determine pharmacokinetics and pharmacodynamics. Nevertheless, it is often the personal interaction of the patient with the physician or other health care provider that first identifies unusual variability in drug actions; maintained alertness to unusual drug responses continues to be a key component of improving drug safety.

Unusual drug responses, segregating in families, have been recognized for decades and initially defined the field of *pharmacogenetics*. Now, with an increasing appreciation of common and rare polymorphisms across the human genome, comes the opportunity to reinterpret descriptive mechanisms of variability in drug action as a consequence of specific DNA variants, or sets of variants, among individuals. This approach defines the field of *pharmacogenomics*, which may hold the opportunity of allowing practitioners to integrate a molecular understanding of the basis of disease with an individual's genomic makeup to prescribe personalized, highly effective, and safe therapies.

IDENTIFYING DRUG TARGETS

Drug therapy is an ancient feature of human culture. The first treatments were plant extracts discovered empirically to be effective for indications like fever, pain, or breathlessness. This symptom-based empiric approach to drug development was supplanted in the twentieth century by identification of compounds targeting more fundamental biologic processes such as bacterial growth or elevated blood pressure; the term "magic bullet," coined by Paul Ehrlich to describe the search for effective compounds for syphilis, captures the essence of the hope that understanding basic biologic processes will lead to highly effective new therapies. An integral step in modern drug development follows identification of a chemical lead with biologic activity with increasingly sophisticated medicinal chemistry-based structural modifications to develop compounds with specificity for the chosen target, lack of "off-target" effects, and pharmacokinetic properties suitable for human use (e.g., consistent bioavailability, long elimination half-life, no high-risk pharmacokinetic features described further below).

A common starting point for contemporary drug development is basic biologic discovery that implicates potential target molecules: examples of such target molecules include HMG-CoA reductase or the *BRAF* V600E mutation in many malignant melanomas. The development of compounds targeting these molecules has not only revolutionized treatment for diseases such as hypercholesterolemia or malignant melanoma, but has also revealed new biologic features of disease. Thus, for example, initial spectacular successes with vemurafenib (which targets *BRAF* V600E) were followed by near-universal tumor relapse, strongly suggesting that inhibition of this pathway alone would be insufficient for tumor control. This reasoning, in turn, supports a view that many complex diseases will not lend themselves to cure by targeting a single magic bullet, but rather single drugs or combinations will need to attack multiple pathways whose perturbation results in disease. The use of combination therapy in settings such as hypertension, tuberculosis, HIV infection, and many cancers highlights potential for such a "systems biology" view of drug therapy.

GLOBAL CONSIDERATIONS

It is true across all cultures and diseases that factors such as compliance, genetic variants affecting pharmacokinetics or pharmacodynamics, and drug interactions contribute to drug responses. In addition, culture- or ancestry-specific factors play a role. For example, the frequency of specific genetic variants modulating drug responses often varies by ancestry, as discussed later. Cost issues or cultural factors may determine the likelihood that specific drugs, drug combinations, or over-the-counter (OTC) remedies are prescribed. The broad principles of clinical pharmacology enunciated here can be used to analyze the mechanisms underlying successful or unsuccessful therapy with any drug.

INDICATIONS FOR DRUG THERAPY: RISK VERSUS BENEFIT

It is self-evident that the benefits of drug therapy should outweigh the risks. Benefits fall into two broad categories: those designed to alleviate a symptom and those designed to prolong useful life. An increasing emphasis on the principles of evidence-based medicine and techniques such as large clinical trials and meta-analyses have defined benefits of drug therapy in broad patient populations. Establishing the balance between risk and benefit is not always simple. An increasing body of evidence supports the idea, with which practitioners are very familiar, that individual patients may display responses that are not expected from large population studies and often have comorbidities that typically exclude them from large clinical trials. In addition, therapies that provide symptomatic benefits but shorten life may be entertained in patients with serious and highly symptomatic diseases such as heart failure or cancer. These considerations illustrate the continuing, highly personal nature of the relationship between the prescriber and the patient.

Adverse Effects Some adverse effects are so common and so readily associated with drug therapy that they are identified very early during clinical use of a drug. By contrast, serious adverse effects may be sufficiently uncommon that they escape detection for many years after a drug begins to be widely used. The issue of how to identify rare but serious adverse effects (that can profoundly affect the benefit-risk perception in an individual patient) has not been satisfactorily resolved. Potential approaches range from an increased understanding of the molecular and genetic basis of variability in drug actions to expanded postmarketing surveillance mechanisms. None of these have been completely effective, so practitioners must be continuously vigilant to the possibility that unusual symptoms may be related to specific drugs, or combinations of drugs, that their patients receive.

Therapeutic Index Beneficial and adverse reactions to drug therapy can be described by a series of dose-response relations (Fig. 5-1). Well-tolerated drugs demonstrate a wide margin, termed the *therapeutic ratio*, *therapeutic index*, or *therapeutic window*, between the doses required to produce a therapeutic effect and those producing toxicity. In cases where there is a similar relationship between plasma drug concentration and effects, monitoring plasma concentrations can be a highly effective aid in managing drug therapy by enabling concentrations to be maintained above the minimum required to produce an effect and below the concentration range likely to produce toxicity. Such monitoring has been widely used to guide therapy with specific agents, such as certain antiarrhythmics, anticonvulsants, and antibiotics. Many of the principles in clinical pharmacology and examples

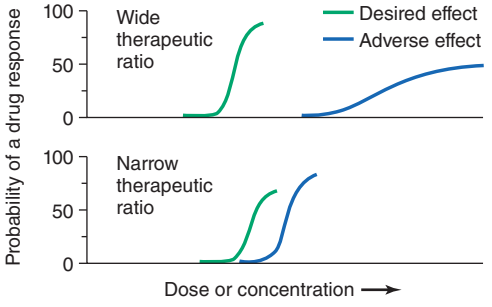

FIGURE 5-1 The concept of a therapeutic ratio. Each panel illustrates the relationship between increasing dose and cumulative probability of a desired or adverse drug effect. ***Top.*** A drug with a wide therapeutic ratio, i.e., a wide separation of the two curves. ***Bottom.*** A drug with a narrow therapeutic ratio; here, the likelihood of adverse effects at therapeutic doses is increased because the curves are not well separated. Further, a steep dose-response curve for adverse effects is especially undesirable, as it implies that even small dosage increments may sharply increase the likelihood of toxicity. When there is a definable relationship between drug concentration (usually measured in plasma) and desirable and adverse effect curves, concentration may be substituted on the abscissa. Note that not all patients necessarily demonstrate a therapeutic response (or adverse effect) at any dose, and that some effects (notably some adverse effects) may occur in a dose-independent fashion.