other tissues, may be asymptomatic until exposed to certain general anesthetics, which trigger the rare syndrome of malignant hyperthermia. Certain antiarrhythmics and other drugs can produce marked QT prolongation and torsades des pointes (Chap. 276), and in some patients, this adverse effect represents unmasking of previously subclinical congenital long QT syndrome. Up to 50% of the variability in steady-state warfarin dose requirement is attributable to polymorphisms in the promoter of *VKORC1*, which encodes the warfarin target, and in the coding region of *CYP2C9*, which mediates its elimination.

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 is a rapidly evolving approach to target therapies to underlying mechanisms and to avoid potentially toxic therapy in patients who would derive no benefit (Chap. 101e). 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). BCR-Abl1 is not only active but may be central to the pathogenesis of CML; its use in BCR-Abl1-positive tumors has resulted in remarkable antitumor efficacy. Similarly, the anti–epidermal growth factor receptor (EGFR) antibodies cetuximab and panitumumab appear especially effective in colon cancers in which K-ras, a G protein in the EGFR pathway, is not mutated. Vemurafenib does not inhibit wild-type *BRAF* but is active against the V600E mutant form of the kinase.

PROSPECTS FOR INCORPORATING PHARMACOGENETIC INFORMATION INTO CLINICAL PRACTICE

The description of genetic variants linked to variable drug responses naturally raises the question of if and how to use this information in practice. Indeed, the U.S. Food and Drug Administration (FDA) now incorporates pharmacogenetic data into information ("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 versus post-hoc analysis of clinical trial data versus randomized prospective clinical trial). 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.

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. The association between HLA-B*5701 and severe skin toxicity with abacavir is an example. In other situations, the arguments are less compelling: the magnitude 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. Ongoing clinical trials are addressing the utility of preprescription genotyping in large populations exposed to drugs with known pharmacogenetic variants (e.g., warfarin). Importantly, technological advances are now raising the possibility of inexpensive whole genome sequencing. Incorporating a patient's whole genome sequence into their electronic medical record would allow the information to be accessed as needed for many genetic and pharmacogenetic applications, and the argument has been put forward that this approach would lower logistic barriers to use of pharmacogenomic variant data in prescribing. There are multiple issues (e.g., economic, technological, and ethical) that need to be addressed if such a paradigm is to be adopted (Chap. 82). While barriers to bringing genomic and pharmacogenomic information to the bedside seem daunting, the field is very young and evolving rapidly. Indeed, one major result of understanding the role of genetics in drug action has been improved screening of drugs during the development process to reduce the likelihood of highly variable metabolism or unanticipated toxicity.

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. *Interactions must be considered in the differential diagnosis of any unusual response occurring during drug therapy.* Prescribers 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 medications. A meticulous drug history should include examination of the patient's medications and, if necessary, calls to the pharmacist to identify prescriptions. It should also address the use of 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. Examples are presented below and in Table 5-3. Accordingly, when these drugs are started or stopped, prescribers must be especially alert to the possibility of interactions.

PHARMACOKINETIC INTERACTIONS CAUSING DECREASED DRUG EFFECTS

Gastrointestinal absorption can be reduced if a drug interaction results in drug binding in the gut, as with aluminum-containing antacids, kaolin-pectin suspensions, or bile acid sequestrants. Drugs such as histamine H_2-receptor antagonists or proton pump inhibitors that alter gastric pH may decrease the solubility and hence absorption of weak bases such as ketoconazole.

Expression of some genes responsible for drug elimination, notably *CYP3A* and *MDR1*, can be markedly increased by inducing drugs, such as rifampin, carbamazepine, phenytoin, St. John's wort, and glutethimide, and by smoking, exposure to chlorinated insecticides such as DDT (CYP1A2), and chronic alcohol ingestion. Administration of inducing agents lowers plasma levels, and thus effects, over 2–3 weeks as gene expression is increased. If a drug dose is stabilized in the presence of an inducer that is subsequently stopped, major toxicity can occur as clearance returns to preinduction levels and drug concentrations rise. Individuals vary in the extent to which drug metabolism can be induced, likely through genetic mechanisms.

Interactions that inhibit the bioactivation of prodrugs will decrease drug effects (Table 5-1).

Interactions that decrease drug delivery to intracellular sites of action can decrease drug effects: tricyclic antidepressants can blunt the antihypertensive effect of clonidine by decreasing its uptake into adrenergic neurons. Reduced CNS penetration of multiple HIV protease inhibitors (with the attendant risk of facilitating viral replication in a sanctuary site) appears attributable to P-glycoprotein-mediated exclusion of the drug from the CNS; indeed, inhibition of P-glycoprotein has been proposed as a therapeutic approach to enhance drug entry to the CNS (Fig. 5-5*A*).

PHARMACOKINETIC INTERACTIONS CAUSING INCREASED DRUG EFFECTS

The most common mechanism here is inhibition of drug elimination. In contrast to induction, new protein synthesis is not involved, and the effect develops as drug and any inhibitor metabolites accumulate (a function of their elimination half-lives). Since shared substrates of a single enzyme can compete for access to the active site of the protein, many CYP substrates can also be considered inhibitors. However, some drugs are especially potent as inhibitors (and occasionally may not even be substrates) of specific drug elimination pathways, and so it is in the use of these agents that clinicians must be most alert to the potential for interactions (Table 5-3). Commonly implicated interacting drugs of this type include amiodarone, cimetidine,