clinical goals of therapy (*e.g.*, shrinkage of a tumor or eradication of an infection). Many clinical goals are, however, difficult to assess (*e.g.*, the prevention of cardiovascular complications associated with hypertension and diabetes). In such cases it is necessary to set intermediate end points to therapy, such as a reduction in blood pressure or the concentration of glucose in plasma. These intermediate end points are based on demonstrated or assumed correlations with the ultimate clinical benefit. In many cases, such as reduction of the concentration of cholesterol in plasma by drugs or the elimination of asymptomatic ventricular arrhythmias, the link between the intermediate goal and the ultimate goal is controversial.

Certain general considerations apply to the individualization of a drug regimen and the concept of intermediate end points. The value or utility of the regimen obviously needs to be assessed at intervals during the course of therapy. The utility of a regimen can be defined as the benefit it produces plus the dangers of not treating the disease minus the sum of the adverse effects of therapy. Another common expression of the usefulness of a regimen is its ratio of risks to benefits (representing a balance between the efficacious and toxic effects of the drug). A definitive evaluation of the utility of a drug is not easy; nevertheless, some sense of the value of a regimen must be established in the minds of the physician and the patient. Knowledge of the usefulness of a given regimen may be a critical determinant of protracted compliance by the patient to a long-term regimen or logical discontinuation by the physician of a marginally efficacious and risky therapy. It must be remembered that the physician, the patient, and the patient's family may have disparate opinions of the utility of a therapeutic regimen. In one study of antihypertensive therapy where all patients were judged to be improved by the physician, only 48% of the patients considered themselves improved and 8% felt worse. Relatives thought that only 1% of the patients were improved and that 99% had evidence of adverse effects of therapy (Jachuck *et al.*, 1982).

DRUG REGULATION AND DEVELOPMENT

Drug Regulation

The history of drug regulation in the United States reflects the growing involvement of governments in most countries to ensure some degree of efficacy and safety in marketed medicinal agents. The first act, the Federal Food and Drug Act of 1906, was concerned with the interstate transport of adulterated or misbranded foods and drugs. There were no obligations to establish drug efficacy and safety. The federal act was amended in 1938, following the deaths of about 100 children that resulted from the marketing of a solution of sulfanilamide in diethylene glycol, an excellent but highly toxic solvent. The amended act, the enforcement of which was entrusted to the FDA, was primarily concerned with the truthful labeling and safety of drugs. Toxicity studies were required, as well as approval of a new drug application (NDA), before a drug could be promoted and distributed. However, no proof of efficacy was required, and extravagant claims for therapeutic indications were commonly made. Drugs could go from the laboratory to clinical testing without approval by the FDA.

In this relatively relaxed atmosphere, research in basic and clinical pharmacology burgeoned in both industrial and academic laboratories. The result was a flow of new drugs, called "wonder drugs" by the lay press, for the treatment of both infectious and organic disease. Because efficacy was not rigorously defined, a number of therapeutic claims could not be supported by data. The risk-to-benefit ratio was seldom mentioned, but it emerged in dramatic fashion early in the 1960s. At that time thalidomide, a hypnotic with no obvious advantage over other drugs in its class, was introduced in the European market. After a short period, it became apparent that the incidence of a relatively rare birth defect, phocomelia, was increasing. It soon reached epidemic proportions, and retrospective epidemiological research firmly established the causative agent to be thalidomide taken early in the course of pregnancy. The reaction to the dramatic demonstration of the teratogenicity of a needless drug was

worldwide. In the United States it resulted in the Harris–Kefauver Amendments to the Food, Drug, and Cosmetic Act in 1962.

The Harris–Kefauver Amendments are sound legislation. They require sufficient pharmacological and toxicological research in animals before a drug can be tested in man. The data from such studies must be submitted to the FDA in the form of an application for an investigational new drug (IND) before clinical studies can begin. Three phases of clinical testing (*see* below) have evolved to provide the data that are used to support a new drug application. For drugs introduced after 1962, proof of efficacy is required, as is documentation of relative safety in terms of the risk-to-benefit ratio for the disease entity to be treated. The 1962 amendments also required manufacturers to provide data to support the claims of efficacy for all drugs marketed between 1938 and 1962.

The provisions of the Harris–Kefauver amendments have greatly increased the time and the cost required to market a new drug. Moreover, although the law requires action on the part of the FDA within a period of 6 months, an NDA may be returned to the applicant for additional basic or clinical research, so that the period actually required for approval of an NDA is on the order of 2 to 3 years. The total time of drug development from the time of filing of an IND application to final approval averages 8 to 9 years (Kaitin *et al.*, 1987). The result has been an increase in the inherent tension that exists between the FDA, which is motivated to protect the public health, and the drug developers, who are motivated to market effective and profitable drug products. Additionally, medical practitioners have criticized the FDA for delaying the approval of new drugs, whereas some consumer groups demand the recall of drugs that may play an important part in the therapeutic regimen of appropriately selected patients. In this climate, the FDA has the difficult task of balancing the requirement to ensure the safety of new drugs with the needs of society for useful medications to be made available in a timely manner. This dilemma has been brought into sharp focus recently by the demands of patients with acquired immunodeficiency syndrome (AIDS) for new and effective therapies. In response to the needs of patients with AIDS and other life-threatening illnesses, the FDA is moving on several fronts (Young *et al.*, 1988). First, the FDA has initiated new "treatment" IND regulations that allow patients with life-threatening diseases for which there is no satisfactory alternative treatment to receive drugs for therapy prior to general marketing if there is limited evidence of drug efficacy without unreasonable toxicity (Figure 4–4). Second, the agency has established a priority review system for potentially useful AIDS-related drugs to assure that the review process is expedited. Finally, the FDA is attempting to be involved more actively in drug development in order to facilitate the approval of drugs designed to treat life-threatening and severely debilitating diseases. By working with the pharmaceutical industry throughout the period of clinical drug development instead of involving themselves only at the end of this process, the FDA hopes to reduce the time from submission of an IND application to the approval of an NDA. This streamlining process will be accomplished by the interactive design of well-planned, focused clinical studies. Sufficient data should then be available earlier in the development process to allow a risk–benefit analysis and a possible decision for approval. In some cases this system may reduce or obviate the need for phase-3 testing prior to approval. Coupled with this expedited development process will be the requirement, when appropriate, for postmarketing studies to answer remaining issues of risks, benefits, and optimal uses of the drug (*Federal Register,* 1988). This new initiative by the FDA is based on the assumption that society is more willing to accept unknown risks from drugs used to treat life-threatening or debilitating diseases. As long as the patient's safety can be reasonably ensured, the new plans to accelerate the drug-development process should prove beneficial to patients with such illnesses.

A seemingly contradictory directive to the FDA is also contained in the Food, Drug, and Cosmetic Act—that is, the FDA cannot interfere with the practice of medicine. Thus, once the efficacy of a new agent has been proven in the context of acceptable toxicity, the drug can be marketed. The physician is then allowed to determine its most appropriate use. However, physicians must realize that new drugs are inherently more risky because of the relatively small amount of data about their effects. Yet there is no practical way to increase knowledge about a drug before it is marketed. A systematic method for postmarketing surveillance is an indispensable requirement for early optimization of drug use.

Before a drug can be marketed, a package insert for use by physicians must be prepared. This is a cooperative effort between the FDA and the pharmaceutical company. The insert usually contains basic pharmacological information, as well as essential clinical information in regard to approved indications, contraindications, precautions, warnings, adverse reactions, usual dosage, and available preparations. Promotional materials cannot deviate from information contained in the insert.

DRUG DEVELOPMENT

Except for concern about the so-called drug lag (Kennedy, 1978) and governmental interference with the practice of medicine, the average physician has not considered it important to understand the process of drug development. Yet an appreciation of this process is necessary if the therapist wishes to have the ability to estimate the risk-to-benefit ratio of a drug and to realize the limitations of the data that support the efficacy and safety of a marketed product.

By the time an IND application has been initiated and a drug reaches the stage of testing in man, its pharmacokinetic, pharmacodynamic, and toxic properties have been evaluated *in vitro* and in several species of animals in accordance with regulations and guidelines published by the FDA. Although the value of many requirements for

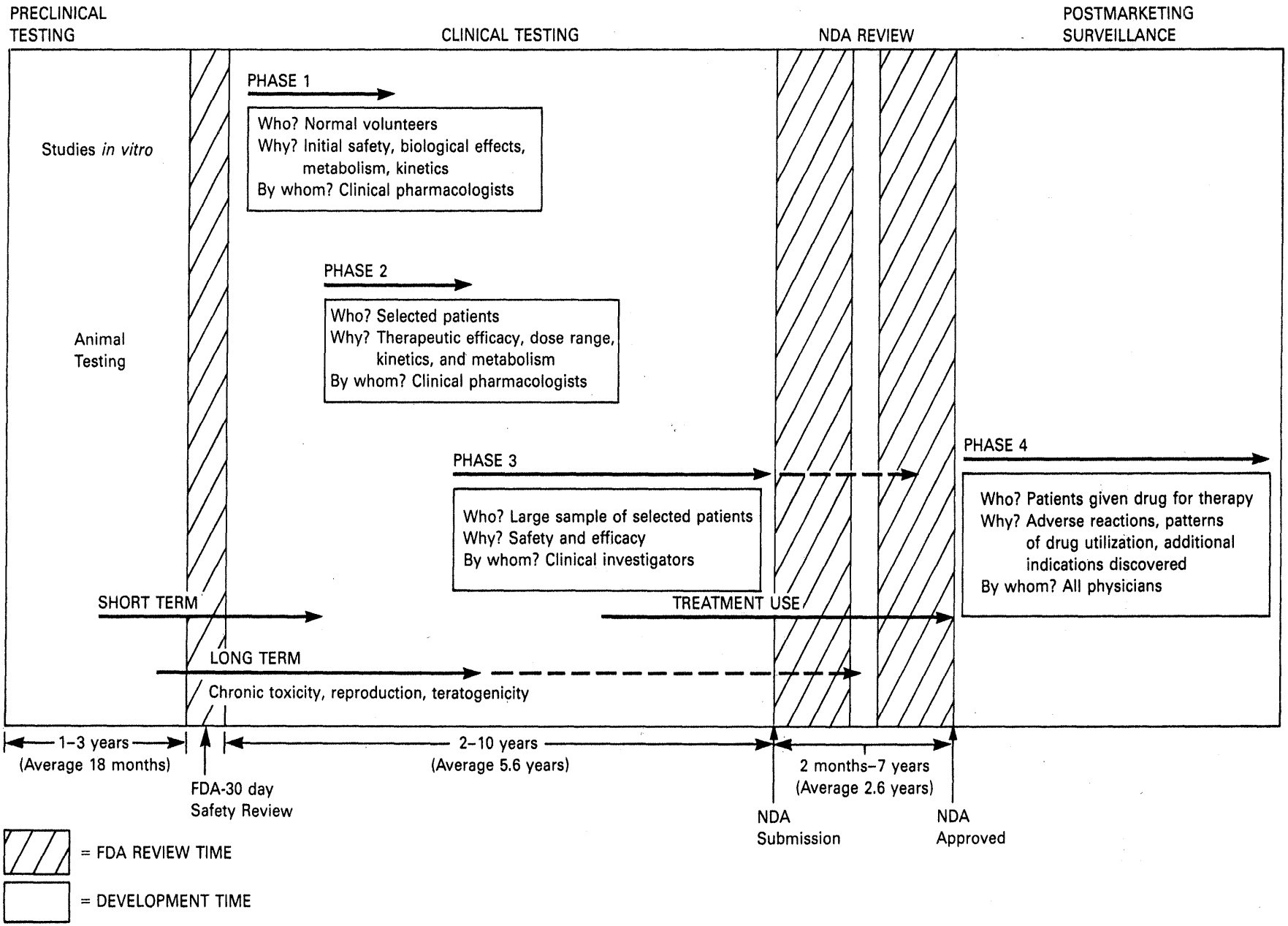

Figure 4–4. *The phases of drug development in the United States.* (Sources: Smith, 1978; Kaitin *et al.*, 1987; Young *et al.*, 1988.)

preclinical testing is self-evident, such as those that screen for direct toxicity to organs and characterize dose-related effects, the value of others is controversial, particularly because of the well-known interspecies variation in the effects of drugs. Interestingly, although many of the preclinical tests have not been convincingly shown to predict effects that are eventually observed in man, the risk of cautious testing of a new drug is surprisingly low.

Trials of drugs in man in the United States are generally conducted in three phases that must be completed before an NDA can be submitted to the FDA for review; these are outlined in Figure 4–4. Although assessment of risk is a major objective of such testing, this is far more difficult than is the determination of whether a drug is efficacious for a selected clinical condition. Usually about 500 to 3000 carefully selected patients receive a new drug during phase-3 clinical trials. At most, only a few hundred are treated for more than 3 to 6 months, regardless of the likely duration of therapy that will be required in practice. Thus, the most profound and overt risks that occur almost immediately after the drug is given can be detected in a phase-3 study, if these occur more often than once per 100 administrations. Risks that are medically important but delayed or less frequent than 1 in 1000 administrations may not be revealed prior to marketing. It is thus obvious that a number of unanticipated adverse and beneficial effects of drugs are only detectable after the drug is used broadly. The same can be more convincingly stated about most of the effects of drugs on children or the fetus, where premarketing experimental studies are restricted. It is for these reasons that many countries, including the United States, have established systematic methods for the surveillance of the effects of drugs after they have been approved for distribution (Joint Commission on Prescription Drug Use, 1980; Venning, 1983; Strom, 1987a; *see also* below).

ADVERSE DRUG REACTIONS AND DRUG TOXICITY

Any drug, no matter how trivial its therapeutic actions, has the potential to do harm. Adverse reactions are a cost of modern medical therapy. Although the mandate of the FDA is to ensure that drugs are safe and effective, both of these terms are relative. The anticipated benefit from any therapeutic decision must be balanced by the potential risks. Patients, to a greater extent than physicians, are unaware of the limitations of the premarketing phase of drug development in defining even relatively common risks of new drugs. Since only a few thousand patients are exposed to experimental drugs in more or less controlled and well-defined circumstances during drug development, adverse drug effects that occur as frequently as 1 in 1000 patients may not be detected prior to marketing. Postmarketing surveillance of drug usage is thus imperative to detect infrequent but significant adverse effects.

Several strategies exist to detect adverse reactions after marketing of a drug, but debate continues about the most efficient and effective method. Formal approaches for estimation of the magnitude of an adverse drug effect are the follow-up or "cohort" study of patients who are receiving a particular drug and the "case–control" study, where the potential for a drug to cause a particular disease is assessed. Cohort studies can estimate the incidence of an adverse reaction, but they cannot, for practical reasons, discover rare events. To have any significant advantage over the premarketing studies, a cohort study must follow at least 10,000 patients who are receiving the drug in order to detect with 95% confidence one event that occurs at a rate of 1 in 3300, and the event can be attributed to the drug only if it does not occur spontaneously in the control population. If the adverse event occurs spontaneously in the control population, substantially more patients and controls must be followed to establish the drug as the cause of the event (Rawlins, 1984; Strom, 1987a). Case–control studies, on the other hand, can discover rare drug-induced events. However, it may be difficult to establish the appropriate control group (Feinstein and Horwitz, 1988), and a case–control study cannot establish the incidence of an adverse drug effect. Furthermore, the suspicion of a drug as a causative factor in a disease must be the impetus for the initiation of such case–control studies.

The magnitude of the problem of adverse reactions to marketed drugs is difficult to quantify. It has been estimated that 3 to 5% of all hospitalizations can be attributed to adverse drug reactions, resulting in 300,000 hospitalizations annually in the United States. Once hospitalized, patients have about a 30% chance of an untoward event related to drug therapy, and the risk attributable to each course of drug therapy is about 5%. The chance of a life-threatening drug reaction is about 3% per patient in the hospital and about 0.4% per each course of

therapy (Jick, 1984). On a university medical service where severely ill patients and patients with complicated courses of disease are treated, adverse reactions to drugs were found to be the most common cause of iatrogenic disease (Steel *et al.*, 1981).

Because of the shortcomings of both cohort and case–control studies, other approaches must be used. Spontaneous reporting of adverse reactions has proven to be an effective way to generate an early signal that a drug may be causing an adverse event (Rawlins, 1988; Rossi *et al.*, 1988). It is the only practical way to detect rare events, events that occur after prolonged use of drug, adverse effects that are delayed in appearance, and many drug–drug interactions (Edlavitch, 1988). In the past few years considerable effort has gone into improving the reporting system in the United States, and the number of reports has increased recently (Faich *et al.*, 1988). Still, the voluntary reporting system in the United States is deficient when compared with the legally mandated systems of the United Kingdom, Canada, New Zealand, Denmark, and Sweden (Rogers *et al.*, 1988). Most physicians feel that detecting adverse reactions is a professional obligation, but relatively few actually report such reactions. Over 40% of physicians are not aware that the FDA has a reporting system for adverse drug reactions, even though the system has been repeatedly publicized in major medical journals.

The most important spontaneous reports are those that describe serious reactions, whether they have been described previously or not. Reports on newly marketed drugs are the most significant, even though the physician may not be able to attribute a causal role to a particular drug. The major use of this system is to provide early warning signals of unexpected adverse effects that can then be investigated by more formal techniques. However, the system also serves to monitor changes in the nature or frequency of adverse drug reactions due to aging of the population, changes in the disease itself, or the introduction of new, concurrent therapies. The primary sources for the reports are responsible, alert physicians; other potentially useful sources are nurses, pharmacists, and students in these disciplines. In addition, hospital based pharmacy and therapeutics committees and quality assurance committees frequently are charged with monitoring adverse drug reactions in hospitalized patients, and reports from these committees should be forwarded to the FDA (Edlavitch, 1988). The simple, one-page forms for reporting are now readily available as the last page of the *Physicians' Desk Reference* and *AMA Drug Evaluations* and are mailed to all physicians at least yearly as part of the FDA "Drug Bulletin." Additionally, physicians may contact the pharmaceutical manufacturer and/or write to the Office of Epidemiology and Biostatistics (HFN-700), Center for Drug Evaluation and Research, Food and Drug Administration, Parklawn Building, Rockville, MD 20857 (Faich *et al.*, 1988).

As with drug interactions, classification of adverse effects of drugs according to information about their causes provides a framework for the transfer of principles to the clinical setting. Such classification appears in Chapter 3. In addition, the clinician obviously also needs to know the frequencies and types of untoward effects caused by each individual drug prescribed; such information is presented throughout this textbook.

GUIDE TO THE "THERAPEUTIC JUNGLE"

The flood of new drugs in recent years has provided many dramatic improvements in therapy, but it has also created a number of problems of equal magnitude. Not the least of these is the "therapeutic jungle," the term used to refer to the combination of the overwhelming number of drugs, the confusion over nomenclature, and the associated uncertainty of the status of many of these drugs. A reduction in the marketing of close congeners and drug mixtures and an improvement in the quality of advertising are important ingredients in the remedy for the "therapeutic jungle." However, physicians can also contribute to the remedy by employing nonproprietary rather than proprietary names whenever appropriate, by using prototypes both as an instructional device and in clinical practice, by

adopting a properly critical attitude toward new drugs, and by knowing and making use of reliable sources of pharmacological information. Most important, they should develop a "way of thinking about drugs" based upon pharmacological principles.

Drug Nomenclature. The existence of many names for each drug, even when reduced to a minimum, has led to a lamentable and confusing situation in drug nomenclature. In addition to its formal *chemical* name, a new drug is usually assigned a *code* name by the pharmaceutical manufacturer. If the drug appears promising and the manufacturer wishes to place it on the market, a *United States Adopted Name* (USAN) is selected by the USAN Council, which is jointly sponsored by the American Medical Association, the American Pharmaceutical Association, and the United States Pharmacopeial Convention, Inc. This *nonproprietary* name is often referred to as the *generic* name. This term has become entrenched, but by definition it should be more properly reserved to designate a chemical or pharmacological class of drugs, such as sulfonamides or sympathomimetics. If the drug is eventually admitted to *The United States Pharmacopeia* (*see* below), the USAN becomes the *official* name. However, the nonproprietary name and the official name of an older drug may differ. Subsequently, the drug will also be assigned a *proprietary* name or *trademark* by the manufacturer. If the drug is marketed by more than one company, it may have several proprietary names. If mixtures of the drug with other agents are marketed, each such mixture may also have a separate proprietary name.

There is increasing worldwide adoption of the same name for each therapeutic substance. For newer drugs, the USAN is usually adopted for the nonproprietary name in other countries, but this is not true for older drugs. International agreement on drug names is mediated through the World Health Organization and the pertinent health agencies of the cooperating countries.

One area of continued confusion and ambiguity is the designation of the stereochemical composition in the name of a drug. The nonproprietary names usually give no indication of the drug's stereochemistry, except for a few drugs such as levodopa and dextroamphetamine. Even the chemical names cited by the USAN Council are often ambiguous. Physicians and other medical scientists are frequently ignorant about drug stereoisomerism and are likely to remain so until the system of nonproprietary nomenclature incorporates stereoisomeric information (Gal, 1988).

The nonproprietary or official name of a drug should be used whenever possible, and such a practice has been adopted in this textbook. The use of the nonproprietary name is clearly less confusing when the drug is available under multiple proprietary names and when the nonproprietary name more readily identifies the drug with its pharmacological class. The best argument for the proprietary name is that it is frequently more easily pronounced and remembered as a result of advertising. For purposes of identification, representative proprietary names, designated by SMALLCAP TYPE, appear throughout the text in chapter sections dealing with preparations as well as in the index. This list is far from complete, since the number of proprietary names for a single drug may be large and since proprietary names differ from country to country.

The Drug Price Competition and Patent Term Restoration Act of 1984 allows more generic versions of brand-name drugs to be approved for marketing. When the physician prescribes drugs, the question arises as to whether the nonproprietary name or a proprietary name should be employed. In practically all states, a pharmacist may substitute a preparation that is equivalent unless the physician indicates "no substitution" on the prescription. Likewise, if the nonproprietary name of a drug is employed, the physician can specify the manufacturer. In view of the discussion above on the individualization of drug therapy, it is understandable why a physician who has carefully adjusted the dose of a drug to a patient's individual requirements for chronic therapy may be reluctant to surrender control over the source of the drug that the patient receives (Strom, 1987b).

Based on a number of considerations, such as the frequency of use of a drug that is only available from a single manufacturer, the cost of filling a prescription, and

the mark-up of the pharmacist, it appears as though the overall savings to society of prescribing the least expensive nonproprietary preparation is about 5% (*see* Trout and Lee, 1981). Of course, savings in individual situations can be very much greater. On the other hand, the lower wholesale cost of the nonproprietary preparation is sometimes not passed on to the consumer (Bloom *et al.*, 1986). More importantly, prescribing by nonproprietary name could result in the patient receiving a preparation of inferior quality or of uncertain bioavailability, and therapeutic failures due to decreased bioavailability have been reported (Strom, 1987b). To address this issue, the FDA has established standards for bioavailability and compiled information about the interchangeability of drug products; unfortunately, data on therapeutic equivalence based on clinical studies do not exist for most of these products (*Approved Prescription Drug Products with Therapeutic Evaluations,* 1987). In spite of this limitation, potential cost savings to the individual patient and simplification of the "therapeutic jungle" dictate that nonproprietary names be used when prescribing, except for drugs with a low therapeutic index and known differences in bioavailability among marketed products (*Medical Letter,* 1986).

Use of Prototypes. It is obviously crucial for the physician to be thoroughly familiar with the pharmacological properties of a drug before it is administered. It follows that the patient will benefit if the physician avoids the temptation to choose from many different drugs for the patient's regimen. A physician's needs for therapeutic agents can usually be satisfied by thorough knowledge of one or two drugs in each therapeutic category. Inevitably, a small number of drugs can be used more effectively. When the clinical setting calls for a drug that the physician uses infrequently, he or she should feel obligated to learn about its effects, to use great caution in its administration, and to apply appropriate procedures in monitoring its effects.

For teaching purposes in this textbook, the confusion created by the welter of similar drugs is reduced by restricting major attention to prototypes in each pharmacological class. Focusing on the representative drugs results in better characterization of a class as a whole, and thereby permits sharper recognition of the occasional member that possesses unique properties. A teaching prototype is often the agent most likely to be employed in clinical use, but this is not always true. A particular drug may be retained as the prototype, even though a new congener is clinically superior, either because more is known about the older drug or because it is more illustrative for the entire class of agents.

Attitude toward New Drugs. A reasonable attitude toward new drugs is summarized by the adage that advises the physician to be "neither the first to use a new drug nor the last to discard the old." Only a minor fraction of new drugs represents a significant therapeutic advance. The limitation of information about toxicity and efficacy at the time of release of a drug has been emphasized above, and this is particularly pertinent to comparisons with older agents in the same therapeutic class. Nevertheless, the important advances in therapeutics in the last 50 years emphasize the obligation to keep abreast of significant advances in pharmacotherapy.

SOURCES OF DRUG INFORMATION

The physician's need for objective, concise, and well-organized information on drugs is obvious. Among the available sources are textbooks of pharmacology and therapeutics, leading medical journals, drug compendia, professional seminars and meetings, and advertising. Despite this cornucopia of information, responsible medical spokesmen insist that most practicing physicians are unable to extract the objective and unbiased data required for the practice of rational therapeutics (*see* Task Force, 1969).

Depending on their aim and scope, pharmacology textbooks provide (in varying proportions) basic pharmacological principles, critical appraisal of useful categories of therapeutic agents, and detailed descriptions of individual drugs or prototypes that serve as standards of reference for assess-

ing new drugs. In addition, pharmacodynamics and pathological physiology are correlated. Therapeutics is considered in virtually all textbooks of medicine, but often superficially. For obvious reasons, textbooks cannot contain information on the most recently introduced drugs.

The source of information described as most often used by physicians in an industry survey is the *Physicians' Desk Reference* (PDR). The brand-name manufacturers whose products appear support this book. No comparative data on efficacy, safety, or cost are included. The information is identical to that contained in drug package inserts, which are largely based on the results of phase-3 testing; its primary value is thus in learning what indications for use of a drug have been approved by the FDA.

There are, however, several inexpensive, unbiased sources of information on the clinical uses of drugs that are preferable to the industry-supported PDR. All recognize that the physician's legitimate use of a drug in a particular patient is not limited by FDA-approved labeling in the package insert. *The United States Pharmacopeia Dispensing Information* (USPDI), first published in 1980, comes in two volumes. One, *Drug Information for the Health Care Provider,* consists of drug monographs that contain practical, clinically significant information aimed at minimizing the risks and enhancing the benefits of drugs. Monographs are developed by USP staff and are reviewed by advisory panels and other reviewers. The *Advice for the Patient* volume is intended to reinforce, in lay language, the oral consultation provided by the therapist, and this may be provided to the patient in written form. It is planned that the volumes will be published frequently. The *American Hospital Formulary Service* (AHFS), published by the American Society of Hospital Pharmacists, is a collection of monographs that are kept current by periodic supplements. The monographs are written on a single drug; there are also general discussions of drugs that are included in a defined class. *AMA Drug Evaluations,* compiled by the American Medical Association Department of Drugs in cooperation with the American Society for Clinical Pharmacology and Therapeutics, includes general information on the use of drugs in special settings (*e.g.,* pediatrics, geriatrics, renal insufficiency, *etc.*) and reflects the consensus of a panel on the effective clinical use of therapeutic agents. *Facts and Comparisons* (Olin, 1988), published by a division of J. B. Lippincott Company, is also organized by pharmacological classes and is updated monthly. Information in monographs is presented in a standard format and incorporates FDA-approved information, which is supplemented with current data obtained from the biomedical literature. A useful feature is the comprehensive list of preparations with a "Cost Index," an index of the average wholesale price for equivalent quantities of similar or identical drugs.

Industry promotion, in the form of direct-mail brochures, journal advertising, displays, professional courtesies, or the detail person or pharmaceutical representative, is intended to be persuasive rather than educational. The pharmaceutical industry cannot, should not, and indeed does not purport to be responsible for the education of physicians in the use of drugs.

Over 1500 medical journals are published regularly in the United States. However, of the two to three dozen medical publications with circulations in excess of 70,000 copies, the great majority are sent to physicians free of charge and paid for by the industry. In addition, special supplements of some peer-reviewed journals are entirely supported by a single drug manufacturer whose product is prominently featured and favorably described. Objective journals, which are not supported by drug manufacturers, include *Clinical Pharmacology and Therapeutics,* which is devoted to original articles that evaluate the actions and effects of drugs in man, and *Drugs,* which publishes timely reviews of individual drugs and drug classes. The *New England Journal of Medicine, Annals of Internal Medicine, Journal of the American Medical Association, Archives of Internal Medicine, British Medical Journal, Lancet,* and *Postgraduate Medicine* offer timely therapeutic reports and reviews. Three publications deserve special emphasis here because they exemplify effective attempts to provide objective drug information in easily assimilable form.

These are *The Medical Letter, Clin-Alert,* and *Rational Drug Therapy. The Medical Letter* provides summaries of scientific reports and consultants' evaluations of the safety, efficacy, and rationale for use of a drug. *Clin-Alert* consists mainly of abstracts from the literature on drugs. *Rational Drug Therapy* presents a monthly review article on groups of drugs or on the management of specific conditions.

The United States Pharmacopeia (USP) and *The National Formulary* (NF) were recognized as "official compendia" by the Federal Food and Drug Act of 1906. The approved therapeutic agents used in medical practice in the United States are described and defined with respect to source, chemistry, physical properties, tests for identity and purity, assay, and storage. The two official compendia are now published in a single volume.

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