10 - PART 3 Pharmacology

01 - 71 Principles of Clinical Pharmacology

71 Principles of Clinical Pharmacology

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Principles of Clinical Pharmacology Drugs are the cornerstone of modern therapeutics. Nevertheless, it is well recognized among health care providers and the lay community that the outcome of drug therapy varies widely among individuals. While this variability has been perceived as an unpredictable, and therefore inevi table, accompaniment of drug therapy, this is not the case. Drugs interact with specific target molecules to produce their ben eficial and adverse effects. The chain of events between administration of a drug and production of these effects in the body can be divided into two components, both of which contribute to variability in drug actions. The first component comprises the processes that determine drug delivery to, and removal from, molecular targets. The resulting description of the relationship between drug concentration and time is termed pharmacokinetics. The second component of variability in drug action comprises the processes that determine variability in drug actions independent of variability in drug delivery to effector drug sites. This description of the relationship between drug concentration and effect is termed pharmacodynamics. This chapter describes how these processes can be analyzed for any drug, and presents examples from multiple areas of therapeutics, each of which is covered in more detail in other chapters. Two important goals of clinical pharmacology are (1) to provide a description of conditions under which drug actions vary among human subjects; and (2) to determine mechanisms underlying this variability, with the goal of improving therapy with available drugs as well as pointing to mechanisms whose targeting by new drugs may be effective in the treatment of human disease. The drug development process is briefly described at the end of this chapter. The first steps in the discipline of clinical pharmacology were empirical descriptions of the influence of disease on drug actions and of individuals or families with unusual sensitivities to adverse drug reactions (ADRs). These important descriptive findings are now being replaced by an understanding of the molecular mechanisms underlying variability in drug actions. One useful unifying framework is to consider that the effects of disease, drug coadministration, or familial factors in modulating drug action reflect variability in expression or function of specific genes whose products determine pharmacokinetics and pharmacodynamics. This idea forms the basis for pharmacogenomic science; a few examples are cited in this chapter, and further details are addressed in Chap. 72. ■ ■A SYSTEMS BIOLOGY VIEW The framework that this chapter, and the

field, use to analyze variable drug actions rests on the premise that the processes occurring between administration of a drug and generation of a drug effect are relatively linear. However, as the complexities of how drugs interact with disease mechanisms are becoming increasingly well-defined, it is apparent that this linear framework represents a first approximation of understanding drug effects. Disease processes change over time, and drugs often exert multiple (and occasionally counterregulatory) effects. The development of complex computational models for these processes, and tools such as gene editing and multiple “omic” measurements (transcriptomics, metabolomics, proteomics) to study and refine those models, are now presenting the opportunity of understanding disease mechanisms and their variable responses to drug challenge at a much finer and more pre cise scale. Thus, this systems biology approach may represent the future in clinical pharmacology and new drug development.

Pharmacology PART 3 ■ ■GLOBAL CONSIDERATIONS It is true across all cultures and diseases that factors such as adher ence, genetic variants affecting pharmacokinetics or pharmacodynamics (which themselves vary by ancestry), and drug interactions contribute to drug responses; the term “adherence” is preferred to the older term “compliance” because it removes the idea that the patient is at fault. Cost issues or cultural factors may determine the likelihood that specific drugs, drug combinations, or over-the-counter (OTC) remedies are prescribed. ■ ■INDICATIONS FOR DRUG THERAPY:

RISK VERSUS BENEFIT It is self-evident that the benefits of drug therapy should outweigh the risks. Benefits fall into broad categories: alleviation of symptoms, preven tion of disease progression or complications, and prolonged life. However, establishing the balance between risk and benefit for an individual patient is not always simple. In addition to variability seen even within highly controlled drug trials, patients treated in clinical settings may display responses that were not observed in trials, sometimes due to comorbidi ties that were trial exclusion criteria. 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. 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 ADRs may be suf ficiently uncommon that they escape detection for many years after a drug begins to be widely used. Potential approaches to detect rare ADRs range from an increased understanding of the molecular and genetic basis of variability in drug actions to expanded postmarketing surveillance mechanisms. Therapeutic Index Beneficial and adverse reactions to drug therapy can be described by a series of dose-response relations (Fig. 71-1). Well-tolerated drugs demonstrate a wide margin, termed the therapeu tic ratio, therapeutic index, or therapeutic window, between the doses required to produce a therapeutic effect and those producing toxicity. In cases where there is an established relationship between plasma drug concentration and effects, monitoring plasma concentrations can be a highly effective aid in managing drug therapy by enabling concentra tions to be maintained above the minimum required to produce an effect and below the concentration range likely to produce toxicity.

Desired effect Adverse effect Wide therapeutic ratio Probability of a drug response

Narrow therapeutic ratio

Dose or concentration FIGURE 71-1 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, that is, 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.

PRINCIPLES OF PHARMACOKINETICS The processes of absorption, distribution, metabolism, and excretion— collectively termed drug disposition—determine the concentration of drug delivered to target effector molecules.

■ ■ABSORPTION AND BIOAVAILABILITY When a drug is administered orally, subcutaneously, intramuscularly, rectally, sublingually, or directly into desired sites of action, the amount of drug eventually entering the systemic circulation may be less than with the intravenous route (Fig. 71-2A). The fraction of drug available to the systemic circulation by other routes is termed bioavailability. Bioavail ability may be <100% for two main reasons: (1) incomplete absorption, or (2) metabolism or elimination prior to entering the systemic circulation. Compared to the same dose given intravenously, a nonintravenous dose will have a later and lower peak plasma concentration (Fig. 71-2B). Drug absorption may be reduced because a drug is incompletely released from its dosage form, undergoes destruction at the site of administration, or has physicochemical properties such as poor solu bility that prevent complete absorption from its site of administration. Slow absorption rates are deliberately designed into “slow-release” or “sustained-release” drug formulations in order to minimize variation in plasma concentrations during the interval between doses. PART 3 Pharmacology “First-Pass” Effect When a drug is administered orally, it must traverse the intestinal epithelium, the portal venous system, and the liver prior to entering the systemic circulation (Fig. 71-3). Once a drug enters the enterocyte, it may undergo metabolism, be transported into the portal vein, or be excreted back into the intestinal lumen. Both excretion into the intestinal lumen and metabolism decrease bioavailability. Once a drug passes this enterocyte barrier, it may also be taken up into the hepatocyte, where bioavailability can be further limited by metabolism or excretion into the bile. This elimination in intestine and liver, which reduces the amount of drug delivered to the systemic circulation, is termed presys temic elimination, presystemic extraction, or first-pass elimination. ■ ■DRUG TRANSPORT Drug movement across the membrane of any cell, including entero cytes and hepatocytes, is a combination of passive diffusion and active A Dose Log concentration IV Elimination Time Concentration Oral B Dose Elimination Distribution Time FIGURE 71-2 Idealized time-plasma concentration curves after a single dose of drug. A. The time course of drug concentration after an instantaneous intravenous (IV) bolus or an oral dose in the one-compartment model shown. The area under the time-concentration curve is clearly less with the oral drug than the IV drug, indicating incomplete bioavailability. Note that despite this incomplete bioavailability, concentration after the oral dose can be higher than after the IV dose at some time points. The inset shows that the decline of concentrations over time is linear on a log-linear plot,

characteristic of first-order elimination, and that oral and IV drugs have the same elimination (parallel) time course. B. The decline of central compartment concentration when drug is distributed both to and from a peripheral compartment and eliminated from the central compartment. The rapid initial decline of concentration reflects not drug elimination but distribution.

Systemic circulation (Bile) Biliary canaliculus Portal vein Orally administered drug Lumen P-glycoprotein Drug Other transporter Metabolite FIGURE 71-3 Mechanism of presystemic elimination. After drug enters the enterocyte, it can undergo metabolism, excretion into the intestinal lumen, or transport into the portal vein. Similarly, the hepatocyte may accomplish metabolism and biliary excretion prior to the entry of drug and metabolites to the systemic circulation. (Reproduced with permission from DM Roden, in DP Zipes, J Jalife [eds]: Cardiac Electrophysiology: From Cell to Bedside, 4th ed. Philadelphia, Saunders, 2003.) transport, mediated by specific drug uptake and efflux molecules. One widely studied drug transport molecule is the drug efflux pump P-glycoprotein, the product of the ABCB1 (or MDR1) gene. P-glycoprotein is expressed on the apical aspect of the enterocyte and on the canalicu lar aspect of the hepatocyte (Fig. 71-3). In both locations, it serves as an efflux pump, limiting availability of drug to the systemic circulation. P-glycoprotein–mediated drug efflux from cerebral capillaries limits drug brain penetration and is an important component of the bloodbrain barrier. Other transporters mediate uptake into cells of drugs and endogenous substrates such as vitamins or nutrients. ■ ■DRUG METABOLISM Drug metabolism generates compounds that are usually more polar and, hence, more readily excreted than parent drug. Metabolism takes place predominantly in the liver but can occur at other sites such as kidney, intestinal epithelium, lung, and plasma. Phase I metabolism involves chemical modification, most often oxidation accomplished by members of the cytochrome P450 (CYP) monooxygenase superfamily. CYPs and other molecules that are especially important for drug metabolism are presented in Table 71-1, and each drug may be a sub strate for one or more of these enzymes. Phase II metabolism involves conjugation of specific endogenous compounds to drugs or their metabolites. The enzymes that accomplish phase II reactions include glucuronyl-, acetyl-, sulfo-, and methyltransferases. Drug metabolites may exert important pharmacologic activity, as discussed further below. Therapeutic antibodies are very slowly eliminated (allowing infrequent dosing, e.g., monthly injections), probably by lysosomal uptake and degradation. Clinical Implications of Reduced Bioavailability Some drugs undergo near-complete presystemic metabolism and thus cannot be administered orally. Nitroglycerin cannot be used orally because it is

TABLE 71-1 Molecular Pathways Mediating Drug Disposition ENZYME SUBSTRATESa INHIBITORSa CYP3A Calcium channel blockers Amiodarone Antiarrhythmics (lidocaine, quinidine, mexiletine) Ketoconazole, itraconazole HMG-CoA reductase inhibitors (“statins”; see text) Erythromycin, clarithromycin Cyclosporine, tacrolimus Ritonavir Indinavir, saquinavir, ritonavir Gemfibrozil and other fibrates CYP2D6b Timolol, metoprolol, carvedilol Bupropion Propafenone, flecainide Quinidine (even at

ultra-low doses) Tricyclic antidepressants Tricyclic antidepressants Fluoxetine, paroxetine Fluoxetine, paroxetine CYP2C9b Warfarin Amiodarone Phenytoin Fluconazole Glipizide Phenytoin Losartan CYP2C19b Omeprazole Omeprazole Mephenytoin Ritonavir Clopidogrel Fluoxetine Fluvoxamine CYP2B6b Efavirenz Ticlopidine Thiopurine S-methyltransferaseb 6-Mercaptopurine,

azathioprine N-acetyltransferaseb Isoniazid Procainamide Hydralazine Some sulfonamides UGT1A1b Irinotecan Pseudocholinesteraseb Succinylcholine TRANSPORTER SUBSTRATESa INHIBITORSa P-glycoprotein Digoxin Quinidine HIV protease inhibitors Amiodarone Many CYP3A substrates Verapamil Cyclosporine Itraconazole Erythromycin SLCO1B1b Simvastatin and some other statins aExamples are presented. Inhibitors affect the molecular pathway and thus may decrease substrate metabolism. bClinically important genetic variants described; see Chap. 72. Note: An extensive listing of CYP substrates, inhibitors, and inducers is maintained at https://drug-interactions.medicine.iu.edu/MainTable.aspx. completely extracted prior to reaching the systemic circulation. The drug is, therefore, used by the sublingual, transdermal, or intravascular routes, which bypass presystemic metabolism. Some drugs with very extensive presystemic metabolism can still be administered by the oral route, using much higher doses than those required intravenously. Thus, a typical intravenous dose of verapamil is 1–5 mg, compared to a usual single oral dose of 40–120 mg. Adminis tration of low-dose aspirin can result in exposure of cyclooxygenase in platelets in the portal vein to the drug, but systemic sparing because of first-pass aspirin deacylation in the liver. This is an example of presys temic metabolism being exploited to therapeutic advantage. ■ ■PLASMA HALF-LIFE Most pharmacokinetic processes, such as elimination, are first-order; that is, the rate of the process depends on the amount of drug present.

Elimination can occasionally be zero-order (fixed amount eliminated per unit time), and this can be clinically important (see “Principles of Dose Selection,” later in this chapter). In the simplest pharmacokinetic model (Fig. 71-2A), a drug bolus is administered instantaneously to a central compartment, from which drug elimination occurs as a firstorder process. Half-life is the time required for 50% of a first-order pro cess to be completed. Thus, 50% of drug elimination is achieved after one drug-elimination half-life, 75% after two, 87.5% after three, etc. In practice, first-order processes such as elimination are near-complete after four to five half-lives.

In some cases, drug is removed from the central compartment not only by elimination but also by distribution into peripheral compart ments. In this case, the plot of plasma concentration versus time after a bolus may demonstrate two (or more) exponential components (Fig. 71-2B). In general, the initial rapid drop in drug concentration represents not elimination but drug distribution into and out of periph eral tissues (also first-order processes), while the slower component represents drug elimination; the initial precipitous decline is usually evident with administration by intravenous but not by other routes. Drug concentrations at peripheral sites are determined by a balance between drug distribution to and redistribution from those sites, as well as by elimination. Once distribution is near-complete (four to five distribution half-lives), plasma and tissue concentrations decline in parallel. CHAPTER 71 Principles of Clinical Pharmacology Clinical Implications of Half-Life Measurements The elim ination half-life not only determines the time required for drug con centrations to fall to near-unmeasurable levels after a single bolus, but it is also the sole determinant of the time required for steady-state plasma concentrations to be achieved after any change in drug dos ing (Fig. 71-4). This applies to the initiation of chronic drug therapy (whether by multiple oral doses or by continuous intravenous infu sion), a change in chronic drug dose or dosing interval, or discon tinuation of drug. Steady state describes the situation during chronic drug administra tion when the amount of drug administered per unit time equals drug eliminated per unit time. With a continuous intravenous infusion, plasma concentrations at steady state are stable, while with chronic oral Initiation of therapy Change of chronic therapy Loading dose

- dose = D Dose = 2•D Dose = 2•D Concentration *10th dose Dose = 0.5•D Change dosing Dose = D Discontinue drug Time FIGURE 71-4 Drug accumulation to steady state. In this simulation, drug was administered (arrows) at intervals = 50% of the elimination half-life. Steady state is achieved during initiation of therapy after ~5 elimination half-lives, or 10 doses.

A loading dose did not alter the eventual steady state achieved. A doubling of the dose resulted in a doubling of the steady state but the same time course of accumulation. Once steady state is achieved, a change in dose (increase, decrease, or drug discontinuation) results in a new steady state in ~5 elimination half-lives. (Reproduced with permission from DM Roden, in DP Zipes, J Jalife [eds]: Cardiac Electrophysiology: From Cell to Bedside, 4th ed. Philadelphia, Saunders, 2003.)

drug administration, plasma concentrations vary during the dosing interval, but the time-concentration profile between dosing intervals is stable (Fig. 71-4).

■ ■DRUG DISTRIBUTION In some cases, pharmacologic effects require drug distribution to peripheral sites. In this instance, the time course of drug delivery to and removal from these sites determines the time course of drug effects; anesthetic uptake into the central nervous system (CNS) is an example. Loading Doses For some drugs, the indication may be so urgent that administration of “loading” dosages is required to achieve rapid elevations of drug concentration and therapeutic effects earlier than with chronic maintenance therapy (Fig. 71-4). Nevertheless, the time required for a true steady state to be achieved is still determined only by the elimination half-life. Rate of Intravenous Drug Administration Although the simu lations in Fig. 71-2 use a single intravenous bolus, this is usually inap propriate in practice because side effects related to transiently very high concentrations can result. Rather, drugs are more usually admin istered orally or as a slower intravenous infusion. PART 3 Pharmacology Transiently high drug concentrations after rapid intravenous admin istration can occasionally be used to advantage. The use of midazolam for intravenous sedation, for example, depends upon its rapid uptake by the brain during the distribution phase to produce sedation quickly, with subsequent egress from the brain during the redistribution of the drug as equilibrium is achieved. Similarly, adenosine must be administered as a rapid bolus in the treatment of reentrant supraventricular tachycardias (Chap. 253) to prevent elimination by very rapid (t1/2 of seconds) uptake into erythro cytes and endothelial cells before the drug can reach its clinical site of action, the atrioventricular node. Clinical Implications of Altered Protein Binding Many drugs circulate in the plasma partly bound to plasma proteins. Since only unbound (free) drug can distribute to sites of pharmacologic action, drug response is related to the free rather than the total circulating plasma drug concentration. In chronic kidney or liver disease, protein binding may be decreased and thus drug actions increased. In some situations (myocardial infarction, infection, surgery), acute phase reac tants transiently increase binding of some drugs and thus decrease effi cacy. These changes assume the greatest clinical importance for drugs that are highly protein-bound since even a small change in protein binding can result in large changes in free drug; for example, a decrease in binding from 99 to 98% doubles the free drug concentration from 1 to 2%. For some drugs (e.g., phenytoin), monitoring free rather than total drug concentrations can be useful. ■ ■DRUG ELIMINATION Drug elimination reduces the amount of drug in the body over time by metabolism or excretion. An important approach to quantifying this reduction is to consider that drug concentrations at the beginning and end of a time period are unchanged, and that a specific volume of the body has been “cleared” of

the drug during that time period. This defines clearance as volume/time. Clinical Implications of Altered Clearance Genetic vari ants, drug interactions, or diseases that reduce the activity of drugmetabolizing enzymes or excretory mechanisms lead to decreased clearance and, hence, a requirement for a downward dose adjustment to avoid toxicity. Conversely, some drug interactions and genetic vari ants increase the function of drug elimination pathways, and hence, increased drug dosage is necessary to maintain a therapeutic effect. Metabolites may produce effects similar to, overlapping with, or dis tinct from those of the parent drug. Prodrugs are inactive compounds that require metabolism to gener ate active metabolites that mediate the drug effects. Examples include many angiotensin-converting enzyme (ACE) inhibitors, the angio tensin receptor blocker losartan, the antineoplastic irinotecan, the

antiestrogen tamoxifen, the analgesic codeine (whose active metabolite morphine underlies the opioid effect during codeine administration), and the antiplatelet drug clopidogrel. Drug metabolism has also been implicated in bioactivation of procarcinogens and in the generation of reactive metabolites that mediate certain ADRs. ■ ■THE CONCEPT OF HIGH-RISK PHARMACOKINETICS When plasma concentrations of active drug depend exclusively on a single metabolic pathway, any condition that inhibits that pathway (be it disease related, genetic, or due to a drug interaction) can lead to dra matic changes in drug concentrations and marked variability in drug action. Two scenarios can generate highly variable drug concentrations and effects through such “high-risk pharmacokinetics.” First, variabil ity in bioactivation of a prodrug can lead to striking variability in drug action; examples include decreased CYP2D6 activity, which prevents analgesia by codeine, and decreased CYP2C19 activity, which reduces the antiplatelet effects of clopidogrel. The second scenario is adminis tration of an active drug whose elimination relies on a single pathway. In this case, inhibition of the elimination pathway by genetic variants or by administration of inhibiting drugs leads to marked elevation of drug concentration and, for drugs with a narrow therapeutic window, an increased likelihood of dose-related toxicity. When drugs undergo elimination by multiple-drug metabolizing or excretory pathways, absence of one pathway (due to a genetic variant or drug interaction) is much less likely to have a large impact on drug concentrations or drug actions. ■ ■PRINCIPLES OF PHARMACODYNAMICS Time Course of Drug Action Pharmacokinetic parameters, such as half-life and clearance, explain drug concentrations over time, but understanding the action of a drug over time (pharmacodynamics) often requires an understanding of its precise mechanism of action. Drugs exert therapeutic or adverse effects by interacting with drug target molecules, often in specific tissues, and with a cascade of downstream consequences. For drugs used in urgent treatment (e.g., vascular thrombosis, shock, status epilepticus), little or no delay is anticipated (or desired) between the administration of the drug, the drug-target interaction, and the development of a clinical effect. For many conditions, the indication for therapy is less urgent, and a delay in the onset of action clinically acceptable. Delay can be due to pharmacokinetic mechanisms such as slow elimination (resulting in slow accumulation to steady state), slow uptake into the target tissue, or slow accumulation of active metabolites. In addition, effects such as platelet inhibition, relief of depression, or control of hypertension may be delayed because the drug’s interaction with its receptor is only the first step in mediating clinical drug actions. Thus, for example, the elimination half-life of clopidogrel in plasma in most subjects is ~6 h, but the antiplatelet effect (which is due to irreversible binding to P2Y12 receptors) persists for the life of the platelet, 7–10 days. Drug Effects May Be Disease Specific A drug may produce no action or a different spectrum of actions in unaffected individuals compared to patients with underlying disease. Further, concomitant disease can complicate

interpretation of response to drug therapy, espe cially ADRs. For example, increasing dyspnea in a patient with chronic lung disease receiving amiodarone therapy could be due to the drug, underlying disease, or an intercurrent cardiopulmonary problem. As a result, alternate antiarrhythmic therapies may be preferable in patients with chronic lung disease. While drugs interact with specific molecular receptors, drug effects may vary over time, even if stable drug and metabolite concentrations are maintained. The drug-receptor interaction occurs in a complex biologic milieu that can vary to modulate the drug effect. For example, ion channel blockade by drugs, an important anticonvulsant and anti arrhythmic effect, is often modulated by membrane potential, itself a function of factors such as extracellular potassium or local ischemia. Receptors may be up- or downregulated by disease or by the drug itself. For example, β-adrenergic blockers upregulate β-receptor density

during chronic therapy. While this effect does not usually result in resistance to the therapeutic effect of the drugs, it may produce severe agonist-mediated effects (e.g., hypertension or tachycardia) if the blocking drug is abruptly withdrawn. As molecular mechanisms of disease become better defined, drugs targeting those mechanisms have been introduced into practice. Anti neoplastic agents targeting mutant kinases overexpressed in cancers and HMG-CoA reductase inhibitors (statins) and PCSK9 inhibitors for hypercholesterolemia are examples. ■ ■PRINCIPLES OF DOSE SELECTION The desired goal of therapy with any drug is to maximize the likelihood of a beneficial effect while minimizing the risk of ADRs. Previous expe rience with the drug, in controlled clinical trials or in postmarketing use, defines the relationships between dose or plasma concentration and these dual effects (Fig. 71-1) and has important implications for initiation of drug therapy:

1. The target drug effect should be defined when drug treatment is started. With some drugs, the desired effect may be difficult to mea sure objectively, or the onset of efficacy can be delayed for weeks or months; drugs used in the treatment of cancer and psychiatric disease are examples. Sometimes a drug is used to treat a symptom, such as pain or palpitations, and here it is the patient who will report whether the selected dose is effective. In yet other settings, such as anticoagulation or hypertension, the desired response can be repeat edly and objectively assessed by simple clinical or laboratory tests.
2. The nature of anticipated toxicity often dictates the starting dose. If side effects are minor, it may be acceptable to start chronic therapy at a dose highly likely to achieve efficacy and down-titrate if side effects occur. However, this approach is rarely, if ever, justified if the anticipated toxicity is serious or life-threatening; in this cir cumstance, it is more appropriate to initiate therapy with the lowest dose that may produce a desired effect. In cancer chemotherapy, it is common practice to use maximally tolerated doses.
3. The above considerations do not apply if these relationships between dose and effects cannot be defined. This is especially relevant to some ADRs (dis cussed further below) whose develop ment is not readily related to drug dose.
4. If a drug dose does not achieve its desired

effect, a dosage increase is justified only if toxicity is absent and the likelihood of seri ous toxicity is small.

Failure of Efficacy Even assuming the diagnosis is correct and the correct drug and dose are prescribed, drugs may fail to be effective. A complete therapeutic response is often absent with antihypertensive or antidepressant drugs, and a major challenge in contemporary therapeutics is to identify patient-specific predictors of response to individual drugs. Other explanations for failure of efficacy include drug interactions, decreased adherence, or unexpectedly low drug concentration due to administration of expired or degraded drug. These are situa tions in which measurement of plasma drug concentrations, if available, can be especially useful. Adherence is an especially frequent problem in the chronic treatment of diseases such as hypertension or HIV infection. Multi drug regimens with multiple doses per day are especially prone to decreased adherence.

Brain

Concentration

Monitoring response to therapy, by physiologic measures or by plasma concen tration measurements, requires an under standing of the relationships between plasma concentration and anticipated effects. For FIGURE 71-5 Drug concentrations in specific tissues may not always parallel those in plasma. For example, the efflux pump P-glycoprotein excludes drugs from the endothelium of capillaries in the brain and so constitutes a key element of the blood-brain barrier. Reduced P-glycoprotein function (e.g., due to drug interactions) can thus increase penetration of substrate drugs into the brain, even when plasma concentrations are unchanged.

example, measurement of QT interval is used during treatment with sotalol or dofetilide to avoid marked QT prolongation that can herald serious arrhythmias. In this setting, evaluating the electrocardiogram at the time of anticipated peak plasma concentration and effect (e.g., 1–2 h postdose at steady state) is most appropriate. Maintained high vancomycin levels carry a risk of nephrotoxicity, so dosages should be adjusted on the basis of plasma concentrations measured at trough (predose). Similarly, for dose adjustment of other drugs (e.g., anticon vulsants), concentration should be measured at its lowest during the dosing interval, just prior to a dose at steady state (Fig. 71-4), to ensure a maintained therapeutic effect.

Concentration of Drugs in Plasma as a Guide to Therapy

Therapeutic drug monitoring can be useful (Fig. 71-1) with certain types of drugs including many anticonvulsants, antirejection agents, antiarrhythmics, and antibiotics. By contrast, if no such relationship can be established (e.g., if drug access to important sites of action out side plasma is highly variable), monitoring plasma concentration may not provide an accurate guide to therapy (Fig. 71-5). CHAPTER 71 The common situation of first-order elimination implies that aver age, maximum, and minimum steady-state concentrations are related linearly to the dosing rate. Accordingly, the maintenance dose may be adjusted on the basis of the ratio between the desired and measured concentrations at steady state; for example, if a doubling of the steadystate plasma concentration is desired, the dose should be doubled. This does not apply to drugs eliminated by zero-order kinetics (fixed amount per unit time), where small dosage increases will produce disproportionate increases in plasma concentration; examples include aspirin and fluoxetine. Principles of Clinical Pharmacology If an increase in dosage is needed, this is usually best achieved by increasing the drug dose and leaving the dosing interval constant (e.g., by giving 200 mg every

8 h instead of 100 mg every 8 h); occasionally the dosing interval is shortened to avoid high peak concentrations rec ognizing that adherence is decreased with regimens requiring frequent dosing. Normal P-glycoprotein function Plasma Time Decreased P-glycoprotein function Plasma Brain Time

EFFECTS OF DISEASE ON DRUG CONCENTRATION AND RESPONSE

■ ■RENAL DISEASE If a drug or its metabolites are primarily excreted through the kidneys and increased drug levels are associated with ADRs (an example of “high-risk pharmacokinetics” described above), drug dosages must be reduced in patients with renal dysfunction to avoid toxicity. Digoxin is one example; another is the antiarrhythmics dofetilide and sotalol, which undergo predominant renal excretion and carry a risk of QT prolongation and arrhythmias if doses are not reduced in renal disease. At approved doses, the anticoagulant edoxaban appears to be somewhat more effective in subjects with mild renal dysfunction, possibly reflecting higher drug levels. The narcotic analgesic meperidine undergoes extensive hepatic metabolism, so that renal failure has little effect on its plasma concentra tion. However, its metabolite, normeperidine, does undergo renal excre tion, accumulates in renal failure, and probably accounts for the signs of CNS excitation, such as irritability, twitching, and seizures, that appear when multiple doses of meperidine are administered to patients with renal disease. Protein binding of some drugs (e.g., phenytoin) may be altered in uremia, so measuring free drug concentration may be desirable. PART 3 Pharmacology In practice, most decisions involving dosing adjustment in patients with renal failure use published recommended adjustments in dosage or dosing interval based on the severity of renal dysfunction indi cated by creatinine clearance. Any such modification of dose is a first approximation and should be followed by plasma concentration data (if available) and clinical observation to further optimize therapy for the individual patient. ■ ■LIVER DISEASE Standard tests of liver function are not useful in adjusting doses in diseases like hepatitis or cirrhosis. First-pass metabolism may decrease, leading to increased oral bioavailability as a consequence of disrupted hepatocyte function, altered liver architecture, and portacaval shunts. The oral bioavailability for high first-pass drugs such as morphine, meperidine, midazolam, and nifedipine is almost doubled in patients with cirrhosis, compared to those with normal liver function. Therefore, the size of the oral dose of such drugs should be reduced in this setting. ■ ■HEART FAILURE AND SHOCK Under conditions of decreased tissue perfusion, the cardiac output is redistributed to preserve blood flow to the heart and brain at the expense of other tissues (Chap. 264). As a result, drugs may be distrib uted into a smaller volume of distribution, higher drug concentrations will be present in the plasma, and the tissues that are best perfused (the brain and heart) will be exposed to these higher concentrations, resulting in increased CNS or cardiac effects. In addition, decreased perfusion of the kidney and liver may impair drug clearance. Another consequence of severe heart failure is decreased gut perfusion, which may reduce drug absorption and thus lead to reduced or absent effects of orally administered therapies. ■ ■DRUG USE IN THE ELDERLY In the elderly, multiple pathologies and medications used to treat them result in more drug interactions and ADRs. Aging also results in changes in organ function, especially of the organs involved in drug disposition. Initial doses should be less than the usual adult dosage and should be increased slowly. The number of medications, and doses per day, should be kept as low as possible. ADRs are especially common in the elderly because of altered phar macokinetics and pharmacodynamics, the frequent use of multidrug regimens, and concomitant disease. For example, use of long half-life benzodiazepines is linked to the occurrence of hip fractures in elderly patients, likely reflecting both a risk of falls from these drugs (due to increased sedation) and the increased incidence of

osteoporosis in elderly patients. ■ ■DRUG USE IN CHILDREN Drug metabolism and drug response pathways mature at different rates after birth, and the relative size of various body compartments and

function of various organs change during development. However, there are few studies providing solid evidence to guide pediatric dosing, so in practice, doses are adjusted for size (weight or body surface area) as a first approximation unless age-specific data are available. INTERACTIONS BETWEEN DRUGS Drug interactions can complicate therapy by increasing or decreasing the action of a drug; interactions may be based on changes in drug disposition or in drug response in the absence of changes in drug levels (Table 71-2). Interactions must be considered in the differential diag nosis of any unusual response occurring during drug therapy. Prescrib ers should recognize that patients often come to them with a legacy of drugs acquired during previous medical experiences, often with multiple physicians who may not be aware of all the patient's medica tions. A meticulous drug history should list all medications, including agents not often volunteered during questioning, such as OTC drugs, health food supplements, and topical agents such as eye drops. Lists of interactions are available from a number of electronic sources. While it is unrealistic to expect the practicing physician to memorize these, certain drugs consistently run the risk of generating interactions, often by inhibiting or inducing specific drug elimination pathways; these include CYP2D6, CYP3A, and P-glycoprotein inhibitors (Table 71-1) and CYP3A/P-glycoprotein inducers (Table 71-2). Accordingly, when these drugs are started or stopped, prescribers must be especially alert to the possibility of interactions. ADVERSE DRUG REACTIONS The morbidity and mortality from ADRs may present diagnostic problems because they can involve every organ and system of the body and may be mistaken for signs of underlying disease. In addition, drug therapy for chronic conditions such as psychiatric disease or hyperten sion does not achieve the desired goal in up to half of treated patients; thus, the most common "adverse" drug effect may be failure of efficacy. ADRs can be classified in two broad groups. Type A reactions result from exaggeration of an intended pharmacologic action of the drug, such as increased bleeding with anticoagulants or bone mar row suppression with some antineoplastics, and these tend to be dose-dependent. Type B reactions result from toxic effects unrelated to the intended pharmacologic actions. The latter effects are often unanticipated (especially with new drugs) and frequently severe and may result from recognized (often immunologic) as well as previously undescribed mechanisms. Type B reactions may occur at low dosages and are often termed dose-independent. Prior to regulatory approval and marketing, new drugs are tested in relatively few patients who tend to be less sick and to have fewer concomitant diseases than those patients who subsequently receive the drug therapeutically. Because of the relatively small number of patients studied in clinical trials and the selected nature of these patients, rare serious ADRs are generally not detected prior to a drug's approval; indeed, if they are detected, the new drugs are gen erally not approved. Therefore, physicians need to be cautious in the prescription of new drugs and alert for the appearance of previously unrecognized ADRs. Elucidating mechanisms underlying ADRs can assist development of safer compounds or allow a patient subset at especially high risk to be excluded from drug exposure. National adverse reaction reporting systems, such as those operated by the Food and Drug Administra tion (suspected ADRs can be reported online at https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reportingprogram) and the Committee on Safety of Medicines in Great Britain, can prove useful. Occasionally, "adverse" effects may be exploited to develop an entirely new indication for a drug. Unwanted hair growth during min oxidil treatment of severely hypertensive patients led to development of the drug for hair growth.

Sildenafil was initially developed as an antianginal, but its effects to alleviate erectile dysfunction not only led to a new drug indication but also to increased understanding of the role of type 5 phosphodiesterase in erectile tissue.

TABLE 71-2 Drug Interactions MECHANISM EXAMPLE Pharmacokinetic Interactions Causing Decreased Drug Effect Decreased absorption due to drug binding in the gut Antacids or bile acid sequestrants decrease the absorption of many drugs: Antacids/tetracyclines Cholestyramine/digoxin Decreased solubility due to altered gastric pH H2 receptor blockers or proton pump inhibitors decrease solubility and absorption of weak bases: Omeprazole/ketoconazole Induction of drug metabolism and/ or drug transport: Rifampin Carbamazepine Phenytoin St. John's wort Glutethimide (also smoking, exposure to Decreased concentrations and effects of: Warfarin Quinidine Cyclosporine Losartan Oral contraceptives Methadone Dabigatran chlorinated insecticides, and chronic alcohol ingestion) Decreased prodrug bioactivation Proton pump inhibitors may prevent clopidogrel bioactivation CYP2D6 inhibitors (fluoxetine, paroxetine, quinidine, and others) may prevent codeine bioactivation Reduced delivery of drug to active sites of action Tricyclics prevent clonidine uptake into adrenergic neurons, preventing antihypertensive effects Pharmacokinetic Interactions Causing Increased Drug Effect Inhibited drug metabolism Cimetidine (inhibits many CYPs): Warfarin Theophylline Phenytoin CYP2D6 inhibitorsa/β blockers CYP3A inhibitorsa: HMG-CoA reductase inhibitors Colchicine (toxicity risk) Decreased cyclosporine dose requirement Inhibited drug transport Amiodarone (inhibits many CYPs and P-glycoprotein): Warfarin Digoxin Dabigatran Inhibition of drug metabolism causing accumulation of toxic metabolites Allopurinol (xanthine oxidase inhibitor) inhibits an alternate pathway for azathioprine and 6-mercaptopurine elimination, increasing risk for toxicity Decreased elimination due to altered renal function Inhibitors of renal tubular transport (phenylbutazone, probenecid, salicylates) increase methotrexate toxicity Pharmacodynamic Drug Interactions Combined effects on the same biologic process Excess bleeding with combinations of antiplatelet drugs, anticoagulants, and NSAIDs Long QT–related arrhythmias with QT-prolonging antiarrhythmics plus diuretics Hyperkalemia with ACE inhibitors plus potassium Hypotension with nitrates plus sildenafil Antagonistic effects on the same biologic process Loss of antihypertensive drug effects with NSAIDs aSee Table 71-1. Abbreviations: ACE, angiotensin-converting enzyme; CYP, cytochrome P; NSAID, nonsteroidal anti-inflammatory drug.

■ ■SCOPE OF THE ADVERSE DRUG REACTION PROBLEM One estimate in the United Kingdom was that 6.5% of all hospital admissions are due to ADRs and that 2.3% of these patients (0.15%) died as a result. The most common culprit drugs were aspirin, non steroidal anti-inflammatory drugs, diuretics, warfarin, ACE inhibitors, antidepressants, opiates, digoxin, steroids, and clopidogrel. One study in the late 1990s suggested that ADRs were responsible for >100,000 in-hospital deaths in the United States, making them the fourth to sixth most common cause of in-hospital death. Another study 10 years later showed no change in this trend.

Serious ADRs are also well recognized with "herbal" remedies and OTC compounds; examples include kava-associated hepatotoxicity, L-tryptophan-associated eosinophilia-myalgia, and phenylpropanol amine-associated stroke, each of which has caused fatalities. ■ ■TOXICITY UNRELATED TO A DRUG'S PRIMARY PHARMACOLOGIC ACTIVITY Drugs or, more commonly, reactive metabolites generated by CYPs can covalently bind to tissue macromolecules (e.g., proteins or DNA) to cause tissue toxicity. Because of the reactive nature of these metabolites, covalent binding

often occurs close to the site of production, typically the liver. CHAPTER 71 Principles of Clinical Pharmacology Acetaminophen A common cause of drug-induced hepatotoxicity is acetaminophen overdosage (Chap. 351). Normally, reactive metabo lites are detoxified by combining with hepatic glutathione. When glutathione becomes depleted, the metabolites bind instead to hepatic protein, with resultant hepatocyte damage. The hepatic necrosis pro duced by the ingestion of acetaminophen can be prevented or attenu ated by the administration of substances such as N-acetylcysteine that reduce the binding of electrophilic metabolites to hepatic proteins. The risk of acetaminophen-related hepatic necrosis is increased in patients receiving drugs such as phenobarbital or phenytoin, which increase the rate of drug metabolism, or ethanol, which exhausts glutathione stores. Immunologic Reactions Generation of an immune response to a drug often requires in vivo activation and covalent linkage to protein, carbohydrate, or nucleic acid. Drug stimulation of antibody produc tion may mediate tissue injury by several mechanisms. The antibody may attack the drug when the drug is covalently attached to a cell and thereby destroy the cell. This occurs in penicillin-induced hemolytic anemia. Antibody-drug-antigen complexes may be passively adsorbed by a bystander cell, which is then destroyed by activation of comple ment; this occurs in quinine- and quinidine-induced thrombocyto penia. Heparin-induced thrombocytopenia arises when antibodies against complexes of platelet factor 4 peptide and heparin generate immune complexes that activate platelets; thus, the thrombocytopenia is accompanied by “paradoxical” thrombosis and is treated with throm bin inhibitors. Drugs or their reactive metabolites may alter a host tissue, rendering it antigenic and eliciting autoantibodies; hydralazine- or procainamide-induced lupus erythematosus is an example. Druginduced pure red cell aplasia (Chap. 107) is due to an immune-based drug reaction. Serum sickness (Chap. 363) results from the deposition of circulating drug-antibody complexes on endothelial surfaces. Many drugs, particularly antimicrobial agents, ACE inhibitors, and aspirin, can elicit anaphylaxis with production of IgE, which binds to mast cell membranes. Contact with a drug antigen initiates a series of biochemi cal events in the mast cell and results in the release of mediators that can produce the characteristic urticaria, wheezing, flushing, rhinor rhea, and (occasionally) hypotension. Drugs may also elicit cell-mediated immune responses. One seri ous reaction is Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), which can result in death due to T-cell-mediated massive skin sloughing. Another probable immune-mediated drug reaction is the DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome, a rare ADR with a chronic relapsing course, often triggered by antiseizure medications and possibly arising from herpes virus reactivation. As described in Chap. 72, specific genetic variants appear necessary but not sufficient to elicit SJS/TEN or DRESS.

While the use of antibodies targeting immune checkpoints is dra matically improving prognosis in many cancers, these agents have also been associated with the unpredictable development of many appar ently immune-related ADRs. Some, like colitis or thyroiditis, may be self-limited or medically manageable, while others, notably myocardi tis, are rarer but can be rapidly fatal.

■ ■DIAGNOSIS AND TREATMENT OF

ADVERSE DRUG REACTIONS A suspected ADR developing after introduction of a new drug natu rally implicates that drug. It is also important to remember that a drug interaction may be responsible. Thus, for example, a patient on a chronic stable warfarin dose may develop a bleeding complication after introduction of amiodarone; this does not reflect a direct reaction to amiodarone

but rather its effect to inhibit warfarin metabolism. Adverse effects such as hypoglycemia with insulin or bleeding with anticoagulants are more readily related to a specific drug than are nonspecific symptoms such as rash; drug fever often escapes initial diagnosis because fever is such a common manifestation of disease. PART 3 Pharmacology Electronic listings of ADRs can be useful. However, exhaustive com pilations often provide little sense of perspective in terms of frequency and seriousness, which can vary considerably among patients. Abnormalities such as G6PD deficiency, serum pseudocholinester ase level, or genotyping may be useful in diagnosis (Chap. 72). Once an ADR is suspected, discontinuation of the suspected drug followed by disappearance of the reaction is presumptive evidence of a drug-induced illness. Confirming evidence may be sought by cau tiously reintroducing the drug and seeing if the reaction reappears. However, rechallenge should be done only if the suspected culprit drug is critical to the patient's care. When the reaction is thought to be immunologic, challenge is generally avoided. Testing for genetic abnormalities (e.g., G6PD deficiency, low serum pseudocholinesterase level, or genotyping; Chap. 72) may be useful in diagnosis. Serious immunologically mediated ADRs have been treated with high-dose steroids; other agents such as rituximab, infliximab, abata cept, or mycophenolate mofetil, as well as plasmapheresis, have been used with variable success. If the patient is receiving many drugs when an ADR is suspected, the drugs likeliest to be responsible can usually be identified; this should include both potential culprit agents as well as drugs that alter their elimination. All drugs may be discontinued at once or, if this is not practical, discontinued one at a time, starting with the ones most suspect, and the patient observed for signs of improvement. The time needed for a concentration-dependent ADR to disappear depends on the time required for the concentration to fall below the range associ ated with the ADR; that, in turn, depends on the initial blood level and on the rate of elimination or metabolism of the drug. Adverse effects of drugs with long half-lives or those not directly related to serum con centration may take a considerable time to disappear. THE DRUG DEVELOPMENT PROCESS Drug therapy is an ancient feature of human culture. The first treat ments 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. A common starting point for the development of many widely used modern therapies has been basic biologic discovery that impli cates potential target molecules: examples of such target molecules include HMG-CoA reductase, a key step in cholesterol biosynthesis, or the BRAF V600E mutation that appears to drive the development of some malignant melanomas and other tumors. The development of compounds targeting these molecules has not only revolutionized treatment for diseases such as hypercholesterolemia or malignant

melanoma but 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 that attack mul tiple pathways whose perturbation results in disease. The use of com bination therapy in settings such as hypertension, tuberculosis, HIV infection, and many cancers highlights the

potential for the “systems biology” view of drug therapy outlined above. A common approach in contemporary drug development is to start with a high-throughput screening procedure to identify “lead” chemical(s) modulating the activity of a potential drug target. The next step is application of increasingly sophisticated medicinal chemistrybased modification of the “lead” 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, and no high-risk pharmacokinetic features). Drug evaluation in human subjects then proceeds from initial safety and tolerance (phase 1) to dose finding (phase 2) and then to large efficacy trials (phase 3). This is a very expensive process, and the vast majority of lead compounds fail at some point. Thus, new approaches to iden tify likely successes and failures early are needed. One idea, described further in Chap. 72, is to use genomic and other high-throughput profiling approaches in drug development. This can identify new drug targets and define disease subsets for which drugs approved for other indications might be “repurposed,” thereby avoiding the costly development process. In addition, drugs whose development includes supporting human genetic data have a decreased chance of failing in the drug development process. SUMMARY Modern clinical pharmacology aims to replace empiricism in the use of drugs with therapy based on in-depth understanding of factors that determine an individual’s response to drug treatment. Molecular phar macology, pharmacokinetics, genetics, clinical trials, and the educated prescriber all contribute to this process. No drug response should ever be termed idiosyncratic; all responses have a mechanism whose under standing will help guide further therapy with that drug. This rapidly expanding understanding of variability in drug actions makes the process of prescribing drugs increasingly daunting for the practitioner. However, fundamental principles should guide this process: • The benefits of drug therapy, however defined, should outweigh the risk. • The smallest dosage necessary to produce the desired effect should be used. • The number of medications and doses per day should be minimized. • Although the literature is rapidly expanding, accessing it is becom ing easier; electronic tools to search databases of literature and unbi ased opinion will become increasingly commonplace. • Genetics play a role in determining variability in drug response and is becoming a part of clinical practice (Chap. 72). • Electronic health records and pharmacy systems will increasingly incorporate prescribing advice, such as indicated medications not used; unindicated medications being prescribed; and potential dosing errors, drug interactions, or genetically determined drug responses. • Prescribers should be particularly wary when adding or stopping specific drugs that are especially liable to provoke interactions and adverse drug reactions. • Prescribers should use only a limited number of drugs, with which they are thoroughly familiar. ■ ■FURTHER READING Chothe PP et al: Drug transporters in drug disposition: The year 2022 in review. Drug Metab Rev 55:343, 2023. Holford N: Pharmacodynamic principles and the time course of immediate drug effects. Transl Clin Pharmacol 25:157, 2017.

02 - 72 Pharmacogenomics

72 Pharmacogenomics

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Pharmacogenomics The previous chapter discussed mechanisms underlying variability in drug action, highlighting pharmacokinetic and pharmacodynamic pathways to beneficial and adverse drug events. Work in the past sev eral decades has defined how genetic variation can play a prominent role in modulating these pathways. Initial studies described unusual drug responses due to single genetic variants in individual subjects, defining the field of pharmacogenetics. A more recent view extends this idea to multiple genetic variants across populations, and the term “pharmacogenomics” is often used. Understanding the role of genetic variation in drug response could improve the use of current drugs, avoid drug use in those at increased risk for adverse drug reactions (ADRs), guide development of new drugs, and even be used as a lens through which to understand mechanisms of diseases themselves. This chapter will outline the principles of pharmacogenomics, cur rently available evidence that genetic factors play a role in variable drug actions, and areas of controversy and ongoing work. The chapter tables are available online. They can be viewed by opening the table of contents of Harrison’s 22nd edition at accessmedicine.com/harrisons. ■ ■PRINCIPLES OF GENETIC VARIATION AND DRUG RESPONSE (SEE ALSO CHAPS. 479 AND 480) A goal of traditional Mendelian genetics is to identify DNA variants associated with a distinct phenotype in multiple related family mem bers (Chap. 480). However, it is unusual for a drug response phenotype to be accurately measured in more than one family member, let alone across a kindred. Some clinical studies have examined drug disposition traits (such as urinary drug excretion after a fixed test dose) in twins and have, in some instances, shown greater concordance in mono zygotic compared to dizygotic pairs, supporting a genetic contribu tion to the trait under study. However, in general, non–family-based approaches are usually used to identify and validate DNA variants con tributing to variable drug actions. Both candidate gene and genomewide studies have been used, and as with any genomic study, results require replication before they should be accepted as valid. Types of Genetic Variants Influencing Drug Response (Table e72-1) The most common type of genetic variant is a single nucleotide polymorphism (SNP), and nonsynonymous SNPs (i.e., those that alter primary amino acid sequence encoded by a gene) are a common cause of variant function in genes regulating drug responses, often termed pharmacogenes. Small insertions and deletions can similarly alter protein function or lead to functionally important splice variation. Examples of synonymous coding region variants

altering pharmacogene function have also been described; postulated mechanisms include an altered rate of RNA translation and thus altered folding of the nascent protein, or altered splicing. Variation in phar macogene promoters or in copy number (gene deletion or multiple functional copies of the same gene) is also well described.

Table e72-1 lists examples of individual types of genomic variation and the impact they can have on function of pharmacogenes. Multiple genotyping approaches may be needed to detect important variants; for example, SNP assays may fail to detect large gene duplications, and highly polymorphic regions (such as the major histocompatibility locus on chromosome 6 that includes multiple genes of the human leukocyte antigen [HLA] family) are best evaluated by sequencing.

Table e72-1 also highlights the fact that the frequency of important variation across pharmacogenes can vary strikingly by ancestry, with the result that certain ethnic groups may be at unusually high risk of displaying variant response to specific drugs. Candidate Gene Approaches Most studies to date have used an understanding of the molecular mechanisms modulating drug action to identify candidate genes in which variants could explain variable drug responses. One very common scenario is that variable drug actions can be attributed to variability in plasma drug concentrations. When plasma drug concentrations vary widely (e.g., more than an order of magnitude), especially if their distribution is non-unimodal as in Fig. 72-1, variants in single genes controlling drug concentra tions often contribute. In this case, the most obvious candidate genes are those responsible for drug metabolism and elimination. Other candidate genes are those encoding the target molecules with which drugs interact to produce their effects or molecules modulating that response, including those involved in disease pathogenesis. CHAPTER 72 Pharmacogenomics Genome-Wide Association Studies The field has also had some success with “unbiased” approaches such as genome-wide association (GWA) (Chap. 479), particularly in identifying single variants associ ated with high risk for certain forms of drug toxicity, and in validating the results of candidate gene studies. GWA studies have identified variants in the HLA locus that are associated with high risk for severe skin rashes during treatment with the anticonvulsant carbamazepine and hepatotoxicity with flucloxacillin, an antibiotic never marketed in the United States. A GWA study of simvastatin-associated myopathy identified a single noncoding SNP in SLCO1B1, encoding OATP1B1, a drug transporter known to modulate simvastatin uptake into the liver, which accounts for 60% of myopathy risk. African-American subjects are known to have higher dose requirements to achieve stable anticoagulation with warfarin, due in part to variations in CYP2C9 and VKORC1, discussed below; in GWA studies, variants in these two genes account for up to 50% of variable warfarin effects. ■ ■GENETIC VARIANTS AFFECTING PHARMACOKINETICS Clinically important genetic variants have been described in mul tiple molecular pathways of drug disposition (Table e72-2). A distinct multimodal distribution of drug disposition (as shown in Fig. 72-1) argues for a predominant effect of variants in a single gene in the metabolism of that substrate. Individuals with two alleles (variants) encoding for nonfunctional protein make up one group, often termed poor metabolizers (PM phenotype). For most genes, many variants can produce such a loss of function, and assessing whether they are on the same or different alleles (i.e., the diplotype) can complicate the use of genotyping in clinical practice. Furthermore, some variants produce only partial loss of function, and the presence of more than one variant may be required to define a specific allele. Individuals with one functional allele, or multiple reduction of function alleles, make up a second group (intermediate metabolizers) and may or may not be distinguishable from those with two functional alleles (normal metabolizers,

sometimes termed extensive metabolizers, EMs). Ultrarapid metabolizers (UMs) with especially high enzymatic activity (usually attributed to specific SNPs or to gene duplication; Table e72-1 and Fig. 72-1) have also been described for some traits. Many drugs in widespread use can inhibit specific drug disposition pathways (see Chap. 71, Table 71-1), and so EM individuals receiving such inhibi tors can respond like PM patients (phenocopying). Polymorphisms in genes encoding drug uptake or drug efflux transporters may be other contributors to variability in drug delivery to target sites and, hence, in

Enzymatic activity Greater Lesser Extensive metabolizers (EMs) Population frequency Poor metabolizers (PMs) 2 mutant alleles 1–2 wild-type alleles Duplication: >2 wild-type alleles A Single dose Chronic therapy PART 3 Pharmacology Concentration PM EM UM B FIGURE 72-1 A. Distribution of CYP2D6 metabolic activity across a population. The heavy arrow indicates an antimode, separating poor metabolizer subjects (PMs, black), with two loss-of-function CYP2D6 alleles (black), indicated by the intron-exon structures below the chart. Individuals with one or two functional alleles are grouped together as extensive metabolizers (EMs, blue). Also shown are ultra-rapid metabolizers (UMs, red), with 2–12 functional copies of the gene, displaying the greatest enzyme activity. (Adapted from M-L Dahl et al: J Pharmacol Exp Ther 274:516, 1995.) B. These simulations show the predicted effects of CYP2D6 genotype on disposition of a substrate drug. With a single dose (left), there is an inverse “gene-dose” relationship between the number of active alleles and the areas under the time-concentration curves (smallest in UM subjects; highest in PM subjects); this indicates that clearance is greatest in UM subjects. In addition, elimination half-life is longest in PM subjects. The right panel shows that these single-dose differences are exaggerated during chronic therapy: steady-state concentration is much higher in PM subjects (decreased clearance), as is the time required to achieve steady state (longer elimination half-life). drug effects. Examples of common pharmacogene polymorphisms are described here. CYP3A Members of the CYP3A family (CYP3A4, CYP3A5) metab olize the greatest number of drugs in therapeutic use. CYP3A4 activity is highly variable (up to an order of magnitude) among individuals, but nonsynonymous coding region polymorphisms (those that change the encoded amino acid) are unusual. Thus, the underlying mechanism likely reflects genetic variation in regulatory regions. Most subjects of European or Asian origin carry a polymorphism that disrupts splicing in the closely related CYP3A5 gene. As a result, these individuals display less CYP3A5 activity compared to subjects of African origin in whom splicing is not disrupted. Decreased efficacy of the antirejection agent tacrolimus in subjects of African origin has been attributed to more rapid CYP3A5-mediated elimination, and a lower risk of vincristine-associated neuropathy has been reported in CYP3A5 “expressers.” CYP2D6 CYP2D6 is second to CYP3A4 in the number of com monly used drugs that it metabolizes. CYP2D6 activity is polymor phically distributed, and 5–10% of European- and African-derived populations (but few Asians) display the PM phenotype (Fig. 72-1). Dozens of loss-of-function variants in CYP2D6 have been described; the PM phenotype arises in individuals with two such alleles. In addition, UMs with multiple functional copies of CYP2D6 have been identified especially in East Africa, the Middle East, and Oceania. PMs have slower elimination rates and lower clearance of substrate drugs; as a consequence (Fig. 72-1B), steady-state concentrations are higher and the time taken to achieve steady state is longer than in EMs (Chap. 71). Conversely, UMs display very low steady-state parent drug concentra tions and an abbreviated time to steady state.

Ultrarapid metabolizers PM UM EM Time Codeine is biotransformed by CYP2D6 to the potent active metabo lite morphine, so its effects are blunted in PMs and exaggerated in UMs. Deaths due to

respiratory depression in children given codeine after tonsillectomy have been attributed to the UM trait, and the U.S. Food and Drug Administration (FDA) has revised the package insert to include a prominent “black box” warning against its use in this set ting and, in fact, forbidding its use in children less than 12 years old. In the case of drugs with beta-blocking properties metabolized by CYP2D6, greater signs of beta blockade (e.g., bronchospasm, bradycar dia) have been reported in PM subjects than in EMs. This can be seen not only with orally administered beta blockers such as metoprolol and carvedilol, but also with ophthalmic timolol and with the sodium channel–blocking antiarrhythmic propafenone, a CYP2D6 substrate with beta-blocking properties. UMs may require very high dosages of nortriptyline and other tricyclic antidepressants to achieve a therapeu tic effect. Tamoxifen is a prodrug that undergoes CYP2D6-mediated biotransformation to active metabolites, so its efficacy may be in part related to this polymorphism. In addition, the widespread use of selec tive serotonin reuptake inhibitors (SSRIs) to treat tamoxifen-related hot flashes may also alter the drug’s effects because many SSRIs, notably fluoxetine and paroxetine, are also CYP2D6 inhibitors (see Table 71-2). CYP2C19 The PM phenotype for CYP2C19 is common (20%) among Asians and rarer (2–3%) in other populations; the frequency of the PM trait is especially high (>50%) in Oceania. The impact of polymorphic CYP2C19-mediated metabolism has been demonstrated with the proton pump inhibitor omeprazole, where ulcer cure rates with “standard” dosages were much lower in EM patients (29%) than in PMs (100%). CYP2C19 is responsible for bioactivation of the antiplatelet drug clopidogrel, and large retrospective and prospective

studies have documented decreased efficacy (e.g., increased myocar dial infarction after placement of coronary stents or increased stroke or transient ischemic attacks) among subjects with one or two reduction of function alleles. In addition, some studies suggest that omeprazole and possibly other proton pump inhibitors phenocopy this effect by inhibiting CYP2C19. CYP2C9 Relatively common loss-of-function alleles in CYP2C9 are associated with increased rates of neurologic complications with phenytoin, hypoglycemia with glipizide, and reduced warfarin dose required to maintain stable anticoagulation. Rare patients homozygous for loss-of-function alleles may require very low warfarin dosages. Up to 50% of the variability in steady-state warfarin dose requirement is attributable to polymorphisms in CYP2C9 and in the promoter of VKORC1, which encodes the warfarin target, with lesser contribu tions by genes such as CYP4F2 controlling vitamin K metabolism. The angiotensin receptor blocker losartan is a prodrug that is bioactivated by CYP2C9; as a result, PMs and those receiving inhibitor drugs may display little response to therapy. DPYD Individuals homozygous for loss-of-function alleles in dihy dropyrimidine dehydrogenase, encoded by DPYD, are at increased risk for severe toxicity when exposed to the substrate anticancer drug 5-fluorouracil (5-FU), as well as to capecitabine and tegafur, which are metabolized to 5-FU. Dose reductions have been recommended in intermediate metabolizers. Transferase Variants Thiopurine S-methyltransferase (TPMT) bioinactivates the antileukemic drug 6-mercaptopurine (6-MP), and 6-MP is itself an active metabolite of the immunosuppressive azathio prine. Homozygotes for alleles encoding inactive TPMT (1/300 indi viduals) predictably exhibit severe and potentially fatal pancytopenia on standard doses of azathioprine or 6-MP. On the other hand, homo zygotes for fully functional alleles may display less anti-inflammatory or antileukemic effect with standard doses of the drugs. GWA studies have also identified loss-of-function variants in NUDT15 that reduce degradation of thiopurine metabolites and, thereby, also increase risk of excessive myelosuppression. N-acetylation is accomplished by hepatic N-acetyl transferase (NAT), which represents the activity of two genes, NAT1 and NAT2. Both enzymes transfer an acetyl group

from acetyl coenzyme A to the drug; polymorphisms in NAT2 are thought to underlie individual dif ferences in the rate at which drugs are acetylated and thus define “rapid acetylators” and “slow acetylators.” Slow acetylators make up ~50% of European and African populations but are less common among East Asians. Slow acetylators have an increased incidence of the druginduced lupus syndrome during procainamide and hydralazine therapy and of hepatitis with isoniazid. Individuals homozygous for a common promoter polymorphism that reduces transcription of uridine diphosphate glucuronosyltrans ferase (UGT1A1) have benign hyperbilirubinemia (Gilbert’s syndrome; Chap. 348). This variant has also been associated with diarrhea and increased bone marrow depression with the antineoplastic prodrug iri notecan, whose active metabolite is normally detoxified by UGT1A1mediated glucuronidation. The antiretroviral atazanavir is a UGT1A1 inhibitor and, thus, can increase bilirubin levels especially in individu als with the Gilbert’s variant. While this is benign, the hyperbilirubi nemia can complicate clinical care because it may raise the question of whether coexistent hepatic injury is present. Transporter Variants The risk for myotoxicity with simvastatin and possibly other statins appears increased with variants in SLCO1B1. Variants in MDR1, encoding the drug efflux transporter P-glycoprotein, may increase digoxin toxicity. Variants in the uptake transporters MATE1 and MATE2 have been reported to modulate metformin’s glucose-lowering activity. ■ ■GENETIC VARIANTS AFFECTING PHARMACODYNAMICS A variant in the VKORC1 promoter, especially common in Asian subjects (Table e72-1), reduces transcriptional activity generating less

protein and, thus, lowering warfarin dose requirement. Multiple poly morphisms identified in the β2-adrenergic receptor appear to be linked to specific drug responses in asthma and congestive heart failure, diseases in which β2-receptor function might be expected to determine drug response. Polymorphisms in the β2-receptor gene have also been associated with response to inhaled β2-receptor agonists, while those in the β1-adrenergic receptor gene have been associated with variability in heart rate slowing and blood pressure lowering.

Drugs may also interact with genetic pathways of disease to elicit or exacerbate symptoms of the underlying conditions. In the porphyrias, CYP inducers are thought to increase the activity of enzymes proximal to the deficient enzyme, exacerbating or triggering attacks (Chap. 428). Variants decreasing activity of glucose-6-phosphate dehydrogenase (G6PD), which occur most often in individuals of African, Mediterra nean, or South Asian descent, increase the risk of hemolytic anemia in response to the antimalarial primaquine (Chap. 105) and the uric acid–lowering agent rasburicase, which does not cause hemolysis in patients with normal amounts of the enzyme. Patients with mutations in RYR1 encoding the skeletal muscle intracellular release calcium (also termed type 1 ryanodine receptor) are asymptomatic until exposed to certain general anesthetics, which can trigger the rare syndrome of malignant hyperthermia. Certain antiarrhythmics and other drugs can produce marked QT prolongation and torsades de pointes (Chap. 253), and in a minority of affected patients, this adverse effect represents unmasking of previously subclinical congenital long QT syndrome. A variant in ACKR1 is common in African ancestry individuals and is associated with white cell counts lower than the conventional “normal range” but not associated with disease. While this has been termed “benign ethnic neutropenia,” these individuals not only undergo more diagnostic testing (including bone marrow biopsies that are almost always normal) but also have chemotherapy (associated with neutro penia) withdrawn at higher rates than noncarriers. CHAPTER 72 Pharmacogenomics Immunologically Mediated Drug Reactions Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a potentially fatal skin and systemic reaction now increasingly

recognized to be linked to specific HLA alleles (Table e72-2), as have cases of drug-induced hepa totoxicity and of the drug rash with eosinophilia and systemic symp toms (DRESS) syndrome. The frequency of risk alleles often varies by ancestry (Table e72-1). The HLA risk alleles appear to be necessary but not sufficient to elicit these reactions. For example, HLA-B∗57:01 is a risk allele for abacavir-related SJS/TEN and flucloxacillin-related hepatotoxicity. However, while 55% of abacavir-exposed subjects will develop a reaction, only 1/10,000 subjects exposed to flucloxacillin develop hepatotoxicity. Thus, a third factor, the nature of which has not yet been established, seems necessary. Tumor and Infectious Agent Genomes The actions of drugs used to treat infectious or neoplastic disease may be modulated by variants in these nonhuman germline genomes. Genotyping tumors to target therapies to underlying mechanisms and to avoid potentially toxic therapy in patients who would derive no benefit is now stan dard in many cancers (Chap. 76). Trastuzumab, which potentiates anthracycline-related cardiotoxicity, is ineffective in breast cancers that do not express the Herceptin receptor. Imatinib targets a specific tyrosine kinase, BCR-Abl1, that is generated by the translocation that creates the Philadelphia chromosome typical of chronic myelogenous leukemia (CML). Imatinib is also an inhibitor of another kinase, c-kit, and the drug is remarkably effective in c-kit–driven cancer, such as gastrointestinal stromal tumors (Chap. 76). Vemurafenib does not inhibit wild-type BRAF but is active against the V600E mutant form of the kinase. Crizotinib is highly effective in non-small-cell lung cancers harboring anaplastic lymphoma kinase (ALK) mutations. ■ ■INCORPORATING PHARMACOGENETIC INFORMATION INTO CLINICAL PRACTICE The discovery of common variant alleles with relatively large effects on drug response raises the prospect that these variants could be used to guide therapy. Desired outcomes could be better ways of choosing likely effective drugs and dosages, or avoiding drugs that are likely

to produce severe adverse drug events or be ineffective in individual subjects. Indeed, the FDA now incorporates pharmacogenetic data into package inserts meant to guide prescribing. A decision to adopt pharmacogenetically guided dosing for a given drug depends on multiple factors. The most important are the magnitude and clinical importance of the genetic effect and the strength of evidence linking genetic variation to variable drug effects (e.g., anecdote vs post hoc analysis of clinical trial data vs randomized clinical trial [RCT]). The evidence can be strengthened if statistical arguments from clinical trial data are complemented by an understanding of underlying physiologic mechanisms. Cost versus expected benefit may also be a factor.

Point of Care Versus Preemptive Approaches Two approaches to pharmacogenetic implementation have been put in place at “early adopter” institutions and are currently being evaluated. In the first, variant-specific assays are ordered at the time of drug prescription and delivered rapidly (often within an hour or two), and the results are then used to guide therapy with that specific drug. The alternative to this “point-of-care” approach is a “preemptive” approach in which pharmacogenetic testing for large numbers of potential variants across many drugs is undertaken prior to prescription of any drug. The data are then available in electronic health record (EHR) systems and coupled to real-time clinical decision support (CDS). When a drug whose effects are known to be influenced by pharmacogenetic variants is prescribed, the EHR system looks up whether variants likely to affect response are present; if so, CDS will alert health care providers that an alternate drug or a different dose may be required. Challenges There are multiple challenges in putting in place either system. Assay validity and reproducibility have been issues in the past but are less likely now. While common variants in genes such as those listed in Table e72-

1 have been clearly associated with variable drug responses, the effect of rare variants, now readily discoverable by large-scale sequencing, remains largely unexplored. The Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group have developed and published guidelines for multiple drug-gene pairs focusing on the question of what might be an appropriate drug dose adjustment given the availabil ity of genetic data. These resources do not directly address the question of when or how such genetic testing should be undertaken. Developing Evidence That Pharmacogenetic Testing Alters Drug Outcomes A major issue is whether pharmacogenetic test ing affects important drug response outcomes. When the evidence is compelling, alternate therapies are not available, and there are clear recommendations for dosage adjustment in subjects with variants, there is a strong argument for deploying genetic testing as a guide to prescribing; HLA-B∗57:01 testing for abacavir is an example described below. In other situations, the arguments are less compelling: the mag nitude of the genetic effect may be smaller, the consequences may be less serious, alternate therapies may be available, or the drug effect may be amenable to monitoring by other approaches. PART 3 Pharmacology One school argues that the physiology and pharmacology are known and that RCTs are, therefore, unnecessary (and conceivably unethical). The analogy is sometimes drawn to well-recognized dose adjustment of renally excreted drugs in the presence of renal dysfunction. RCTs have not been conducted and the idea of such dose adjustment is well accepted in the medical community and recommended in FDA-approved drug labels. Others have argued that the effect of genetic variants is generally modest and variability in drug actions has many nongenetic sources, so genetic testing might provide marginal benefit at best. Efforts to demonstrate the value of pharmacogenetic testing have met with mixed results. An RCT clearly showed that HLA-B∗57:01 testing eliminates SJS/TEN due to abacavir. Similarly, regulatory authorities in some countries in Southeast Asia mandated HLA-B∗15:02 testing prior to initiation of carbamazepine; however, in this case, an unfortunate out come in some jurisdictions was that prescribers stopped using carbam azepine, often substituting phenytoin (another drug associated with SJS/ TEN), so the incidence of the severe ADR was unchanged. RCTs evaluating the effect of using pharmacogenetically guided therapy to optimize warfarin treatment have shown either no effect or a

modest benefit of incorporating genetic information into prescribing the drug. New effective alternate therapies to clopidogrel that appear to lack important pharmacogenetic variants have emerged. One approach to therapy, therefore, is to use pharmacogenetic testing to identify subjects in whom variants are absent and, therefore, a standard dose of clopidogrel is likely to be effective and to reserve alternate more expensive therapies for subjects likely to have variant responses to warfarin or clopidogrel. Two large trials have randomized patients with acute coronary syndromes to newer antiplatelet therapies (ticagrelor or prasugrel) or clopidogrel if CYP2C19 variants were absent; in one, clopidogrel was superior, and in the second, there was a trend in the same direc tion. A meta-analysis including these trials and others suggested that therapy guided by platelet function testing and genotyping resulted in improved efficacy and decreased minor bleeding with clopidogrel. A 6944-patient trial conducted in seven European countries reported in 2023 that genotyping for 50 pharmacogene variants in 12 genes reduced serious ADRs (associated with 42 drugs) by 30% compared to standard prescribing pharmacogenetically guided treatment. Although there was heterogeneity in the effect across countries, the result of this large trial further supports the idea of preemptive pharmacogenetic screening. ■ ■GENETICS AND DRUG DEVELOPMENT Genetic tools are now being increasingly used to identify or validate new drug

targets. Available data suggest that a new drug development program is more likely to succeed if evidence from human genetics supports the role of a possible drug target in disease pathogenesis and suggests that the risk of toxicity due to high-risk pharmacokinetics or other mechanisms is small. Furthermore, studies of the relationships between variants in genes encoding drug target molecules and a range of phenotypes (e.g., those in EHRs) are being used for drug “repurpos ing,” identifying new indications for existing drugs. Finding Protective Alleles Can Identify Drug Targets One example of using genetics to identify a new drug target started with the discovery that very rare gain-of-function variants in PCSK9 are a rare cause of familial hypercholesterolemia. Subsequently, popula tion studies showed that carriers of loss-of-function SNPs (2.5% of African Americans) had decreased low-density lipoprotein cholesterol, decreased incidence of coronary artery disease, and no deleterious conse quences in other organ systems. These data triggered the development of PCSK9 monoclonal antibodies, which were marketed <10 years after the initial population studies. Other targets implicated by similar popula tion genetic studies include HSD17B13 for prevention of chronic liver disease and ANGPTL3 for hyperlipidemia. Discovering rare protec tive alleles may require very large data sets (>100,000), such as EHR systems coupled to DNA biobanks as in the U.S. All of Us cohort or epidemiologic cohorts like the UK Biobank. Cancer In cancer, tumor sequencing has identified new targets for drug development, often constitutively active kinases. A problem in this area has been the rapid emergence of drug resistance, often after extraordinary initial responses. For example, 40% of melano mas appear to be driven by the V600E mutant form of BRAF, and the specific inhibitor vemurafenib can produce clinically spectacular remission. However, durable responses are rare, and it is now apparent that combination therapy, often with inhibitors of the MEK pathway, can provide improved therapy. Another approach that is rapidly gain ing wide use in cancer involves drugs that reverse immune system inhibition (Chap. 78). In some patients, the release of this “brake” can provide durable remissions, whereas in others, severe adverse events, including colitis, pneumonitis, and myocarditis, have been reported. Understanding the mechanisms underlying variability to these thera pies is a major emerging challenge in the field. Using Multiple Data Types The development of methods to understand associations across multiple large data sets is another approach that is being explored in drug development. For example, a GWA study of risk of rheumatoid arthritis identified multiple risk loci, many encoding proteins that are known targets for intervention in the disease. Interestingly, others encode proteins that are targets for drugs

used in other conditions, such as certain cancers, raising the question of whether such drugs could be “repurposed” for rheumatoid arthritis. While the field has, to date, focused on individual high effect size variants (that are often common in a population), newer approaches combining many (dozens to millions) common variants into polygenic risk scores to predict drug responses are also being explored. An exten sion of this approach is the broader issue of systems pharmacology (see Chap. 71), in which multiple sources of data are used to identify potential molecules or pathways that would be amenable to treatment, by new drugs or by existing agents, using analysis of genomic, tran scriptomic, proteomic, and other large data sets. SUMMARY The science of pharmacogenomics has evolved from isolated examples of rare adverse drug actions to a more comprehensive view of the role of genetic variation in mediating the effects of most drugs. Current principles include: • Genetic variants with an important effect on drug actions can be common, and their frequencies often vary by ancestry. • One common mechanism is modulation of drug concentrations.

• No practitioner can be expected to remember all variants impor

tant for all drugs. Electronic data systems can now be accessed to describe this information. Ultimately, this information will be used by linking individual pharmacogenetic data to smart EHR systems. • Incorporating genetic approaches into drug development projects holds the promise of more rapid development of targeted, safe, and effective therapies. ■ ■FURTHER READING Diogo D et al: Phenome-wide association studies across large population cohorts support drug target validation. Nat Commun 9:4285, 2018. Galli M et al: Comparative effects of guided vs. potent P2Y12 inhibi tor therapy in acute coronary syndrome: A network meta-analysis of 61 898 patients from 15 randomized trials. Eur Heart J 43:959, 2022. Osanlou O et al: Pharmacogenetics of adverse drug reactions. Adv Pharmacol 83:155, 2018. Roden DM et al: Pharmacogenomics. Lancet 394:521, 2019. Swen JJ et al: A 12-gene pharmacogenetic panel to prevent adverse drug CHAPTER 72 reactions: An open-label, multicentre, controlled, cluster-randomised crossover implementation study. Lancet 401:10374, 2023. Pharmacogenomics

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