# 5 Drug Toxicity

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## INTRODUCTION

Physicians prescribe drugs to prevent or treat disease. Those same drugs can be toxic to certain patients, however, because of genetic predisposition, nonselective action, or inappropriate use or administration of the drug. The United States Food and Drug Administration (FDA) spends a significant portion of its $1 trillion budget to ensure that new drugs are not overtly or unnecessarily dangerous. Moreover, pharmaceutical and biotechnology companies spend years and millions of dollars in clinical trials to understand the safety and inherent toxicity of their drugs. Potential drug candidates often fail because of unacceptable levels of toxicity in preclinical experiments or in clinical studies (see Chapter 48, Drug Discovery and Preclinical Development, and Chapter 49, Clinical Drug Evaluation and Regulatory Approval). Despite all of these efforts, even common over-the-counter drugs such as **acetaminophen** can be lethal (in this case, by causing fulminant hepatitis) if taken in supratherapeutic doses.

It must be recognized that no drug is entirely specific. All drugs have both primary intended effects and secondary unintended effects, the latter known as **side effects** or **adverse effects**. Although side effects can be neutral or even beneficial, side effects are typically undesirable. Adverse effects can range in severity from nuisance to life threatening. These effects make many patients unwilling to take drugs on a regular basis, and this lack of compliance represents a major practical limitation of pharmacotherapy.

Drug toxicology focuses on the harmful effects of drugs in the animal and human body. In virtually all respects, the pharmacologic principles discussed in the preceding chapters apply to the study of drug toxicity. Thus, just as drug-receptor interactions are fundamental to understanding the beneficial properties of a drug, so too are these interactions crucial in understanding the adverse effects of a drug. Although understanding the various toxicities of every drug is important, it can be an arduous and daunting task to learn and remember the myriad adverse drug effects. Thus, instead of repeating the general principles discussed in Chapters 1 through 4, or presenting extensive tables of information that can be found in many digital resources, this chapter focuses on the *common mechanisms* that underlie the toxic effects of drugs. Toxicities that derive from inappropriate activation or inhibition of the intended drug target (**on-target adverse effects**) or unintended targets (**off-target adverse effects**) begin the discussion. The phenotypic effects of these drug toxicities are then discussed at the physiologic, cellular, and

molecular levels. A number of general principles and specific examples are also illustrated in the Workbook that accompanies this text (Farrell SE. *Principles of Pharmacology Workbook*. Baltimore: Lippincott Williams & Wilkins; 2007), and important drug-specific toxicities are also highlighted in the Drug Summary Tables at the ends of most chapters throughout this book. The toxicity of nondrug xenobiotics—such as carbon monoxide, lead, and pesticides—and the treatment of poisoning are discussed in Chapter 51, Poisoning by Drugs and Environmental Toxins.

## Case

Ms. G is an 80-year-old piano teacher with progressively severe right leg pain over a period of 5 to 10 years. She has continued to teach in her studio but at the cost of increasing pain and fatigue. Imaging studies reveal severe osteoarthritis of the right hip. She is scheduled for elective replacement of the right hip with a prosthetic joint.

The total hip replacement is performed without immediate complications. During the first few days after the operation, Ms. G is given low-molecular-weight heparin and warfarin as prophylaxis against deep vein thrombosis. Six days after the operation, she develops excruciating pain in the area of the operation. Right lateral hip and buttock swelling is noted on physical examination. A complete blood count reveals significant blood loss (drop in hematocrit from 35% to 25%), and she is taken back to the operating room for evacuation of a large hematoma around the prosthetic joint. Although the hematoma does not appear to be grossly infected, cultures of the hematoma are positive for *Staphylococcus aureus*.

Because prosthetic joint infections are difficult to treat successfully without removal of the prosthesis, Ms. G is started on an aggressive 12-week course of combination antibiotics in which intravenous vancomycin and oral rifampin are administered for 2 weeks followed by oral ciprofloxacin and rifampin for 10 weeks. She tolerates the first 2 weeks of antibiotics without complications. However, 36 hours after switching her antibiotic from vancomycin to ciprofloxacin, she develops a high fever to 103°F and extreme weakness. Aspiration of the hip reveals only a scant amount of straw-colored (i.e., nonpurulent) fluid. Ms. G is therefore admitted to hospital for close observation.

Twelve hours after her admission, Ms. G develops an extensive maculopapular rash over her chest, back, and extremities. Her ciprofloxacin and rifampin are discontinued and vancomycin is restarted. Gradually, over the next 72 hours, her temperature returns to normal and her rash begins to fade. There is no growth in the culture of the right hip aspirate. Ms. G is continued on vancomycin as a single agent for the next 4 weeks without incident; rifampin is restarted, again without incident; and the 12-week antibiotic course is eventually completed using a combination of trimethoprim-sulfamethoxazole and rifampin.

Four months after her hip surgery, Ms. G is back to teaching her piano students and making slow but steady progress in her rehabilitation program.

## QUESTIONS

1. What was the rationale for coadministration of low-molecular-weight heparin and warfarin in the immediate postoperative period?
2. Was there a cause-and-effect relationship between administration of the prophylactic anticoagulants and Ms. G's life-threatening bleeding complication?
3. What was the rationale for administration of vancomycin and rifampin followed by ciprofloxacin and rifampin for treatment of the *S. aureus* infection?
4. How likely was it that Ms. G's high fever, weakness, and skin rash represented a drug reaction to ciprofloxacin?

## MECHANISMS OF DRUG TOXICITY

Whether a drug will do more harm than good in an individual patient depends on many factors, including the patient's age, genetic makeup and preexisting conditions, the dose of the drug administered, and other drugs the patient may be taking. For example, the very old or the very young may be more susceptible to the toxic effects of a drug because of age-dependent differences in pharmacokinetic profiles or in drug-metabolizing enzymes. As discussed in Chapter 4, Drug Metabolism, genetic factors can alter how a patient metabolizes or responds to a drug. Therefore, individual responses can also occur because of genetic differences in drug metabolism or receptor activity, as well as differences in the activities of repair mechanisms. Adverse drug reactions may be more likely in patients with preexisting conditions, such as liver or kidney dysfunction, depressed immune function, or pregnancy. The clinical determination of a drug's toxicity may not always be straightforward: as seen in the case of Ms. G, for example, a patient being treated with an antibiotic to combat an infection can develop a high fever, skin rash, and significant morbidity due either to recurrence of the infection or an adverse reaction to the antibiotic.

While a spectrum of adverse effects may be associated with the use of any drug or drug class, it is helpful to conceptualize the mechanisms of drug toxicity based on several general paradigms:

- ''On-target'' adverse effects, which are the result of the drug binding to its intended receptor, but at an inappropriate concentration, with suboptimal kinetics, or in the incorrect tissue (Fig. 5-1)
- ''Off-target'' adverse effects, which are caused by the drug binding to a target or receptor for which it was not intended (Fig. 5-1)
- Production of toxic metabolites (Figs. 5-1 and 5-2)
- Production of harmful immune responses (Fig. 5-2 and Table 5-1)
- Idiosyncratic responses

Each of these mechanisms is discussed below.

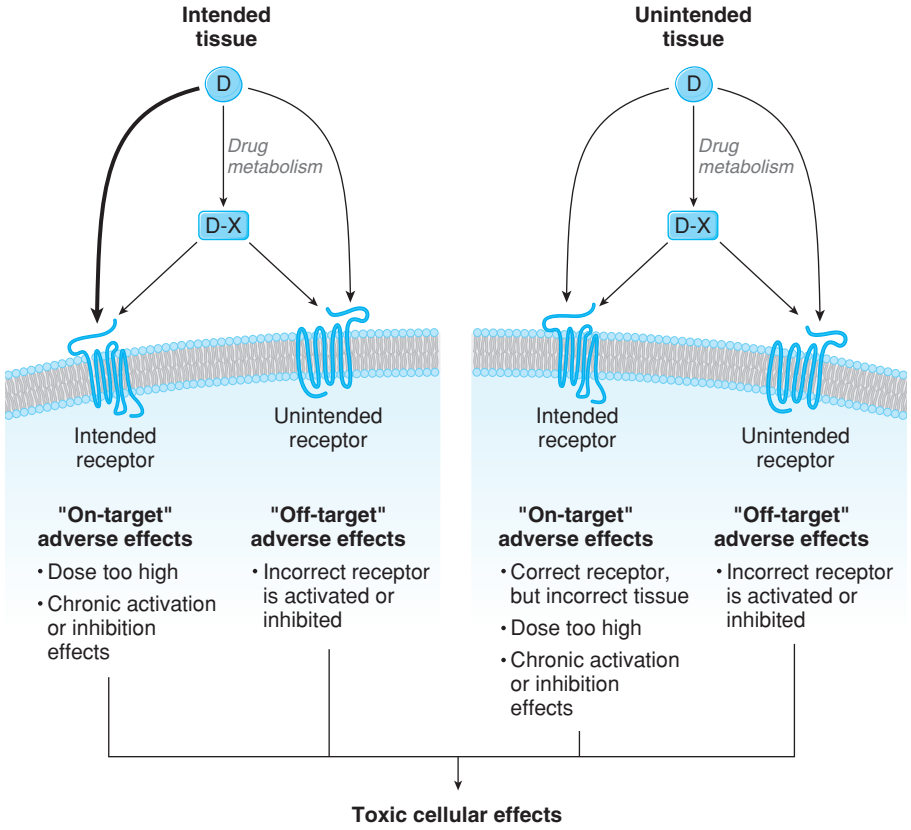


**Figure 5-1. On-target and off-target adverse drug effects.** Drug D is intended to modulate the function of a specific receptor (*Intended receptor*) in a particular tissue (*Intended tissue*). On-target adverse effects in the intended tissue could be caused by a supratherapeutic dose of the drug or by chronic activation or inhibition of the intended receptor by Drug D or its metabolite D–X. The same on-target effects could occur in a second tissue (*Unintended tissue*); in addition, the intended receptor could mediate an adverse effect because the drug is acting in a tissue for which it was not designed. Off-target effects occur when the drug and/or its metabolites modulate the function of a target (*Unintended receptor*) for which it was not intended.

## ON-TARGET EFFECTS

An important concept in drug toxicity is that an adverse effect may be an exaggeration of the desired pharmacologic action due to alterations in exposure to the drug (see Fig. 5-1). This can occur by deliberate or accidental dosing error, by alterations in the pharmacokinetics of the drug (e.g., due to liver or kidney disease or to interactions with other drugs), or by changes in the pharmacodynamics of the drug-receptor interaction that alter the pharmacologic response (e.g., changes in receptor number). All such changes can lead to an increase in the effective concentration of the drug and thus to an increased biological response.

An important class of on-target adverse effects may occur because the drug, or one of its metabolites, interacts with the appropriate receptor but in the incorrect tissue. Many drug targets are expressed in more than one cell type or tissue. For example, the antihistamine **diphenhydramine hydrochloride** is an $H_1$ receptor antagonist used to reduce the unpleasant symptoms of histamine release in allergic conditions. Diphenhydramine also crosses the blood-brain barrier to antagonize $H_1$ receptors in the central nervous system, leading to somnolence. This adverse effect led to the design of second-generation $H_1$ receptor antagonists that do not cross the blood-brain barrier, and so do not induce drowsiness.

Sometimes on-target side effects unmask important and previously unknown functions of the biologic target. A prominent example of this phenomenon occurs with administration of hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors (so-called *statins*), which are used clinically to decrease cholesterol levels. The intended target tissue of these drugs is the liver, where they inhibit HMG CoA reductase, the rate-limiting enzyme of isoprenoid synthesis. A rare adverse effect of statin therapy is muscle toxicity, including rhabdomyolysis and myositis; this side effect is due to the physiologic role of HMG CoA reductase in regulating the posttranslational modification of several muscle proteins through a lipidation process called *geranyl-geranylation.*

## OFF-TARGET EFFECTS

Off-target adverse effects occur when the drug interacts with unintended targets. Indeed, few drugs are so selective that they interact with only one molecular target. An example of an off-target effect is given by the antihistamine **terfenadine**, which also inhibits a cardiac potassium channel (hERG). The unintended inhibition of the ion channel unfortunately led to fatal cardiac arrhythmias in some patients, and terfenadine was withdrawn from the market for this reason. The active metabolite of terfenadine, **fexofenadine**, was later discovered to inhibits the hERG channel only weakly, and fexofenadine is now marketed as a safer antihistamine.

Enantiomers (mirror-image isomers) of a drug can also cause off-target effects. As described in Chapter 1, Drug-Receptor Interactions, drug receptors are often exquisitely sensitive to the three-dimensional arrangement of atoms in the drug molecule; therefore, receptors can distinguish between enantiomers of a drug. A tragic and well-known example of this phenomenon occurred with the administration of racemic thalidomide (only weakly inhibits mixture of [*R*]

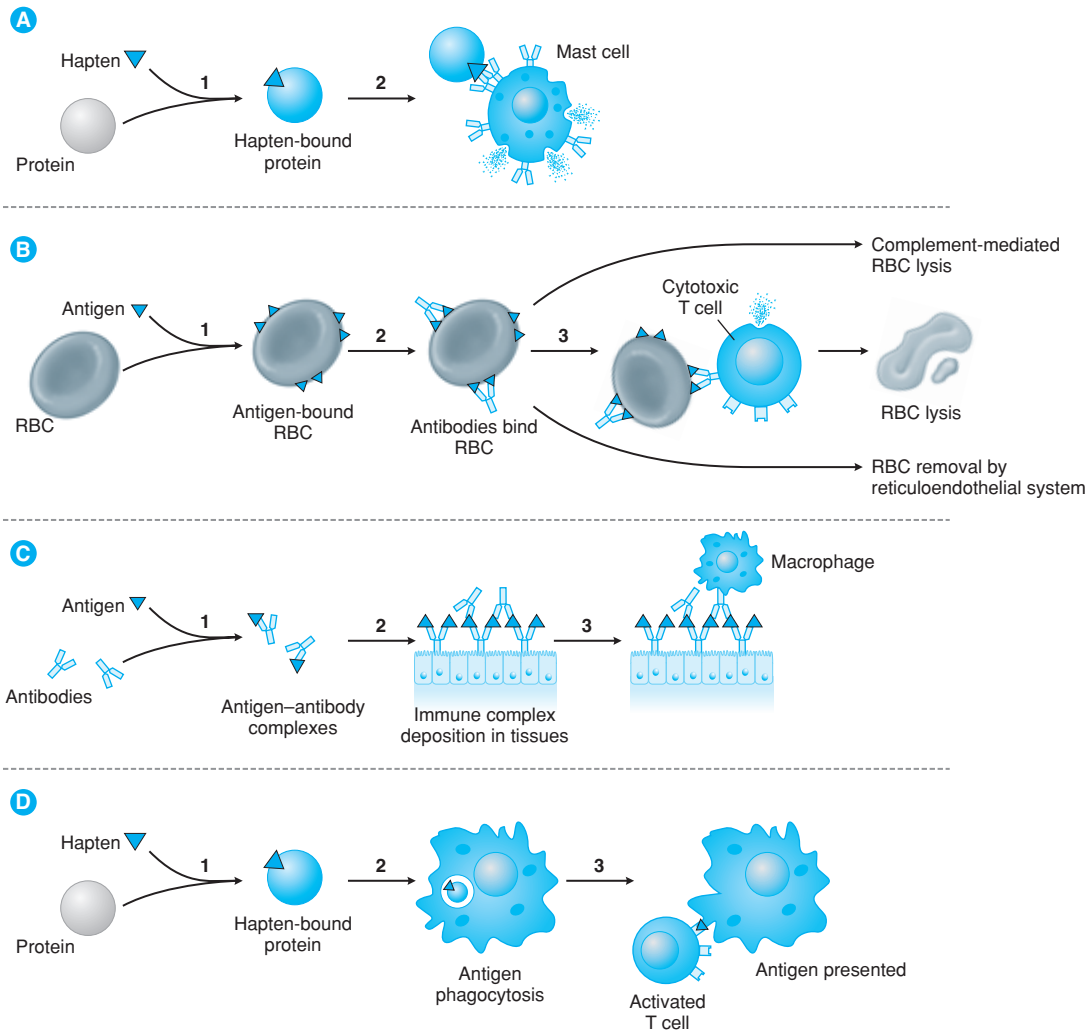


**Figure 5-2. Mechanisms of hypersensitivity reactions. A.** Type I hypersensitivity reactions occur when a hapten binds to a protein (1). The antigen crosslinks IgE antibodies on the surface of a mast cell, leading to mast cell degranulation (2). Mast cells release histamine and other inflammatory mediators. **B.** Type II hypersensitivity reactions occur when an antigen binds to the surface of a circulating blood cell, usually a red blood cell (RBC) (1). Antibodies to the antigen then bind the surface of the RBC (2), attracting cytotoxic T cells (3), which release mediators that lyse the RBC. Binding of antibody to RBCs can also directly stimulate complement-mediated RBC lysis and RBC removal by the reticuloendothelial system. **C.** Type III hypersensitivity reactions occur when antibodies bind to a soluble toxin, acting as an antigen (1). The antigen–antibody complexes are then deposited in the tissues (2), attracting macrophages (3) and starting a complement-mediated reaction sequence (*not shown*). **D.** Type IV hypersensitivity reactions occur when a hapten binds to a protein (1) and the hapten-bound protein is phagocytosed by a Langerhans cell (2). The Langerhans cell migrates to a regional lymph node, where it presents the antigen to a T cell, thereby activating the T cell (3).

and [*S*]-enantiomers) in the 1960s as a treatment for morning sickness in pregnant women. While the (*R*)-enantiomer of thalidomide was an effective sedative, the (*S*)-enantiomer was a potent teratogen, which caused severe birth defects such as phocomelia in an estimated 10,000 newborns in 46 countries. These defects are now known to be linked to the anti-angiogenic properties of (*S*)-thalidomide. Notably, thalidomide was never approved for this indication in the United States because FDA pharmacologist Frances Kelsey believed that the initial toxicity testing results were inadequate.

The potential for pronounced pharmacologic differences between enantiomers has led the FDA to treat enantiomers of drugs as separate chemical entities. If a single enantiomeric preparation of a drug can be shown to have improved pharmacologic properties over a racemic version, then the purified enantiomer can be recognized as a new drug. For example, the racemic proton pump inhibitor **omeprazole** and its (*S*)-enantiomer **esomeprazole** (as in [*S*]-omeprazole) are marketed as separate drugs.

Another common off-target effect is the unintended activation of different receptor subtypes. For example, the $\beta_1$-adrenergic receptor is expressed in the heart, and its activation increases heart rate and myocardial contractility. Closely related $\beta_2$-adrenergic receptors are expressed primarily in smooth muscle cells in the airways and in the vasculature, and activation of $\beta_2$ receptors leads to smooth muscle relaxation and dilation of these tissues (see Chapter 9, Adrenergic Pharmacology). The clinical uses of β-adrenergic receptor antagonists (so-called *β-blockers*) are often targeted to the $\beta_1$ receptor to control heart rate and reduce

TABLE 5-1 **Types of Hypersensitivity Reactions**

| CLASSIFICATION | PRIMARY TRIGGERS | PRIMARY MEDIATORS | EXAMPLES OF SIGNS AND SYMPTOMS | EXAMPLES OF DRUGS |
|---|---|---|---|---|
| Type I or immediate-type hypersensitivity (humoral) | Antigen-binding IgE on mast cells | Histamine and serotonin | Hives and urticaria, bronchoconstriction, hypotension, and shock | Penicillin |
| Type II or antibody-dependent cellular cytotoxicity (humoral) | IgG and complement-binding cell-bound antigen | Neutrophils, macrophages, and natural killer cells | Hemolysis | Cefotetan |
| Type III or immune-complex disease (humoral) | IgG and complement-binding soluble antigen | Neutrophils, macrophages, and natural killer cells; reactive oxygen species and chemokines | Cutaneous vasculitis | Mitomycin C |
| Type IV or delayed-type hypersensitivity (cell-mediated) | Antigen in association with major histocompatibility complex (MHC) protein on the surface of antigen-presenting cells | Cytotoxic T lymphocytes, macrophages, and cytokines | Macular rashes and organ failure | Sulfamethoxazole |

The four types of hypersensitivity reactions and their triggers, mediators, and clinical manifestations are shown. Examples of drugs that cause each type of hypersensitivity reaction are also provided. (Adapted from Table 2, Bugelski PJ. Genetic aspects of immune-mediated adverse drug effects. *Nat Rev Drug Discov* 2005;59–69.)

myocardial oxygen demand in patients with angina or heart failure. However, some $\beta_1$ receptor antagonists are not entirely selective for the $\beta_1$ receptor and can also antagonize the $\beta_2$ receptor. β-Adrenergic receptor antagonists with nonselective effects are therefore contraindicated in patients with asthma, because these drugs could inadvertently cause airway constriction by antagonizing $\beta_2$ receptors.

Interestingly, the off-target effects of a drug can be explored by using genetically modified animals in which the intended target receptor is genetically deleted. If the mice lacking the intended target respond to the drug in some way, then the actions of the drug must be occurring via a target other than the intended target. Modern molecular biology techniques have also made possible tissue-specific deletion of the target receptor, making it easier to identify off-target effects and previously unknown on-target adverse effects.

## PRODUCTION OF TOXIC METABOLITES

As described in Chapter 4, virtually all drug molecules are metabolized by the liver and/or other tissues. Sometimes metabolism produces a pharmacologically active metabolite, as with the angiotensin receptor antagonist **losartan** and the antihistamine **ebastine**, which are converted from inactive prodrugs to the active drugs **E3174** and **carebastine**, respectively.

In other cases, a drug metabolite can have an adverse effect. A clinically significant example is that of acetaminophen, a commonly used analgesic and antipyretic. In its therapeutic dose range, acetaminophen is metabolized predominantly by glucuronidation and sulfation, and these conjugated products account for approximately 95% of the total excreted metabolites. P450 enzymes oxidize a small percentage of acetaminophen to a reactive intermediate, ***N*-acetyl-benzoquinoneimine**, which is immediately conjugated to glutathione. However, when the level of acetaminophen exceeds the therapeutic range, the glucuronidation and sulfation pathways become saturated and the stores of glutathione in the liver become depleted. This results in excessive accumulation of *N*-acetyl-benzoquinoneimine, an electrophile that reacts with nucleophilic groups on proteins to produce covalent protein derivatives.

Although the biological mechanisms are still not well understood, some of these complexes between the drug metabolite and cellular proteins are highly toxic to the liver and, in the case of acetaminophen overdose, can cause fulminant hepatotoxicity and death. An antidote for acetaminophen overdose is ***N*-acetylcysteine**, which reacts directly with (and thereby detoxifies) the iminoquinone. Administered within 8 to 16 hours of an overdose of acetaminophen, *N*-acetylcysteine can be lifesaving. This example demonstrates the importance of **dose**, an axiom of toxicology. Although acetaminophen is used safely by millions of individuals every day, the same drug is responsible for roughly 50% of the cases of acute liver failure in the United States.

The toxicity of drug metabolites can only be determined empirically. This underscores the importance of extensive drug testing, both in preclinical experiments and in clinical trials. Despite such testing, some rare drug toxicities are discovered only when exposure occurs in a much larger pop-

ulation than that required for clinical trials. For example, **fluoroquinolones**, a class of broad-spectrum antibiotics derived from nalidixic acid, had minimal toxicities in preclinical studies and clinical trials. However, wider clinical exposure of these drugs led to reports of anaphylaxis, QTc-interval prolongation, and potential cardiotoxicity, resulting in the removal of two drugs of this class, **temafloxacin** and **grepafloxacin**, from the market. Use of another drug in this class, **trovafloxacin**, is significantly restricted due to liver toxicity. In comparison, **ciprofloxacin** and **levofloxacin** are generally well-tolerated fluoroquinolones and are frequently used for treatment of bacterial infections. As seen in the introductory case, however, even these agents can occasionally cause a severe drug hypersensitivity reaction.

## HARMFUL IMMUNE RESPONSES

Drugs are xenobiotics that can be recognized by the immune system as foreign substances. Most small molecule drugs with a mass of less than 600 daltons are not direct immunogens, but act as **haptens**, where the drug binds (often covalently) to a protein in the body and is then capable of triggering an immune response. If a drug is sufficiently large (e.g., a therapeutic peptide or protein), it may directly activate the immune system. The two principal immune mechanisms by which drugs can produce damage are **hypersensitivity responses** (allergic responses) and **autoimmune reactions.**

The hypersensitivity responses are classically divided into four types, which are described further in Figure 5-2. Table 5-1 provides more detailed information about the mediators of hypersensitivity reactions and the clinical manifestations of the four types of hypersensitivity reactions. Prior exposure to a substance is required for each of the four types of hypersensitivity reactions.

A **type I** hypersensitivity response (**immediate hypersensitivity**) results from the production of IgE after exposure to an antigen. The antigen may be a foreign protein, such as the bacterially derived thrombolytic drug **streptokinase**, or it may be an endogenous protein modified by a **hapten** to become immunogenic. **Penicillin** fragments formed either in vivo or in the administered drug formulation can act as haptens and are responsible for such hypersensitivity reactions. Subsequent exposure to the antigen causes mast cells to degranulate, releasing inflammatory mediators such as histamine and leukotrienes that promote bronchoconstriction, vasodilatation, and inflammation. Manifested in the skin, a type I hypersensitivity response results in a **wheal-and-flare reaction.** In the upper respiratory tract, symptoms of ''hay fever'' such as conjunctivitis and rhinitis develop, while in the lower respiratory tract, asthmatic bronchoconstriction may occur (see Chapter 46, Integrative Inflammation Pharmacology: Asthma).

A **type II** hypersensitivity response (**antibody-dependent cytotoxic hypersensitivity**) results when a drug binds to cells, usually red blood cells, and is recognized by an antibody, usually IgG. The antibody triggers lysis of the cell by enabling complement fixation or by the action of cytotoxic T cells or phagocytosis by macrophages. Type II responses are rare adverse responses to several drugs, including penicillin and **quinidine**.

**Type III** hypersensitivity responses (**immune complex-mediated hypersensitivity**) occur when antibodies, usually IgG or IgM, are formed against soluble antigens. The antigen–antibody complexes are deposited in tissues such as kidneys, joints, and lung vascular endothelium (Table 5-1). These complexes cause damage by initiating an inflammatory response called **serum sickness**, in which leukocytes and complement are activated within the tissues. For example, type III hypersensitivity can be caused by the administration of **antivenins,** horse serum proteins obtained by inoculating a horse with the venom to be neutralized. Examples of other drugs that may pose a risk of serum sickness are **buproprion** and **cefaclor**.

A **type IV** hypersensitivity response (**delayed-type hypersensitivity**) results from the activation of $T_H1$ and cytotoxic T cells. It most commonly presents as **contact dermatitis** when a substance acts as a hapten and binds to host proteins. The first exposure does not normally produce a response; however, subsequent dermal exposures can activate Langerhans cells, which migrate to local lymph nodes and activate T cells. The T cells then return to the skin and initiate an immune response. Well-known type IV hypersensitivity responses include the reactions to poison ivy and the development of latex allergies. Repeated exposure to a drug that the immune system recognizes as foreign can trigger a massive immune response. This ''cytokine storm'' can lead to fever, hypotension should, and even organ failure. Thus, physicians should consider possible immune reactions to any drug treatment, even those that have appeared to be safe in broader populations. In the case at the beginning of the chapter, Ms. G had fever and rash that were likely caused by a T-cell mediated hypersensitivity reaction to ciprofloxacin. Once this was recognized and the ciprofloxacin was stopped, her complication resolved as well.

**Autoimmunity** results when the organism's immune system attacks its own cells (see Chapter 44, Pharmacology of Immunosuppression). Several drugs and a number of other chemicals can initiate autoimmune reactions. **Methyldopa** can cause hemolytic anemia by eliciting an autoimmune reaction against the Rhesus antigens (Rh factors). Several other drugs, such as **hydralazine, isoniazid,** and **procainamide,** can cause a lupus-like syndrome by inducing antibodies to myeloperoxidase (hydralazine and isoniazid) or DNA (procainamide).

## IDIOSYNCRATIC TOXICITY

Idiosyncratic drug reactions are rare adverse effects for which no obvious mechanism is apparent. These idiosyncratic reactions are often thought to reflect unique individual genetic differences in the response to the drug molecule, possibly through variations in drug metabolism or immune response. As the classification denotes, idiosyncratic reactions are difficult to explain and often difficult to study in animal models, precisely because the genetic variation that may be causing the adverse response is not known. It is believed that the systematic study of patient variations in response to different drugs (pharmacogenomics) may help to elucidate the mechanisms that underlie idiosyncratic drug reactions.

# CONTEXTS OF DRUG TOXICITY

## DRUG OVERDOSE

The Swiss physician and chemist Paracelsus noted nearly 500 years ago that ''all substances are poison; there is not which is not a poison. The right dose differentiates a poison and a remedy.'' In some cases, such as a suicide attempt, the overdose of a drug is intentional. However, many more cases of overdose occur accidentally in both the hospital and outpatient setting. Adverse drug events due to accidental dosing errors are estimated to affect nearly 775,000 people each year, with associated hospital costs of $1.5 to $5.5 billion annually. This significant cost to both the patient and the health care system has led to significant changes in prescribing and dosing practices in an attempt to avoid such adverse events.

## DRUG-DRUG INTERACTIONS

As the population has aged and increasing numbers of patients have been prescribed multiple medications, the potential for drug-drug interactions has grown. Numerous adverse interactions have been identified, and the mechanisms often involve pharmacokinetic or pharmacodynamic effects. Drug-herb interactions are also an important subset of drug-drug interactions.

### Pharmacokinetic Drug-Drug Interactions

Pharmacokinetic interactions between drugs arise if one drug changes the absorption, distribution, metabolism, or excretion of another drug, thereby altering the concentration of active drug in the body. These mechanisms are discussed more extensively in Chapter 4, but reviewed here for emphasis.

As discussed in Chapter 4, drugs can *inhibit* or *induce* hepatic P450 enzymes. If two drugs are metabolized by the same P450 enzyme, the competitive or irreversible inhibition of that P450 enzyme by one drug can lead to an *increase* in the plasma concentration of the second drug. On the other hand, the induction of a specific P450 enzyme by one drug can lead to a *decrease* in the plasma concentrations of other drugs that are metabolized by the same enzyme.

In addition to altering the activity of P450 enzymes, drugs can affect the transport of other drugs into and out of tissues. As discussed in Chapter 4, the multidrug resistance 1 (MDR1) efflux pump transports drugs into the intestinal lumen. A drug that inhibits MDR1 can lead to an increase in the plasma concentration of other drugs that are normally pumped out of the body by this mechanism. Other transporters, such as the organic anion transporting polypeptide 1 (OATP1), mediate the uptake of drugs into hepatocytes for metabolism and the transport of drugs across the tubular epithelium of the kidney for excretion; both of these mechanisms promote clearance of drug from the body. Interactions of a drug or one of its metabolites with these classes of transporters can lead to inappropriately high plasma concentrations of other drugs that are handled by the same transporter.

A pharmacokinetic interaction can sometimes be desirable. For example, because **penicillin** is cleared via tubular-secretion in the kidney, the elimination half-life of this drug can be increased if the drug is given concomitantly with **probenecid**, an inhibitor of renal tubular transport. A second example is provided by the combination of **imipenem**, a broad-spectrum antibiotic, and **cilastatin**, a selective inhibitor of a renal brush border dipeptidase (dehydropeptidase I). Because imipenem is rapidly inactivated by dehydropeptidase I, coadministration of imipenem with cilastatin is required to achieve therapeutic plasma concentrations of the antibiotic.

A drug that binds to plasma proteins, such as albumin, may displace a second drug from the same protein to increase its free plasma concentration and thereby increase its bioavailability to target and nontarget tissues. This effect can be enhanced in a situation where circulating albumin levels are low, such as liver failure or malnutrition (decreased albumin synthesis) or nephrotic syndrome (increased albumin excretion).

### Pharmacodynamic Drug-Drug Interactions

Pharmacodynamic interactions arise when one drug changes the response of target or nontarget tissues to another drug. Toxic pharmacodynamic interactions can occur when two drugs activate complementary pathways, leading to an exaggerated biological effect. One example of such a drug interaction is provided by the coadministration of **sildenafil** (for erectile dysfunction) and **nitroglycerin** (for angina pectoris). Sildenafil inhibits phosphodiesterase type 5 (PDE5) and thus prolongs the action of cyclic GMP, and nitroglycerin stimulates guanylyl cyclase to increase cyclic GMP levels in vascular smooth muscle. Co-exposure to the two drugs increases cGMP to an even greater degree, increasing the risk of severe hypotension (see Chapter 21, Pharmacology of Vascular Tone).

A second example is the coadministration of antithrombotic drugs. After hip replacement surgery, patients are treated with prophylactic warfarin for a number of weeks to prevent the development of postoperative deep vein thrombosis. Because plasma warfarin concentrations may not reach a therapeutic level for several days, patients are sometimes coadministered low-molecular-weight heparin and warfarin during this time. As seen in the case of Ms. G, however, significant bleeding may result if the effects of the heparin and warfarin synergize to produce supratherapeutic levels of anticoagulation.

### Drug-Herb Interactions

The safety and efficacy of a drug may also be altered by co-exposure with various non-pharmaceuticals, such as foods, beverages, and herbal and other dietary supplements. Many herbal products are complex mixtures of biologically active compounds, and their safety and effectiveness have rarely been tested in controlled studies. The wide use of unregulated herbal products among the public should lead clinicians to inquire about patient use of such products.

The literature contains a number of reports of therapeutic failure of drugs taken in conjunction with herbal products, and some reports of toxicity. For example, the herbal preparation **ginkgo biloba** (from the tree of the same name) inhibits platelet aggregation. Simultaneous use of ginkgo and

**nonsteroidal anti-inflammatory drugs (NSAIDs)**, which also inhibit platelet aggregation, may increase the risk of bleeding. **Echinacea** products contain alkaloids that may deplete hepatic glutathione stores, increasing the risk of acetaminophen toxicity. In combination with **selective serotonin reuptake inhibitors**, **St. John's wort** may cause a mild serotonergic syndrome.

## PATHOLOGY OF DRUG TOXICITY

As illustrated in Figure 5-3, drugs and their metabolites can interact with a diverse array of receptors to mediate adverse effects in vivo. Sometimes the parent, unmetabolized drug causes toxicity, but often a metabolite of the drug reacts with proteins, DNA, and oxidative defense molecules (such as glutathione) to cause cellular damage and other adverse reactions.

### TEMPORAL ASPECTS OF TOXICITY

Drug toxicity can occur on many different time scales. **Acute toxicity** results from a single exposure to a drug, with adverse effects resulting in minutes to hours. Examples of acute toxicity are the massive hepatic necrosis that can occur after a single toxic dose of **acetaminophen** and exacerbations of acute bronchoconstriction in patients with **aspirin**-intolerant asthma. Many immune-mediated adverse effects occur within hours to days after administration of the drug.

**Chronic toxicity**, on the other hand, refers to an adverse effect of a drug that occurs over a prolonged period of time. Long-term treatment with dopamine receptor antagonists for schizophrenia can result in tardive dyskinesia, an unfortunate on-target adverse effect that results from the critical role of dopamine as a neurotransmitter in the motor cortex (see Chapter 12, Pharmacology of Dopaminergic Neurotransmission).

Sometimes the toxicity of a drug is not revealed until it has been on the market for a number of years. For example, the insulin-sensitizing agent **troglitazone** was removed from the market only after it was noted that approximately 1 in 10,000 patients taking the drug died from acute liver failure.

**Hormone replacement therapy** for postmenopausal women is another important example of chronic toxicity. While the administration of estrogens significantly reduces several of the effects of menopause (e.g., hot flashes, vaginal atrophy, and skin thinning), continued activation of the estrogen receptor pathway can lead to endometrial cancer. As discussed below, prolonged exposure to certain drugs or their metabolites can lead to fibrosis, organ dysfunction, and birth defects as well as cancer.

### CELLULAR TOXICITY: APOPTOSIS AND NECROSIS

Cells have mechanisms for damage repair, and toxic exposures that cause cellular dysfunction do not necessarily lead to cell death. One example of macromolecular damage repair is the reduction of oxidized thiol groups on proteins by **thioredoxin** and **glutaredoxin**. Denatured proteins can be refolded by molecular chaperones, such as heat shock proteins. DNA damage, such as adduct formation due to covalent binding of cancer cytotoxic drugs to double-stranded DNA or to specific nucleotides, can be reversed by DNA repair mechanisms. In some cases, chronic exposure to DNA-damaging drugs can overwhelm these repair mechanisms, leading to mutagenesis, carcinogenesis (see below), or cell death.

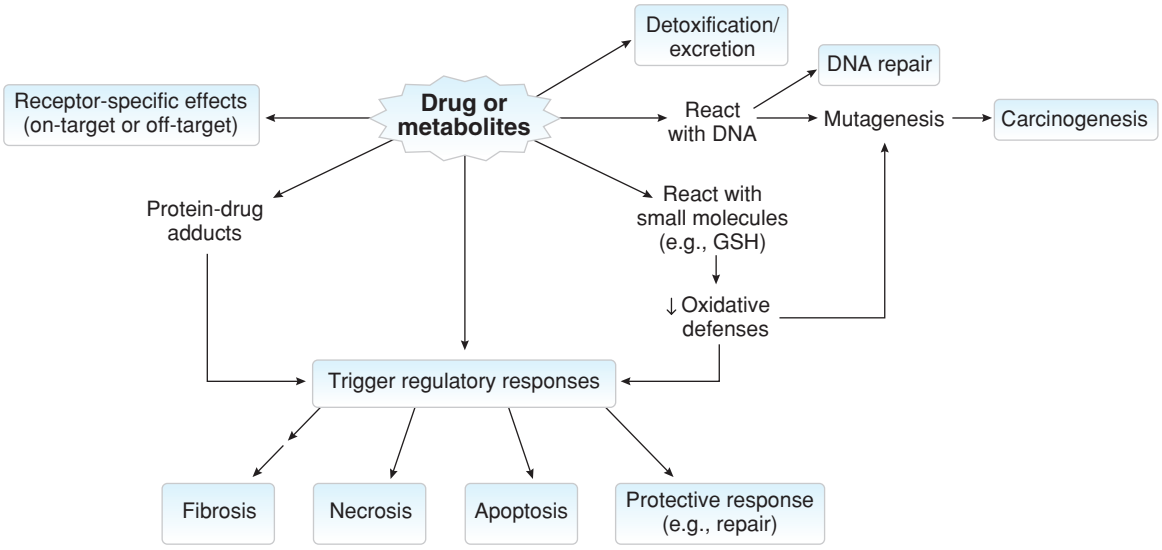


**Figure 5-3. Mechanisms of drug toxicity.** A drug or its metabolites or both interact with specific receptors to mediate on-target or off-target adverse effects. In addition, metabolites can be detoxified and excreted, or can react with a variety of macromolecules including DNA, small antioxidants such as glutathione (GSH), or cellular or plasma proteins. The formation of unrepaired or misrepaired DNA adducts is often mutagenic and may lead to cancer. The impairment of oxidative defenses can lead to inflammation and cell death (apoptosis or necrosis). The formation of drug-protein adducts can trigger immune responses that can damage cells and tissues (see Fig. 5-2). Regardless of the mechanism of damage, a gradation of acute responses from protective to apoptosis (programmed cell death) and necrosis can result, depending on the extent of damage and the temporal and dose relationships. Chronic inflammation and repair can also lead to tissue fibrosis.

Depending on the severity of the toxic insult, a cell may undergo **apoptosis** (programmed cell death). Apoptosis allows the cell to undergo ordered self-destruction by the coordinated activation of a number of dedicated proteins. Apoptosis can be beneficial when it is able to eliminate damaged cells. Inhibition of apoptosis is common in many cancer cells.

If the toxic insult is significant enough that ordered cell death cannot be accomplished, the cell undergoes **necrosis.** Necrosis is characterized by enzymatic digestion of cellular contents, denaturation of cellular proteins, and disruption of cellular membranes. While apoptotic cells undergo cell death with minimal inflammation and disruption of adjacent tissue, necrotic cells attract inflammatory cells and can damage nearby healthy cells.

## ORGAN AND TISSUE TOXICITY

### Fibrosis

The response to injury after cellular damage is largely determined by the regenerative capacity of the target organ. In organs that are capable of regeneration, such as the liver, repeated insults may be followed by regeneration. Over time, however, cellular injury can lead to excessive deposition of collagen and extracellular matrix proteins, causing **fibrosis.** Organ systems with limited or no regenerative function, such as cardiac and neuronal tissue, lose function as tissue is destroyed.

Chronic toxicity in the lungs can be manifested as both loss of function and fibrosis. Emphysematous changes are caused by the destruction of pulmonary **elastin** by neutrophil-derived **elastase.** Agents that elicit an inflammatory response, such as those found in cigarette smoke, can lead to **emphysema. Pulmonary fibrosis,** on the other hand, is caused by excessive and abnormal collagen deposition in the alveolar interstitium. The antiarrhythmic drug **amiodarone** and the chemotherapeutic agent **bleomycin** are known to cause pulmonary fibrosis; therefore, these drugs are contraindicated in patients with existing disease of the lung parenchyma.

Because of its central role in drug metabolism, the liver is particularly susceptible to toxic insult. Drugs or their metabolites can injure hepatocytes by disruption of calcium homeostasis (leading to cell membrane blebbing and cell lysis), canalicular injury, mitochondrial injury, and induction of apoptosis. Repeated exposure to toxic drug metabolites may cause drug-induced liver disease, a spectrum of clinical injuries that include inflammation **(hepatitis),** necrosis, fibrosis (in this case, **cirrhosis**), **cholestasis**, and **liver failure**. Nonalcoholic steatohepatitis (NASH) can also be an adverse drug effect; NASH may be caused, in part, by the release of cytokines after hepatocellular injury.

The kidney is also susceptible to toxic insult because it concentrates many xenobiotics for excretion. Nephrotoxicity may manifest as alterations in renal hemodynamics, tubular damage and obstruction, glomerular nephropathy, and interstitial nephritis. When a sufficient number of nephrons are lost, compensatory hemodynamic changes increase glomerular pressures, leading to glomerular sclerosis, further glomerular loss, diminished glomerular filtration rate, and progressive renal failure. Examples of drugs that can cause renal failure include certain antibiotics, NSAIDs, and angiotensin-converting enzyme inhibitors.

### Carcinogenesis

**Carcinogenesis** occurs when a normal cell transforms to a neoplastic cell and the neoplastic cell undergoes clonal expansion. A **carcinogen** is a chemical, physical, or biologic insult that acts by causing DNA damage (mutations). Carcinogenesis is a complex process, involving multiple genetic changes, that usually takes place over years to decades in human beings.

The development of cancer requires sequential genetic changes (the first of which is termed **initiation**) and epigenetic changes (characterized as **promotion** and **progression**). **Initiators** act by damaging DNA, interfering with DNA replication, or interfering with DNA repair mechanisms. Most initiators are reactive species that covalently modify the structure of DNA, preventing accurate replication and, if unrepaired or misrepaired, leading to a mutation(s). If the mutation(s) affects a gene(s) that controls cell cycle regulation, neoplastic transformation may be initiated.

Carcinogenesis may involve mutations in at least two types of genes, **proto-oncogenes** and **tumor suppressor genes** (of which there are several dozen). **Proto-oncogenes** encode proteins that encourage cell cycle progression. **Tumor suppressor genes** often encode proteins responsible for inhibiting growth and cell cycle progression. Tumor suppressors can down-regulate important signaling pathways for growth, such as the phosphoinositide 3-kinase pathway, or they may directly suppress cell cycle progression. A mutation in a tumor suppressor gene thus encourages neoplastic growth by removing the normal inhibitory checks on cell growth.

An important on-target adverse effect of cytotoxic alkylating agents used in cancer chemotherapy (**chlorambucil**, **cyclophosphamide**, **melphalan**, **nitrogen mustards**, and **nitrosoureas**) is that they not only kill cancer cells but also damage normal blood cell progenitors. These agents are therefore toxic to bone marrow and can cause myelodysplasia and/or acute myeloid leukemia (AML). Indeed, 10% to 20% of cases of AML in the United States are secondary to treatment with such cancer drugs.

**Tamoxifen**, an estrogen receptor antagonist, is an effective treatment in patients with breast cancer. While tamoxifen is an antagonist of estrogen receptors in the breast, it acts as a *partial agonist* in other tissues that express the estrogen receptor, most notably the uterus. Therefore, an adverse effect of breast cancer treatment with tamoxifen can be the development of endometrial cancer. Newer estrogen receptor antagonists, such as **raloxifene**, do not stimulate uterine estrogen receptors and may therefore be safer drug choices for treatment or prevention of breast cancer.

### Teratogenesis

Drugs given to pregnant women may have serious, unwanted effects on the health of the fetus. **Teratogenesis** is the induction of defects in the fetus, and a **teratogen** is a substance that can induce such defects. Exposure of the fetus to a teratogen necessarily involves maternal exposure. For this reason, the interaction between maternal tissues and the terato-

genic drug is important to the severity of fetal exposure. In particular, the fetus's exposure to the agent is determined by maternal absorption, distribution, metabolism, and excretion of the drug, by the toxification of inert precursors to toxic metabolites in maternal tissues, and by the ability of the active teratogen to cross the placenta. These issues are further discussed in Box 5-1.

Because development of the fetus is precisely timed, the teratogenic effect of any substance is dependent on the developmental timing of the exposure. Thus, drugs that might have few adverse effects on the mother may cause substantial damage to the fetus. For example, **retinoic acid** (vitamin A) possesses significant on-target teratogenic toxicity. Retinoic acid activates nuclear retinoid receptors (RAR) and retinoid X receptors (RXRs) that regulate a number of key transcriptional events during development. In humans, **organogenesis** generally occurs between the 3rd and 8th weeks of gestation. It is during the period of organogenesis that teratogens have the most profound effect. Before the 3rd week, most toxic compounds result in death to the embryo and spontaneous abortion, whereas after organogenesis, teratogenic compounds may affect growth and functional maturation of organs but do not affect the basic developmental plan. Given the severity of birth defects that can occur, women who take RAR/RXR agonists such as **isotretinoin** for the treatment of acne must sign FDA-mandated informed consent forms to demonstrate that they are aware of the risk of serious drug-related birth defects.

Another example of an on-target teratogenic effect is *in utero* exposure of the fetus to ACE inhibitors. Although ACE inhibitors were previously not contraindicated in the first trimester of pregnancy, recent data indicate that fetal exposure during this period significantly increases the risks of cardiovascular and central nervous system malformations. ACE inhibitors can cause a group of conditions including oligohydramnios, intrauterine growth retardation, renal dysplasia, anuria, and renal failure, reflecting the importance of the angiotensin pathway on renal development and function.

## Conclusion and Future Directions

This chapter has presented a mechanism-based approach to understanding drug toxicity. Using these concepts, pharma-

### BOX 5-1. Application to Therapeutic Decision-Making: Drugs in Pregnancy
by Vivian Gonzalez Lefebre and Robert H. Rubin

Pregnancy introduces several special considerations in therapeutic decision-making. These factors include the health of the woman as well as the delivery of a healthy baby; the altered pharmacokinetics and pharmacodynamics associated with pregnancy; and a lack of information regarding the effects of drugs on the developing fetus.

Most drugs are labeled with disclaimers regarding their use during pregnancy. This paucity of data makes it difficult to estimate the risk-benefit ratio for use of a drug in pregnancy. Physicians depend partly on animal studies and epidemiologic studies (which may be fraught with confounding factors) to establish the teratogenic potential of a drug. **Teratogenesis** refers to the structural or functional dysgenesis of developing organs; each tissue and organ of a fetus has a critical period during which its development may be disrupted by the administration of a teratogenic drug.

The FDA has established a system that classifies drugs on the basis of human and animal data, ranging from class A (safe) to class X (proven teratogenicity) drugs. For example, methyldopa has an excellent safety record in the treatment of hypertension during pregnancy; it is therefore considered a class A drug for use in pregnancy. In contrast, ACE inhibitors (another class of antihypertensives) are absolutely contraindicated during the second and third trimesters of pregnancy (class X) because of their association with fetal and neonatal renal dysfunction, including oligohydramnios, neonatal anuria, and renal failure. This classification system is helpful when a drug fits one of the two extremes; classifications in the middle, though, are often confusing and ambiguous. Therefore, the physician relies heavily on clinical judgment to decide whether a drug's potential benefits to the mother outweigh the risk to the fetus. Often, physicians err on the side of not treating.

The following issues should be addressed when prescribing a drug to a pregnant woman:

- the probability of placental transfer of the drug, given the drug's molecular weight, charge, hydrophobicity, and potential for carrier-mediated transport into or out of the placental circulation
- a physiologic explanation for how the drug could affect the fetus, e.g., through effects on organogenesis, organ development, organ function, or a delivery complication
- the risk to both fetus and mother associated with the underlying maternal illness for which the drug is being considered

When assessing the risk-benefit ratio for administering a drug, it should also be recognized that there are drugs that have teratogenic effects in animals when administered in high doses (e.g., aspirin) may not present a risk to humans when given in therapeutic doses. Other drugs, such as thalidomide and 13-cis-retinoic acid, are teratogenic in both animals and humans. Furthermore, it is important to remember that the population baseline risk of birth malformations is 3% to 5%. When appropriate, drugs that have proven effective for treating a patient's underlying condition should be continued, and experimenting with new drugs should be avoided. Finally, to minimize fetal risk, drugs should be prescribed at the lowest therapeutic dose, taking into account the normal metabolic and physiologic changes that occur during pregnancy (e.g., placental metabolism; increased water retention, renal filtration, heart rate, and plasma volume).

ceutical companies are investigating how to predict which patient populations will be most susceptible to an adverse drug reaction. One approach is to find correlations between individual single nucleotide polymorphisms (SNPs) and possible adverse reactions by comparing the SNPs of patients who have adverse reactions with those who do not. The identification of patients with genetic variants of the molecular target (and closely related targets) of a drug could also provide useful information about patients who might be more likely to experience adverse effects.

Certain pharmacokinetic drug-drug interactions may be better predicted with the advent of P450 chips that allow investigators to screen many compounds for the ability to inhibit specific P450 enzymes. Drug-related cellular toxicity is now being predicted by the ability of drugs to bind important antioxidants, such as glutathione, in large-scale preclinical drug screening. During clinical trials, plasma alanine aminotransferase (ALT) levels are measured to approximate the risk of hepatotoxicity that could occur in a broader population. An ALT reading three times greater than normal is considered to be predictive of impending liver damage. Vigilant postmarketing surveillance of a drug in a large population can also help to identify rare adverse drug reactions.

The therapeutic benefit of a drug must always be weighed against its toxic effects in the context of a patient's disease, treatment, and genetic makeup. The use of evolving biomarkers and genetic tests may help to identify patients at greatest risk for adverse drug reactions.

## *Suggested Reading*

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