Chapter

13

Adverse Drug Reactions

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OUTLINE

13.1 INTRODUCTION

Adverse drug reactions (ADR) are far more commonplace than one would think. It is estimated that ADRs represent the fourth leading cause of death in the United States and Canada behind heart disease, cancer, and stroke. Further, it is estimated that ADRs are the sixth leading cause of death worldwide. Recent meta-analysis of prospective ADR studies estimates that over 180,000 Americans will die from ADRs and over one million will be injured from ADRs in 2008. Although these data are controversial and the actual incidence of ADRs is impossible to assess, there is no doubt that ADRs have a significant impact on both the healthcare delivery and the drug development industries.

The monetary costs to society due to these ADRs are equally hard to assess accurately, but recent studies have estimated the costs to range from $75 to $180 billion each year for adults alone. When compared to the costs of treating diseases such as diabetes ($45 billion), cardiovascular disease ($120–150 billion), or cancer ($130–195 billion) we begin to truly realize the impact of this aspect of pharmacology on healthcare delivery. Yet another way to demonstrate the impact of ADRs is to realize that approximately 5% of all hospital admissions are a direct result of ADRs, and unfortunately incidence has not changed over the past 30 years.

If ADRs are such a drain on our healthcare delivery system, what are ADRs? The World Health Organization has put forth the definition of ADR as "any response to a drug which is noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis or treatment." In other words, an ADR could be an unexpected or unwanted effect that is a direct extension of the mechanism of drug action; in an organ system that is not the target of drug therapy; an allergic response; a hypersensitive response; an idiosyncratic response (one totally unpredictable); or a drug interaction with unexpected results. In each case the ADR represents an unwanted toxic effect as a result of taking a given drug or set of drugs. The purpose of this chapter is discuss in detail the various types of ADRs using specific examples to demonstrate the types of ADRs that can be encountered when drugs are administered as well as factors that may affect the incidence or severity of a given ADR.

13.2 TYPE A ADRs

13.2.1 How Are Type A Reactions Caused?

Type A reactions represent approximately 70 to 80% of all ADRs and are both dependent on the dose of drug administered and related to the desired pharmacological effect of the drug administered. Since these

types of ADRs are in fact a direct extension of the desired drug action, such ADRs are often preventable and predictable. A classic and predictable form of toxicity is one that results from a direct extension of the therapeutic mechanism of action of the drug. If a patient is taking an immunosuppressant following organ transplantation and the patient suffers an increased incidence of infection, this is a predicted adverse effect or toxicity since the drug is designed to lower the immune system of the patient. Similarly, a patient taking a drug to treat hypertension suddenly suffers from orthostatic hypotension; this too is a direct extension of the therapeutic use of the drug and the dizziness may well have resulted from drug-induced hypotension.

The major step forward that moved organ transplantation from a potentially important therapeutic modality to a routinely used surgical technique was the development drugs that could suppress the immune system of the patient. With the advent of this class of drugs it is now possible to control the recipient's immune system such that the donated organ is far less likely to be rejected by the recipient. Unfortunately, the suppression of the immune system hampers the ability of the organ recipient to fend off infectious diseases and increases the risk of infection for this individual. Thus, increased number of infections following organ transplantation would be expected.

In a related vein, most anticancer drugs kill cells in mitosis. Although these drugs have had a dramatic effect in certain tumors, they do have very serious ADRs and are considered the most dangerous of drugs given to humans with respect to toxicities. One such toxicity is immunosuppression due to the killing of actively dividing immune cells by the drugs and the increased risk of serious infections. In this case however the immunosuppression is an unwanted side effect, not desired pharmacological effect as described for the immunosuppressants.

Hypertension is often referred to as the silent killer since a person can be totally unaware of dangerously high blood pressure. If life style changes do not control hypertension, then pharmacological approaches are required. Since blood pressure is a product of the amount of blood pumped by the heart (cardiac output) and the force required to push the blood through the vasculature (peripheral resistance), drugs have been developed to modify both components of blood pressure. Drugs can decrease cardiac output or lower peripheral resistance to lower blood pressure and in either case there is the potential of lowering either parameter excessively and inducing hypotension. In fact, with the case of certain vasodilators (decreasing peripheral resistance) there is a risk of orthostatic hypotension in which patients standing too quickly can actually suffer dizziness or even loss of consciousness. Here again, the ADR is a direct extension of the desired effect of the drug.

Patients with congestive heart failure must have increased cardiac output while decreasing the workload on the damaged heart. The cardiac glycosides are most frequently used to enhance cardiac output. This class of drugs appears to work by increasing the calcium concentration of the myocardiocyte and thus increase the force of contraction by the cardiac muscle. Thiazide diuretics enhance urine output and thereby decrease peripheral resistance and workload placed on the heart. The thiazides function by increasing potassium and water excretion from the body and can induce hypokalemia, which can result in serious ADRs in patients treated with the cardiac glycosides. The reason for this rests on the fact that as extracellular potassium concentrations decrease (hypokalemia), the effect of the cardiac glycosides on calcium levels in the heart increases. With hypercalcemia in the cardiac muscle comes the risk of cardiac arrhythmias and even cardiac fibrillations. These ADRs can occur if a patient ingests excessive amounts of the cardiac glycoside (here a direct extension of the desired pharmacological effect the cardiac glycosides); however, the combination of cardiac glycosides and the thiazide diuretics can also increase the risk of such ADRs through the mechanism just described.

We recently reported on yet another type of ADR resulting from drug interactions. Second-generation antihistamines are less sedative than first-generation antihistamines because the levels of the former drug in the CNS are less than that of the latter type of antihistamine. It has been reported that the second-generation antihistamines do not cross the blood–brain barrier (see Chapter 12 for a discussion of this anatomical feature). However, when we administered desloratidine (a second-generation antihistamine) to mice in combination with verapamil (drug that inhibits a membrane protein found in the blood–brain barrier that effluxes drug from the CNS back into the blood), it resulted in a sedation of mice that was equivalent to that seen in mice treated with a classic first-generation, sedating antihistamine. Here the effects of one drug resulted in an ADR not thought to occur in the other drug.

Although this is a relatively mild ADR, such interactions have the potential to cause catastrophic ADRs. For example, an important anticancer drug is the plant product vincristine, which stops cells from dividing by interrupting microtubule polymerization. This prevents chromosomal segregation and cell division in the M phase of the cell cycle. A significant ADR with vincristine is a potentially irreversible neurotoxicity, thought to be related to the microtubular effects of the drug (thus an extension of the desired drug activity). Approximately two to three times per year vincristine is administered accidentally intrathecally in cancer patients and is a uniformly fatal ADR. Vincristine is an excellent substrate for the membrane-bound efflux pump discussed. This protein is also expressed on the plasma membrane of certain drug resistant cancer cells and is thought to be a mechanism of multidrug resistance (MDR) by preventing intracellular drug accumulation (see Chapter 15 for a discussion of drug resistance). Our results suggest that the use of inhibitors of the membrane pump such as that discussed earlier has the very possibility of increasing CNS levels of vincristine and could result in serious neurotoxicities (thus a toxic risk enhanced through drug interactions).

13.2.2 How Are the Risks of Type A ADRs Reduced?

During the preclinical and premarketing testing of the drug under study, a great deal of information has been accumulated regarding the doses to be used, the schedule and duration of drug administration, the route of administration, drug absorption, pharmacokinetics, and pharmacodynamics. From these data, the dose, the route of administration, and treatment schedule are designed to provide the greatest therapeutic benefit with the least risk of toxicity to the individual taking the drug. Further, during the development of a given drug, the therapeutic index (discussed elsewhere in the text) can be calculated for that drug. A drug with a small therapeutic index is one in which the serum concentration required to attain a therapeutic benefit is close to the serum level expected to cause some toxicity. A drug with a large therapeutic index has a much larger difference between serum levels needed for therapeutic benefit and the toxic serum levels. Thus, a drug with a small therapeutic index is much more likely to cause adverse effects during therapeutic use (the best examples here are the anticancer drugs) whereas the drug with a large therapeutic index (drugs such as penicillin) are much safer to use.

Keep in mind, however, that there can be a wide variance in response to a given drug among a given population. These variances can be related to a number of factors including gender, age, race, genetics, diet, underlying diseases, and so on. Associated with these variances in response within a given population is the variance in dose needed to provide therapeutic benefit in a given member of that population and a dose that can cause an ADR in that individual.

13.2.3 The Concept of Dose Response in Type A ADRs

A characteristic described in detail elsewhere in this text is the concept of dose response. Briefly, as the dose of a given administered drug increases, the pharmacological effect likewise increases (Figure 13.1). Note that once a specific dose has been exceeded no further increase in the desired pharmacological effects is expected. This plateau is dependent upon a number of factors and is critical to remember because once the plateau dose is reached the only possible outcome of increasing the dose administered is an increased likelihood of ADR incidence and severity. There is another equally important dose response curve to take into consideration when evaluating the use of a given drug and that is the toxicity dose response curve. Note that in this figure the shape of the efficacy dose response curve is identical to that of the toxicity dose response curve, but the curve is shifted to the left with respect to the toxicity dose response curve. This situation usually indicates that the efficacy and the toxicity arise from the same mechanism. Therefore this ADR is a direct extension of the desired efficacy of the drug.

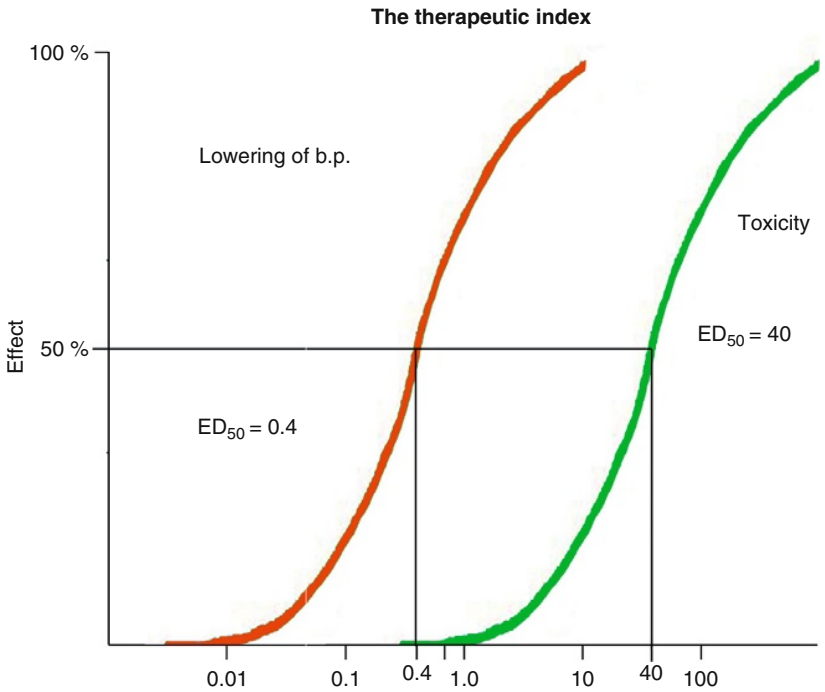

Figure 13.1 Dose response curve for both efficacy and toxicity.

13.2.4 The Importance of the Therapeutic Index in Type A ADRs

The therapeutic index for a given drug can be calculated using a variety of ratios of efficacy and toxicity. As shown in this example the Therapeutic Index (TI) would be:

TI = TD50/ED50 in this case ED50 = 0.4 mg/kg and TD50 = 40 mg/kg thus 40/0.4 = 100
TI = TD10/ED 90 in this case TD10 = 10mg/kg and ED90 = 4 mg/kg and TI = 2.5

As is shown here, the more conservative approach results in a much smaller TI, which indicates that the drug is much less safe than the previous calculation, but may be a more realistic assessment of the risk of a given drug to cause an ADR in a given population.

13.2.5 Population Distribution and Drug Sensitivity

The therapeutic index is calculated for the average person taking the drug, and for approximately 95% of the patients treated with the drug, we can anticipate the type and extent of drug toxicity that might be encountered. For the remaining 5% of the patients, half will be resistant to the therapeutic benefit of the drug, thus requiring increased drug dosage to attain the desired response, if possible. These individuals are referred to as hyporesponsive. For these individuals there may an equal resistance to the toxic effects of the drug, and thus no increased risk of toxicity exists. In other patients hyporesponsiveness to the therapeutic benefit is *not* accompanied by a hyporesponsiveness to the toxic effects of the drug; in these patients increased dosage is risky or even inappropriate. The remaining 2.5% of the population is referred to as hyperresponsive and require significantly less drug to elicit a given response. These individuals are at risk of ADRs at doses recommended for the general population.

During the clinical development of a drug through Phase 1, 2, and 3 studies the range of sensitivity to the drug from hypo- to hypersensitivity is identified and dose range is well defined prior to marketing the drug. Unfortunately, this is not always the case and unexpected ADRs are encountered. With the advent of pharmacogenomics, it is possible that within the foreseeable future these problems will be overcome as we design individualized therapies based on the genomic information for a given patient.

The reasons for hypo- and hypersensitivity are discussed elsewhere in the textbook; however, the terms are based on population distribution as shown in Figure 13.2.

Within any given population there exists variation in the sensitivity of the individual to a given drug. Figure 13.2 describes the typical bell-shaped curve and indicates a Gaussian distribution of the population with respect to the response of that population to a given dose of drug administered to that population. This figure could also describe the dose of drug required to attain a given response to that drug (this is the basis of the dose response curve shown earlier) within any population there are individuals who respond to low doses of the drug whereas others require a much higher dose of drug to attain the same response, but approximately two-thirds of the population respond similarly to a relatively narrow dose range. The reasons for this variation were described previously.

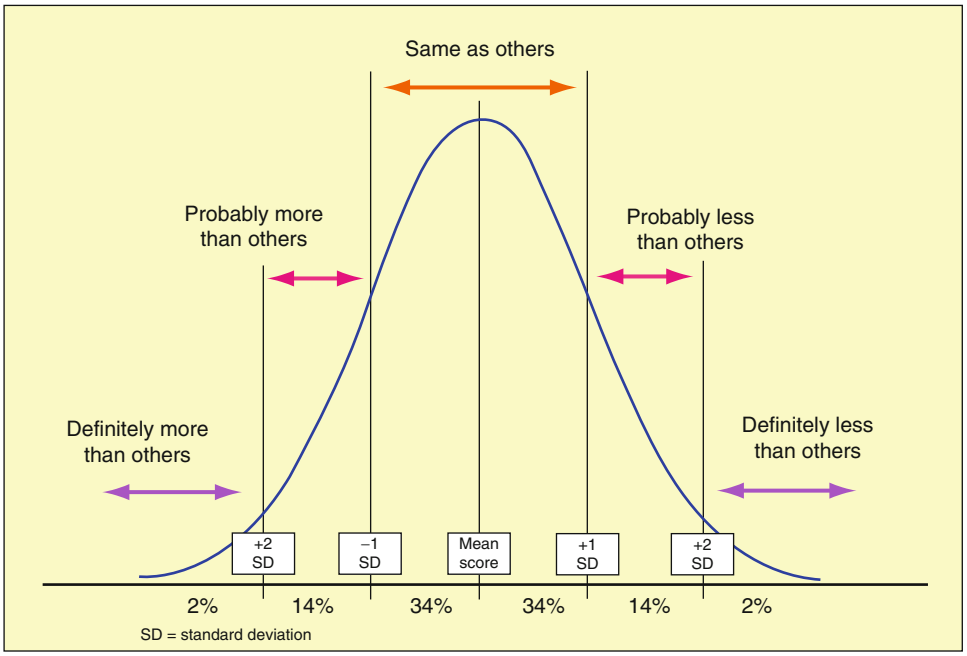

Figure 13.2 Population distribution with respect to drug sensitivity.

13.3 EXAMPLES OF TYPE A ADRs

As stated earlier, Type A ADRs are often extensions of the desired pharmacological effects and can often be predicted. The actual dose or duration of exposure to the drug required to induce an ADR cannot be accurately predicted given the Gaussian distribution of a human population. A perfect example of Type A ADRs, sometimes with life-threatening consequences, is myelosuppression following cytotoxic chemotherapy. Most anticancer drugs are designed to kill dividing cells, and since the bone marrow has a large population of dividing cells, it is not surprising that patients treated with such drugs are at risk of myelosuppression. Noncytotoxic drugs may also cause myelosuppression, but these toxicities most often are categorized as Type B ADRs.

The bone marrow must maintain proper levels of circulating peripheral blood cells. The average sized adult human has about 3.5 kg of marrow tissue distributed throughout the axial skeleton, which produces some 2.5×10^9 red cells, 2.5×10^9 platelets, and 1×10^7 white blood cells daily. There can be considerable daily fluctuations according to demand and these fluctuations are regulated by a variety of growth and maturation factors. The therapeutic efficacy of most anticancer drugs relies on interference with cellular mitotic activity. Nonmalignant cells usually recover from these toxic effects if drug is removed and subsequent rounds of therapy can be initiated following recovery.

During the interval of myelosuppression the patient is at risk of anemia, bleeding problems, and loss of immune protection, depending on the drug(s) being administered to the patient. Although these toxicities are dangerous, they are reversible and as stated previously, once the patient has recovered subsequent drug regimens can be administered. The therapeutic advantage of these drugs may rest in the fact that most malignant cells recover from the toxic effects of anticancer drugs more slowly than do nonmalignant cells, hence the concept of aggressive therapy followed by a rest period. During the aggressive stage cell kill both malignant and nonmalignant cells are killed, whereas during the rest period nonmalignant cell levels return to normal and the malignant cells remained suppressed.

As will be discussed under Type B ADRs there are other toxicities associated with selected cytotoxic drugs that damage tissues without a high mitotic index. These types of toxicities are unexpected, occur in specific organs depending on the drug in question, most often are irreversible, and most often are referred to as organ directed dose limiting toxicities. Since these toxicities were not expected as they occur in organs with a low mitotic index, these organ directed toxicities were not appreciated until a large number of patients had been treated with the drug. Once these toxicities were recognized, ways to prevent or at least minimize the risk or extent of toxicity were developed, but the overall efficacy of anticancer drugs causing organ directed toxicities remains compromised.

This raises an interesting problem regarding the classification of such toxicities. Some apparently Type B toxicities may become more appropriately classified as predictable Type A ADRs for individuals having certain constitutional risk factors, once the mechanism of toxicities are elucidated and risk factors become better understood. An in-depth discussion of such is beyond the scope of this textbook, but the role of genetic make-up and drug toxicity, especially those exceedingly rare types of toxicity, are becoming increasingly better understood as our appreciation and understanding of the human genome increases. Again, this is another excellent example of how pharmacogenomics will play an increasingly important role in the treatment of disease.

Aspirin, or acetylsalicylic acid, has been used for more than 100 years for its analgesic, antipyretic and anti-inflammatory activities. More recently an array of NSAIDs have been developed and introduced into the clinic. For the most part these drugs are well tolerated, but a variety of Type A ADRs, some of which can be life threatening, have been reported for these drugs. An important mechanism of action of the NSAIDs efficacy is the inhibition of the enzyme cyclo-oxygenase 2 (COX-2), which prevents the overproduction of prostaglandins and decreases the pain, fever, and inflammation associated with COX-2 activity.

Until recently all NSAIDs inhibited both COX-1 and COX-2 enzymes. The problem with this effect is the that COX-1 produces low levels of prostaglandins associated with homeostasis whereas COX-2 produces high levels of prostaglandins associated with the inflammatory process. As a result conventional NSAIDs have the capacity to cause such side effects as peptic ulcers and gastritis due to the inhibition of COX-1 and thus are an extension of the drug action. Less frequent ADRs but still Type A ADRs include respiratory distress, NSAID-induced asthma and rhinitis, and urticaria in individuals with no underlying risk factors. These remain type A ADRs since these toxicities appear to be related to the decreased prostaglandin levels resulting from COX-1 inhibition.

Given that the overwhelming evidence indicates that the most frequent toxicities observed with traditional NSAIDs are a consequence of COX-1 inhibition, the industry has struggled to develop a COX-2 selective inhibitor. To date four such drugs have been approved: These drugs entered the market with a great deal of fanfare but as clinical use increased a troubling increase in cardiovascular-related disorders, including strokes, clots, and heart attacks was noted. Vioxx subsequently has been removed from the market but the remaining two are still marketed. These relatively rare toxicities are considered to be Type B ADRs and are discussed later in this chapter. Other Type B ADRs associated with NSAID use are cutaneous and pulmonary in nature. These ADRs appear to mediated through IgE production and are also discussed later in the chapter.

An important consideration when discussing ADRs is the role of drug metabolism in drug toxicity. Often, the parent drug is vastly different from its metabolites

with respect to efficacy and toxicity. Due to large number of such events we will not discuss all metabolically induced ADRs. Rather we will provide a limited number to provide some insight into interaction between drug metabolism and Type A ADRs (a similar discussion will be presented later in the chapter regarding Type B ADRS).

Cholesterol-lowering drugs have been a major mainstay for controlling the cholesterol levels in patients presenting with hypercholesterolemia. The tolerability of these drugs during long-term administration is an important issue since hypercholestolremia is a chronic disease. Adverse reactions involving skeletal muscle are not uncommon, and sometimes serious adverse reactions involving skeletal muscle such as myopathy and rhabdomyolysis may occur, requiring discontinuation of the drug. Occasionally, arthralgia, alone or in association with myalgia, has been reported. We will focus on HMG-CoA reductase inhibitor-related musculoskeletal system toxicities. Cytochrome P450 (CYP) 3A4 is the main isoenzyme involved in the metabolic transformation of HMG-CoA reductase inhibitors. Individuals with both low hepatic and low gastrointestinal tract levels of CYP3A4 expression may be at an increased risk of myotoxicity due to potentially higher HMG-CoA reductase plasma concentrations.

The next example addresses two issues regarding metabolic-induced drug toxicity—the role of drug metabolism in ADRs and the effect of age on metabolism. ADRs can vary depending on the age of the individual. For example children often respond differently to a drug than do adults. Some of these differences are related to differences in liver metabolism. Altered drug disposition in the developing child occurs as a result of both biochemical and physiological changes. The clearance of many drugs is dependent on their biotransformation in the liver and small bowel and consequently is developmentally determined by a number of factors including both the activity and abundance of enzymes involved in Phase 1 and 2 drug metabolism. Altered drug metabolism can lead to the development of adverse effects in neonates and small infants that are not generally seen in the adult population. For instance, the altered metabolism of sodium valproate in children under 3 years of age is thought to be responsible for a higher incidence of hepatotoxicity; the impaired metabolism of chloramphenicol in neonates has resulted in the grey baby syndrome (cyanosis and respiratory failure); and metabolic acidosis following the use of propranolol in the critically ill child may be due to altered drug metabolism.

On the other extreme the elderly represent a challenge regarding the prediction of ADRs. Older people are major consumers of drugs and because of this, as well as comorbidity and age-related changes in pharmacokinetics and pharmacodynamics, they are at risk of associated adverse drug reactions. Although age does not alter drug absorption in a clinically significant way, and age-related changes in volume of drug distribution and protein binding are not of concern in chronic therapy, reduction in hepatic drug clearance is clinically important. Liver blood flow falls by about 35% between young adulthood and old age, and liver size decreases by about 24 to 35% over the same period. First-pass metabolism of oral drugs avidly cleared by the liver and clearance of capacity-limited hepatically metabolized drugs fall in parallel with the fall in liver size, and clearance of drugs with a high hepatic extraction ratio falls in parallel with the fall in hepatic blood flow. In normal aging, in general, activity of the cytochrome P450 enzymes is preserved, although a decline in frail older people has been noted, as well as in association with liver disease, cancer, trauma, sepsis, critical illness, and renal failure. Because the contribution of age, comorbidity, and concurrent drug therapy to altered drug clearance is impossible to predict in an individual older patient, it is wise to start any drug at a low dose and increase this slowly, monitoring carefully for beneficial and adverse effects.

13.4 AVOIDING TYPE A ADRs

Here the adage "an ounce of prevention is worth a pound of cure" rings so true. That means careful defining of dose, treatment schedule, and likely toxicities during the development of a drug is vitally important. These values are defined during drug development using data obtained from a number of clinical trials usually performed throughout the world. Careful and accurate reporting of all data obtained from such studies is essential to minimize ADRs once the drug has been approved for marketing. Further, continued surveillance for ADRs following drug marketing approval (Phase 4 of drug development) is equally essential to minimize the risk of ADRs that may have been overlooked or never occurred due to the rarity during premarketing. For physicians in the hospital or office practice using an approved drug the filing of ADRs is purely voluntary, which can lead to underreporting of ADRs. In contrast the pharmaceutical industry is required to report all ADRs.

Recently, Hazell and Shakir reviewed the incidence of ADR underreporting in 37 spontaneous reporting system studies from 12 countries that used a variety of surveillance methods and found an underreporting rate of 94% (interquartile range 82–98%) with drugs that were in the postmarketing phase. There was no difference in underreporting when private practice studies were compared to hospital-based studies. Although underreporting was less for ADRs considered to be serious to severe, the underreporting rate was still greater than 80%. The implications of these results are obvious—the incidence and types of ADRs encountered are not adequately quantified in postmarketing studies. Why would such a problem exist given the importance of ADR reporting? Physicians state that it is lack of time, lack of ability to ascribe the ADR to the drug, poor understanding of the report forms, and lack of understanding of the role of the spontaneous reporting system (SRS).

Even more troubling would be underreporting of ADRs observed during premarketing clinical trials. During these studies it is vital to report all likely ADRs

as they provide an important profile of potential ADRs that may be encountered later. During the tightly controlled and carefully regulated premarketing clinical trials, ADRs are negative events and often result in the cessation of further clinical development of a drug. Given the amount of time and money invested in a given drug, especially those drugs that have reached Phase 3 clinical trials, reporting ADRs to the FDA is a necessary but difficult endeavor for any pharmaceutical company sponsoring the clinical development of a drug. Reporting ADRs during preclinical trials is much more controlled than in postmarketing clinical studies described previously, but even in these preclinical trials underreporting ADRs is possible.

A number of strategies have been proposed to encourage and facilitate the reporting of ADRs such as greater accessibility to the SRS database through electronic and online reporting, including the pharmacist and nurse in the reporting cadre, increased understanding for the purpose and importance of pharmacovigilance by the physician, and continued training of the medical profession to maintain the quality and quantity of ADR reporting.

How do we assess the likelihood that the adverse event noted in a given study in fact is related to the drug under study? This question is a major contributor to underreporting of ADRs in drug studies. The most logical approach is to develop an algorithm that enables the observer to determine with a higher degree of certainty that the adverse effect is drug-related. Such an algorithm has been proposed by Koh and Li (Table 13.1).

The degree of likely causal relationship between drug administration and ADR is based on the total number of points accrued by the given ADR. Scores greater than 12 = definite; 8 to 11 = probable; 0 to 7 = possible; less than 0 = unlikely. This algorithm is actually a modified form of the 56-question Kramer algorithm, and is considered the gold standard for these types of assessment when compared to the Kramer algorithm in a total of 450 different ADR reports. The algorithm was found to have a greater than 98% congruency with the far more time-consuming and bulky Kramer algorithm.

Another approach to proper reporting of ADRs is systematic reviews of clinical trials. Although it would seem logical to have experts review the clinical data to quantify ADRs, there are some significant obstacles facing the experts conducting such reviews. First, the methodology for performing such reviews mostly results from poor indexing of ADRs in medical databases. Second, interpretation of ADR reporting in randomized clinical trials is hampered by the poor quality of the reports. Although database searching of the literature has improved dramatically during the last few years, searching for relevant articles remains a challenge.

A more recent approach to controlling the quality and quantity of ADR reporting is at the publication stage. Several medical journals are requiring that the clinical trial data conform to CONSORT (consolidated standard of reporting clinical trials), a newly developed way to systematize ADR reporting in clinical data, in order to be published in the journal. Given that these journals include the British Medical Journal, JAMA, Lancet, and New England Journal of Medicine there is a good chance that CONSORT will have a positive impact on the ADR activities.

13.5 PHARMACOVIGILANCE AND ADR

While premarketing clinical trials are important it must be remembered that upon completion of all premarketing studies, only a limited number of individuals, usually less than 3000, have been treated with the test drug. This small subset of the entire population can often miss important but infrequent ADRs. Once a drug has been awarded an NDA, marketing is now possible. The drug can now be prescribed for use in all appropriate patients and vast numbers of humans can be treated with the drug. Now an accurate profile of toxicities can be developed if rigorous good postmarketing surveillance process (GPMSP) is properly carried out. GPMSP is essential if good pharmacovigilance practices are to be effective.

During this time of GPMSP, data accrual is dependent on accurate and complete spontaneous adverse reaction report submission. As described earlier, this is at best a questionable state of affairs as underreporting is widespread. However, there is an increasing awareness among all involved in drug discovery, development, and use that the only way to lower the ADR

Table 13.1 Determining Cause of ADR

Questions	Yes	No	Unknown	NA[a]
Is the time between dosing and ADR reasonable?[b]	2	−4	0	—
Has the ADR been associated with this drug before?	2	−2	0	—
Could the ADR be related to an existing clinical condition?	0	4	0	—
Is there an overdose of the drug?	2	0	0	—
If the drug is withdrawn does the ADR disappear?	1	−2	0	0
Did the ADR resolve with continued treatment?	−2	0	0	0
Did the ADR occur if a specific antagonist was administered?	4	0	1	0
Did the ADR recur if the drug was re-administered?	4	−2	0	0

a = not applicable; *b* = depending on the drug and the ADR

rate is to maintain careful pharmacovigilance processes. Successful pharmacovigilance requires both careful planning and strict adherence to the described standard operating procedures (SOP).

Spontaneous reports have been the cornerstone of pharmacovigilance; the central goal of these efforts is to develop scientifically strong indicators of ADR and accurately identify rare, serious, unusual, or unexpected ADRs as soon as possible after marketing launch. The basic principles of this activity include:

- Effectiveness, including rigorous alerting of suspected ADRs, signal detection, and handling of reports
- Efficiency focusing on the important reactions
- Consistency providing a unified corporate opinion on type and severity of the ADR
- Validity insuring that the tools utilized yield correct results

How do we reduce these principles into practice? Pharmacovigilance should be a stepwise approach:

- Data triage
- Information acquisition
- Single case assessment
- Technical checks
- Case series
- Interpretation
- Communication

The goal of data triage is to sort reports that are likely of clinical importance from those that are less likely to be important. Given the volumes of reports submitted, especially on drugs with a large market, it is vital to have an efficient and accurate means to triage data. What makes a set of data important includes the potential severity of the ADR, the medical significance of the ADR, and whether the ADR is "usually related to drug ADRs." Only those reports labeled as important require a clinical review at the individual case level. Those reports considered less important can be handled in aggregate and carefully data mined. Only those less important reports that meet an alerting threshold as described next need individual case review.

As stated previously, underreporting is a significant problem in any effort to identify ADRs quickly and accurately. Thus enhanced acquisition of important data is essential. All reports deemed important need an active query with the reporter to increase the likelihood of making a causality determination. For a subset of these important reports, which are related to organ systems that are historically linked to drug toxicity, there exist a set of data collection instruments that provide an efficient, effective, and structured query. Given that such reports can result in the removal of a drug from the market it is critical that all such reports and the reporter are accurate. Further, it is recommended in such situations, the company selling the drug has a team in place that can be mobilized to travel to the site of the report to obtain the relevant laboratory or biopsy samples.

The third step in the process of pharmacovigilance has two parts—single case assessment and signal-based evaluation. The initial step is to add a quality score using algorithms such as that discussed earlier, which enables the reviewers to sort the reports into three levels of quality reports. This evaluation is done prior to regulatory submission. After the report is submitted to the regulators, the main pharmacovigilance assessment and evaluation occurs. The risk assessor compares these new data to similar cases and assigns a level of importance to the report. All reports deemed important at this point warrant an issuance of an alert, which is simply an initial warning to look at the data carefully. If the data have sufficient substance to require further investigation then a signal is issued.

Yet another series of checks are now required in technical checks. The primary purpose of the technical checks is to send alerts to the reviewers for assessment and judgment as to whether the alert warrants a signal status. There must be in place methodologies, such as the FDA Baysian ratio technique discussed elsewhere in the text, to evaluate the reports since most reports are not evaluated on an individual basis.

The next step in data analysis is the case series, which remains the clinical mainstay. There is more to be learned from a carefully assembled series of like cases than can be extracted from the isolated review of an individual case. This is the first time that the risk assessors view the data both clinically and epidemiologically. Here the quality of reports probably exceeds the quantity of reports, and underreporting of spontaneous reports becomes less important. It is at this point that the signal determination can be assessed, which results in informing the proper level of corporate management, and a full signal work-up and report is required. Once a signal determination has been issued the work-up begins. Factors to consider include epidemiological context, exposure data, age and gender demographics, natural history of the disease and the observed outcome, alternative risk factors, plausibility of results, and whether they employed good pharmacoepidemiological practices.

Finally, if the risk assessors evaluation results in the assessment of a true signal indicator, it requires notification of the corporation, the medical field, and business stakeholders. At this point the ADR may be placed on the label as a risk of drug ADR. A sufficiently severe ADR may result in the "black box" label on the drug. The name refers to the black box placed around that specific ADR and is considered the most serious of possible ADRs.

13.6 TYPE B ADRs

This class of ADRs includes drug allergies (hypersensitivity reactions), idiosyncratic responses, or intolerance. These types of ADRs are difficult if not impossible to predict and are therefore unavoidable until sufficient knowledge of the drug and the patients taking this drug allows the development of

characteristics that increase the risk of Type B ADRs. Obviously, although we discussed the importance of pharmacovigilance in the preceding portion of this chapter, diligent reporting of Type B ADRs is even more critical as these ADRs are difficult to predict and most often encountered in the postmarketing clinic. In this section of the chapter we will discuss examples of Type B ADRs based on different organ systems of the body.

13.6.1 Drug Allergies

The importance of this drug toxicity is probably best exemplified by penicillin, a drug that revolutionized the treatment of bacterial infections, converting what had been potentially lethal diseases into manageable diseases with excellent clinical outcomes. This class of drugs is the closest thing we have to the silver bullet described by Ehrlich in the 1800s as there is virtually no Type A ADR associated with penicillin. However, it soon became apparent that penicillin does cause a drug allergy that can range from a mild itching of the skin to life threatening anaphylactic shock. Other drugs that cause drug allergies include the nonsteriodal anti-inflammatories, the thiazides, sulfa drugs, anticonvulsants, barbiturates, and iodine as well as the protein-based formulations such as vaccines, insulin, and TSH. In fact, drug allergies account for approximately 20% of all reported ADRs. In this portion of the chapter we will discuss the types of drug allergies, mechanism of drug allergies, and specific examples of important drug allergies.

A controversial aspect of drug allergies is one commonly referred to as multiple drug allergy syndrome, in which patients have experienced allergic reactions to two or more noncross-reacting medications. It has been hypothesized that such a reaction results from an individual's underlying heightened propensity to develop allergic responses (both IgE- and non IgE- mediated).

13.6.1.1 Classification of Drug Allergies

The term hypersensitivity is often associated with drug allergy. However, as was discussed earlier, the term hypersensitivity has a different connotation in pharmacology that it does in immunology. Drug hypersensitivity is considered to be a dose-related response to a drug such that the hypersensitive individual responds to a much lower dose of the drug than does the general population. The immune system plays no role in drug hypersensitivity. Drug allergies on the other hand are not dose related and do involve the immune system centrally in this type of ADR, but are often called hypersensitivity reactions. A hypersensitive individual is quite different from an individual suffering a hypersensitive reaction.

Allergies are mediated by a variety of immune responses and because of this, allergies are most commonly classified based on immune response mechanisms responsible for the allergic response. In 1963, Gell and Coombs divided allergic responses into four subtypes; this classification remains virtually intact today (Table 13.2).

13.6.1.2 Activation of the Immune System

The immune system is designed to eliminate foreign proteins, invading organisms, and damaged or malignant cells and is composed of macrophages or antigen presenting cells and lymphocytes. In the case of an allergic response the mast cell, basophil, and/or eosinophil provide the histamine to help drive the allergic response. The general scheme for activation of the humoral immune response, the branch of the immune system response for allergic responses, is shown in Figure 13.3.

Antigen presenting cells (APC) ingest a foreign protein and present a portion of the protein (the antigen) on the surface of the APC through a surface receptor known as the HLA II (human leukocyte antigen II). T-Helper cell (Th) binds to the antigen through the T Cell Receptor (TCR), and this initiates the response. A second costimulatory signal is then activated by two proteins on the surface of the APC (CD80 and CD86) binding to a Th cell surface molecule (CD28). These cosignals then activate the Th cell to release the protein cytokine IL-4, which then activates a subset of the helper T cells, Th 2 cells, to produce more IL-4. In the presence of antigen and the released IL-4, B cells then mature to plasma cells that recognize the antigen and produce antibodies on subsequent exposure to the antigens. There exist a number of different classes of antibodies including IgA, IgG, IgM, IgD, and IgE. With immediate allergic responses the critical antibody class is IgE. The IgE then binds to high

Table 13.2 Allergic Response Subtypes

Allergic Response	Involves	Characteristics
Type 1	IgE and T-helper 2 cells orchestrate response Maximal response within 30 minutes	Immediate hypersensitivity Hay fever, urticaria, atopic asthma
Type II	Cytotoxic autoantibodies	Antibody-dependent cytotoxic hypersensitivity
Type III	Tissue damage secondary to immune complex formed Maximal response 3–8 hrs post exposure	Immune complex mediated hypersensitivity (Arthus reaction)
Type IV	Erythema and induration T-helper 1 cells mediated Seen 24–48 hrs post exposure	Delayed hypersensitivity. Contact hypersensitivity, TB dermal test, poison ivy

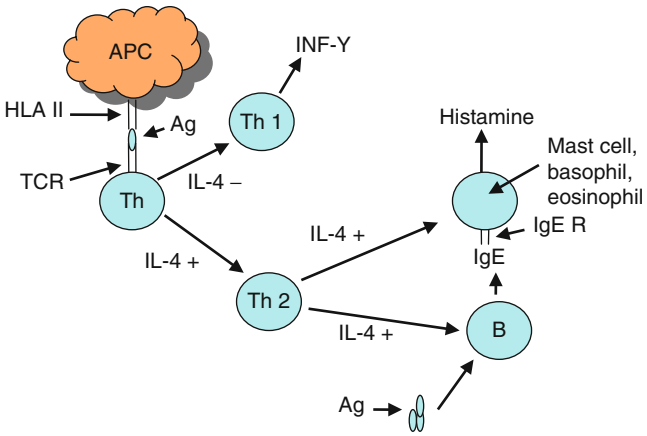

Figure 13.3 Allergic response to drug (Ag).

affinity IgE receptors on the surface of histamine releasing cells including mast cells, basophils, and eosinophils.

The IgE molecule cross links two IgE receptors on the histamine releasing cell, which signals the cell to release histamine into the extracellular fluid. Histamine is rapidly deactivated by the enzymes histamine N-methyl transferase or diamine oxidases, which normally limits the effect of histamine to the cells near the histamine releasing cell. The released histamine diffuses into the ECF and binds to histamine receptors, of which the two most studied are H1 and H2. Binding of histamine to its receptor initiates the physiological effect of histamine, which is dependent on the cell type activated by the histamine. Typical effects of histamine binding to H1 receptors include bronchoconstriction, vasodilation, allergic rhinitis, itching, pain, and edema formation. In contrast, binding of histamine to H2 receptors initiates increased acidity of the stomach. Thus as will be demonstrated, drug allergies have a large variability in pathophysiological pathways, clinical signs and symptoms, severity, and in the drugs that can elicit these responses.

13.6.1.3 Latency Period in Drug Allergies

Drug allergies are classified by the latency period between drug exposure and the onset of allergic reactions and include immediate, late, and delayed. The symptoms of an immediate type reaction are urticaria, angioedema, rhinitis, asthma, and anaphylaxis. Thus, the immediate onset type of drug allergy can range from mild itching of the skin to the life-threatening anaphylaxis. What dictates the degree of allergic reaction is, as discussed earlier, directly related to extent and sites of histamine release. In urticaria, histamine release is limited to the skin whereas in anaphylaxis histamine release is generalized resulting in alterations in pulmonary and cardiovascular function.

Late reactions can present as allergic vasculitis (characterized by damage to the blood vessels and skin), pupura pigmentosa (a discoloration of the skin), erythema multiforme (lesions of the skin leading to open sores that may or may not have systemic symptomatology), and serum sickness (characterized by hives, rash, itching of the skin, joint pain, fever, and malaise). Unlike the immediate reaction, which is solely driven by rapid onset histamine release, the pathogenesis of the late reaction is the complexation of an antibody, most frequently IgG, with antigen. These complexes can then lead to the activation of complement or binding of the complex to cells with cytotoxic effects. Keep in mind that the late reaction may also have an IgE-histamine component leading to rhinitis or skin reactions, but these occur much later than would be expected of an immediate reaction and appear to be a result of histamine release by the basophil rather than mast cells. Drugs known to cause this type of reaction are the oral contraceptives, pyrazolones, and sulfonamides.

The delayed type reaction presents as allergic contact dermatitis (as seen after exposure to poison ivy in 85% of the population) and morbilliform exanthemas (lesions that burst forth on the skin or mucous membranes). The delayed type reaction can result in far more serious consequences such as TEN (Toxic Epidermal Necrosis), a skin erosion that can affect large patches of skin including mucous membranes of the eyes, oropharynx, and genitalial and has a 30% mortality rate or SJS (Stevens-Johnson Syndrome, which includes fever, malaise, myalgia, arthralgia, and extensive erythema multiforme of the trunk and face). A surprisingly large number of drugs are capable of causing this type of drug allergy:

Antituberculous drugs, Barbiturates, Carbamazepine, Cephalosporins, Erythromycin, Frusemide, Gold, Gentamicin, Isoniazid, Nitrofurantoin, Penicillins, Phenothiazines, Phenylbutazone, Phenytoin, Sulphonamides, Thiazides.

Fortunately, the incidence is low. The cause of this reaction appears to be an activation of the CD8+ T-cell, the immune cell responsible for cellular immunity, which then attacks and destroys autologous epidermal keratinocytes.

How do small molecular weight chemicals such as the vast majority of drugs cause an immune-mediated drug allergy?

13.6.1.4 Development of Drug Allergies

There are two models put forth for the development of drug allergies—the hapten model and the direct recognition model. The hapten model, which states that a drug must attach to a protein to become an allergen, is the more established explanation. The direct recognition model states that the T cell recognizes the drug itself together with the MHC/peptide complex to initiate the drug allergy. The direct recognition model does not require metabolism and may provide a more straightforward explanation as to why the skin plays such a prominent role in drug allergies.

Hapten Model Antigens are commonly thought of as portions of proteins metabolized by the APC and are recognized by the T cell only after being attached to the MHC on the surface of the APC. Given that drugs are often considered too small to act as antigens in this manner an alternative pathway for Th cell activation must be considered. A drug (direct hapten) or drug metabolite (indirect hapten) binds covalently to an extracellular or intracellular protein (haptenization). If the haptenization occurs extracellularly then the APC can endocytose the haptenized protein, digest the complex in the lysosome, and then couple the antigens to MHC II prior to the complex migrating to the surface of the APC. This MHC II bound complex can then interact with the Th cell as described earlier. The Th cell can then interact with T cells to activate either the Th 1 or Th 2 pathways or can activate B cells to initiate the humoral response to the antigen.

As shown earlier, the Th 1 pathway results in the release of the pro-inflammatory molecule INF-γ and is involved primarily in the Type IV delayed hypersensitivity responses, which includes allergic contact dermatitis, exanthemas, TEN, or SJS. Activation of the drug specific Th 2 cells can result in the activation and attraction of eosinophils, which reflects the prevalence of eosinophils present in allergic skin eruptions seen in late drug allergies. Finally, activated Th cells can stimulate mature plasma cells in the presence of the drug antigen to release antibodies that result in antibody-antigen complexes and the resulting late drug hypersensitivity, or in the release of histamine seen in either rapid onset hypersensitivity or late drug reactions.

The Direct Recognition Model This model was developed in an attempt to explain how APC that have been fixed and metabolically inactive could activate an immune response to a drug. In this situation the APC presents an intact drug molecule or a metabolite of the drug *without* being covalently linked to a protein and activation of the T cells can still occur. This is a fairly recent observation and more work is required to better understand the mechanism of this reaction and the significance of the reaction in drug-induced allergies.

13.6.2 Hypersensitivity Reactions to β-lactam Antibiotics

Allergies to this class of drugs are the most commonly reported of all drug-related allergies, with a reported incidence of penicillin allergy of around 10% of all patients. A complicating feature of penicillin allergies is the fact that more than 90% of patients who claimed to have penicillin allergy lack the penicillin-specific IgE antibodies seen in patients with true immediate onset penicillin allergy. Further, most allergic patients do not respond to classic skin tests for allergic sensitivity. What is the basis of the discrepancy between "claimed" and "true" penicillin allergy is not completely understood. Drug-induced ADRs observed when hypersensitivity to β-lactams is encountered are summarized in Table 13.3.

Table 13.3 Drug Allergy Induced ADRs with β-lactams

Multisystem	**Skin**
Anaphylaxis	Maculopapular/morbilliform eruptions
Serum sickness-like reaction	Urticaria/angioedema
Drug fever	SJS
Vasculitis	TEN
Generalized lymphadenopathy	Contact dermatitis
Bone Marrow	**Lung**
Hemolytic anemia	Eosinophilic pulmonary infiltrates
Thrombocytopenia	
Neutropenia	
Aplastic anemia	
Eosinophilia	
Heart	**Liver**
Myocarditis	Hepatitis
Kidney	
Interstitial nephritis	
Nephrotic syndrome	

As can be seen from Table 13.3, the β-lactams have been implicated in a wide variety of allergic ADRs, but in many cases these reactions do not fit into the traditional Gell and Coombs classification. As was discussed earlier these ADRs are more than likely a result of both IgE- and T-cell mediated reactions and constitute potential immediate, late, and delayed hypersensitivity responses. For the remainder of this chapter we will focus on the IgE-related reactions since we have the greatest understanding of the pathogenesis of such ADRs in β-lactam antibiotics.

13.6.2.1 Epidemiology of Beta Lactam Drug Allergies

As stated earlier, the β-lactams are reported in 10% of all patients treated with penicillin, yet 90% of patients claiming to be allergic to penicillin do not have the penicillin-specific IgE. What could account for the glaring discrepancy? Several factors, including the previous reaction attributed to the administration of the drug may actually have been related to the disease and not the drug, the reaction may have been a predictable reaction and not an allergic response at all, or patients tend to lose IgE antibody titers with time following drug exposure. Unfortunately, there has been no prospective study to evaluate the sensitization rate of patients during a course of therapy. Retrospective studies have supported the claim that β-lactams cause the greatest number of cutaneous ADRs (between 1 and 5% of patients treated, depending on the β-lactam administered) but it is unknown how many of these reactions were accompanied by a rise

in IgE titer. Further, with surprising consistency, retrospective studies also have demonstrated that penicillin-induced anaphylactic responses are rare (1–4/10,000 patients treated) and are seen most frequently in patients receiving multiple parental treatments. Finally, though not well studied, the data accumulated with the cephalosporins suggest that the incidence of immune-mediated ADRs are approximately one order of magnitude lower for the cephalosporins than that observed with the penicillins.

13.6.2.2 Risk Factors for the Development of β-lactam Allergies

Patients between 20 and 49 appear to be at greatest risk of developing acute allergic reactions to penicillin. It is interesting that children, who receive significant antibiotic therapy, have a lower incidence of allergic reactions. It is possible that the discrepancy in age may be related to immune response differences in different age populations. Children with allergies to bee stings lose venom IgE far more rapidly than do adults. It is possible that a similar mechanism exists for penicillin allergy.

Patients suffering from atopy (the genetic susceptibility to develop allergies) were at one time thought to be at a significantly higher risk to develop penicillin allergies. Meta-analysis of large scale studies have proven this to be inaccurate although asthmatics may be more likely to develop anaphylactic reactions to penicillin.

An interesting phenomenon is the fact that patients treated with penicillin while infected with Epstein Barr virus are more likely to develop mobilliform eruption, but at the same time lack penicillin-specific IgE antibodies. Further, these patients appear to tolerate future course of penicillin therapy quite well. The actual mechanism of this infection-associated phenomenon is unknown but viral infection is associated with increased release of interferons. Interferons have been reported to increase MHC expression on the surface membranes of APC in the skin and thus increase activity of dermal immune activity.

Given that the route of antigen exposure is known to be important in determining the type of immune response initiated, it is perhaps not surprising that parentally administered penicillin (either IM or IV) is far more likely to develop Type 1 allergic response than those receiving oral penicillin. The frequency of treatment may also play a role as patients with cystic fibrosis who undergo frequent IV antibiotic treatments are particularly prone to developing IgE mediated penicillin allergies.

13.6.3 Multiple Drug Allergy Syndrome

This term refers to patients who have experienced allergic reactions to two or more noncross-reacting medications, and is controversial. One theory concerning this syndrome states that a patient who develops an allergy to one drug is more likely to develop an allergy to a second unrelated drug due to the patient's propensity to develop allergic reactions (both IgE and non-IgE related). Limited studies are available to state conclusively that such a syndrome exists and if so, the mechanism of the multidrug allergies. In fact, several investigators have published studies contradicting the multidrug allergy syndrome. Khoury et al., using age and sex matched groups of patients that were either positive or negative to penicillin skin tests, reported that penicillin reactive patients were least likely to react to other antibiotics.

13.6.4 Mechanisms of Allergic Responses

As discussed earlier in this chapter, the most widely accepted concept for the development of drug-induced allergies is that the drug (hapten), too small to initiate an immune response on its own, must first covalently bind to a carrier protein (haptenation). This newly formed multivalent complex can then elicit an immune response, which in the case of penicillins is most frequently the immediate type and correlates with the presence of IgE antibodies. An interesting feature of β-lactam allergies is that the route of administration seems to play a role in the type of allergic response seen. Although not conclusively demonstrated in prospective studies there is a significant body of literature to suggest that the parental route of administration is more likely to induce Type 1 allergies and more likely to cause anaphylaxis than the oral route of administration.

There is at best limited data to support or refute the role of heredity in the susceptibility to antibiotic allergies. Few reports have been published regarding this phenomenon and unfortunately those that have been reported lack confirmatory testing or provocative testing but rely almost exclusively on patient histories. Even more confounding is the fact that these reports do not separate IgE mediated from non-IgE mediated allergic responses. Further these studies focused on drug allergies and not purely on antibiotic drug allergies and reported a familial predilection for drug allergies across drug classes. One explanation for an apparent but not yet proven familial predilection for drug allergies across drug classes is that these individuals are likely to mount a humoral immunological response to drug protein complexes formed during therapy. Since we lack the necessary data to clarify whether heredity plays a distinct role of beta-lactam antibiotic allergies, further research is needed.

Although it well accepted that drug allergies are the most common with beta-lactam antibiotics, other drug classes have the potential of inducing such an immunological response. Sulfonamide-induced allergic reactions occur in as many 20 to 30% of AIDS patients. Often AIDS patient allergies present as skin rashes. Yet another nonurticarial rash hypersensitivity (Stevens-Johnson syndrome discussed elsewhere in the chapter) are thought to be a response reactive

to metabolites such as the hydroxylamines, N-acetylated sulfonamides, or the nitroso-metabolites. Given the interesting history of the sulfa-based compounds and the variety of nonantibiotic uses of these compounds there is a very real concern about cross-allergic responses to nonantibiotic sulfa compounds in sulfonamide allergic patients. To date no such increased incidence has been noted in sulfonamide allergic patients.

13.6.4.1 NSAIDs Allergic Responses

Even nonantibiotic drugs can induce allergic responses. Aspirin and nonselective NSAIDs can cause an idiopathic urticaria and upon rechallenge 20 to 30% will develop urticaria or angioedema. For this reason, such drugs are contra-indicated in patients developing such skin reactions following drug therapy. In contrast, if a patient is rechallenged with a COX-2 selective drug no skin reactions are noted in the vast majority of patients. There are interesting reports that a patient may develop skin reactions to one nonselective NSAID but have no reaction to a different NSAID. The mechanism of this selective reactivity is very poorly understood at the present time but may be related to the pharmacological effects of these drugs.

In addition to skin eruptions aspirin can cause a syndrome referred to as aspirin exacerbated respiratory disease (AERD) in which the classic triad of asthma, rhinitis, and aspirin sensitivity was first described by Samter. It is important to note that AERD has as its precursor an underlying respiratory disease such as asthma that is exacerbated by aspirin but not caused by aspirin. Briefly, the natural history of this disease indicates that the patient first develops an upper respiratory tract inflammation that persists rather than subsides. Sinusitis develops, which progresses to pansinusitis with nasal polyps and asthma noted. At some point the patient takes aspirin or some other COX-1 inhibitor and an AERD reaction occurs. Although this is truly an idiopathic reaction to NSAIDs, adult patients with chronic sinusitis and nasal polyps should be observed carefully for the potential development of AERD.

At present there is very little that can be used to identify individuals with NSAID sensitivity using *in vitro* tests. Consequently challenges to the patient must be used and in this case only oral challenges are approved in the United States. Such tests are risky and should be performed only by well-trained physicians who are ready to rapidly and aggressively treat a variety of responses including severe bronchospasm, cutaneous, GI, and vascular effects.

The pathogenesis of AERD is confusing because the symptoms of AERD mimic those of a true immediate hypersensitivity reaction; no antibody-antigen mechanism has ever been established. Rather, it appears as though the initiation may be related to the inhibition of intracellular COX enzymes causing a rapid decrease in prostaglandin production and the leukotriene pathway becoming dominant. Given that prostaglandins induce bronchodilation and leukotrienes induce bronchoconstriction, the subsequent bronchoconstriction is not surprising. However, if this were the only cause then all individuals taking an NSAID would be at risk of AERD. Recent data suggest that AERD susceptible individuals have upregulated leukotriene receptors in the bronchiolar tree. Another potential explanation for this AERD response in a select number of individuals is the observation that following NSAID exposure urine levels of leukotriene metabolites increase two- to 10-fold. In summary, NSAID-induced AERD is of interest because it represents a class A ADR (since inhibition of COX, the pharmacologic target of NSAIDs appears to induce the response) but since it is so rare it is classified as an idiosyncratic response or class B ADR.

13.6.4.2 Allergies to Cancer Chemotherapeutic Drugs

Discussion of all hypersensitivity reactions is beyond the scope of this chapter, however one more example will be discussed—that being the case of hypersensitivity to anticancer drugs. At present there are more than 85 drugs used to treat cancer, yet few drugs are actually associated with hypersensitivity responses. These drugs include bleomycin, platinum complexes, epipodophyllotoxins, taxanes, anthracyclines, and asparginase. It is of interest that each of these examples, with the notable exception of the platinum complexes, are drugs derived from a microbial or plant source (natural products). As with previous examples of drug-induced hypersensitivity, we must be careful in defining hypersensitivity. Here we define hypersensitivity as signs and symptoms not normally associated with those given that occur within hours of drug administration, almost always following a parenteral drug administration. Symptoms most commonly observed include skin flushing, bronchospasm, altered cardiac activity, dyspnea, fever, back pain, nausea and vomiting, and skin rashes of all types. Although these responses are most frequently associated with specific drugs, there also exist responses to drug formulations such as the excipient Cremaphor EL or pegylation of the drug.

L-Asparaginase L-asparaginase is an enzyme used to treat acute lymphocytic leukemia (ALL) and is associated with a high frequency of hypersensitivity responses. Route of administration plays a significant role in the incidence of hypersensitivity as IV administration causes a significant number of hypersensitive responses (6–43%) whereas IM or subcutaneous routes cause far lower incidences (6–14%). Because of the high incidence of hypersensitivity it is prudent to test a patient for hypersensitivity before the first dose or any dose that an interval of one week or more has elapsed between doses. The actual mechanism responsible for the immediate hypersensitivity response remains unclear. Studies have shown that a pegylated form of L-asparaginase is tolerated by many who have

had hypersensitivity responses to native L-asparaginase, suggesting that it may not be a simple reaction to the enzyme protein. Further, production of L-asparaginase in a different bacteria (*Erwinia*) rather than *E.* coli results in a protein that can be administered to patients previously shown to be hypersensitive to the *E.* coli product. These results suggest that the hypersensitivity may be related to the bacterial source of the enzyme.

The mechanism of this drug-induced hypersensitivity remains unknown but IgE antibodies have been identified in some but not all patients. In others, complement activation has been reported but no clear-cut mechanism can be identified. A study in children reported that 35% had IgG specific for L-asparaginase and 50% of these children had hypersensitivity responses to the drug but only 18% of the children not expressing IgG had similar hypersensitivity response. Patients suffering hypersensitivity to *E.* coli derived L-asaparaginase could be treated safely with pegylated drug or L-asparaginase from *Erwinia*. It is highly encouraged that any patient should be skin tested prior to receiving L-asparaginase.

Platinum-based Drugs The platinum complexes have been a mainstay of cancer chemotherapy for more than 25 years. The complexes consist of a central platinum-two stable ammines and leaving groups as shown in Figure 13.4.

The proposed mechanism of action for the platinum complexes is that the leaving groups hydrolyze from the central platinum in a process known as aquation, enabling the drug to form intrastrand crosslinks with DNA, thereby inhibiting DNA synthesis. Cisplatin was the first platinum complex to be used clinically but is being replaced by carboplatin. Cisplatin can cause typical type A ADRs such as marrow depression and GI problems but is associated with significant type B toxicities including hypersensitivity (discussed now) and neurological and renal toxicities (discussed later in this chapter). Unfortunately, the incidence of hypersensitivity responses for carboplatin are approximately equivalent to that of cisplatin.

Oxaliplatin was developed in an attempt to circumvent the problem of cisplatin resistance noted in patients treated with cisplatin who subsequently relapse and are retreated with cisplatin. This drug and the resistance to cisplatin are described in Chapter 15. Transplatin was included to demonstrate one of the primary structural requirements of the platinum complexes, that being that the stable ammines must be in the cis configuration. Ammines in the trans configuration, as in the case of transplatin, result in platinum complexes that lack antitumor activity.

Anaphylactic responses have been reported in 10 to 30% of patients treated with the platinum complexes. Symptoms, including facial edema, bronchoconstriction, hypotension, and tachycardia, occur within minutes of drug administration in patients previously exposed to the platinum complexes. The incidence of hypersensitivity increases with increasing courses of platinum therapy. There appears to be cross-reactivity among the platinum complexes in that patients reactive to cisplatin have a much higher incidence of hypersensitivity to carboplatin than do previously nontreated patients.

The severity of reactions ranges from mild pruritis and erythema to immediate life-threatening generalized anaphylaxis. Those patients with mild reactions most often are able to complete a given treatment schedule. Interestingly, patients treated intraperitoneally with the drug, most often used to treat metastatic ovarian cancer, seemed to develop platinum complex hypersensitivity far less frequently and with far less severity than patients treated intravenously with the same platinum complex. Once again showing that drug hypersensitivity can be depend on the route of drug administration. The explanation for this dependence on route of administration remains an enigma for most drugs but may be related to hypersensitivity to drug metabolites for some drugs as discussed previously in this chapter.

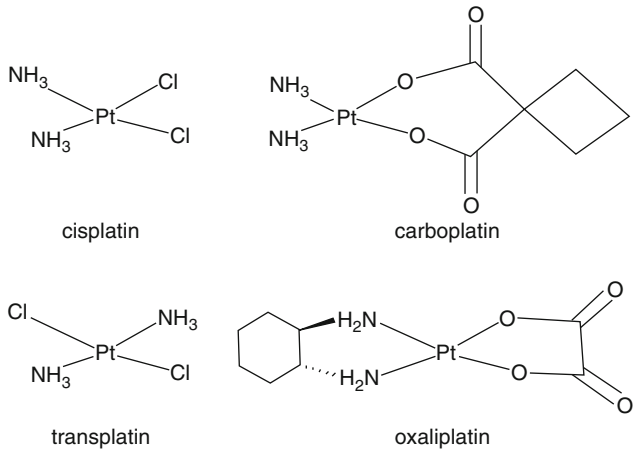

Figure 13.4 Chemical structures of platinum complexes.

Epipodophyllotoxins The epipodophyllotoxins, VM-26 and VP-16, used in selected tumor types, are semisynthetic derivatives of the podophyllotoxin isolated from the Mayapple plant. Both drugs inhibit the enzyme topoisomerase II and block DNA replication in dividing tumor cells. Again, these drugs cause both type A ADRs such as marrow depression and type B ADRs such as hypersensitivity and possible hepatotoxicity.

Hypersensitivity responses occur shortly after rapid IV drug perfusion and include hypotension, fever, chills, urticaria, and bronchospasm. The fact that about a third of all reactions occur following the first exposure to the drug and that the severity of the responses is dose related suggest that this is not a true immune response to the drug but may be related to a drug-induced histamine release.

Given that the incidence and severity of these responses can by diminished dramatically by administering the drug via slow infusion over a period of 30 to 60 minutes rather than a one- or two-minute bolus

injection has led to the hypothesis that the vehicle, cremophor, rather than the drug itself may be causing these responses. Factors arguing against this are that both drugs cause hypersensitive response yet only teniposide utilizes cremophor and second, teniposide formulated in a vehicle other than cremophor also induces the hypersensitivity.

Taxanes Taxanes are a class of anticancer drugs first isolated from the bark of the Yew tree. Subsequently semisynthetic derivatives have been introduced and proved to be very important anticancer drugs. These drugs languished for quite some time until they were shown to be mechanistically distinct from the established anticancer drugs vincristine and vinblastine. The vincas prevent the polymerization of microtubules and thus prevent mitosis by inhibiting the segregation if chromosomes during the M-phase of the cell cycle. The taxanes, paclitaxel and docetaxel, prevent the depolymerization of microtubules and thus prevent the progression of cells through the M-phase of the cell cycle, albeit through a completely different effect on microtubular function.

Severe anaphylactic reactions occur in 2 to 4% of patients treated with these drugs. The symptoms are similar to those previously discussed and can range from minor discomfort to life-threatening crises. Patients with atopy have a higher incidence of hypersensitivity than the normal population of patients but the reaction to the taxanes does not appear to be IgE related. Experimental evidence supports the idea that these reactions are caused by drug-induced histamine release from basophils. Because of the potential severity of these reactions, all patients are pretreated with a steroid, an H1 blocker, and an H2 blocker within 60 minutes of drug administration. If a patient has had a hypersensitive response to paclitaxel yet needs further paclitaxel, the patient can either be desensitized to the drug or be treated with docetaxel. Desensitization appears quite effective but there are a limited number of clinical trials supporting this. Patients are usually not cross-reactive to these two taxane drugs.

13.6.5 Nonallergic Type B ADRs

A comprehensive discussion of all nonhypersensitive type B ADRs is beyond the scope of this chapter. Rather, we will discuss a limited number of toxicities as examples of the types of type B ADRs that can be encountered.

13.6.5.1 Myelosuppression

A type B ADR encountered with a number of drugs from varying classes of therapeutic agents is drug-induced myelosuppression. Although myelosuppression is an accepted type A ADR of cytotoxic chemotherapy, type B ADR class of myelosuppression is usually far more insidious and may occur up to several months following the last course of drug therapy.

Examples of type B ADR myelosuppression are shown in Table 13.4.

Table 13.4 Type B ADR Myelosuppression

Antimicrobials	Chloramphenical, sulfonamides, nitrofurantoin, Ziodvudine, quinacrine, amodiaquine, mepacrine, pyrimethamine, chloroquine, mebendazole
Antirheumatics	Gold, penicillamine, indomethacin, oxyphenbutazone, phenbutazone, piroxicam, sulfsalazine, diclofenac, suldinac, allopurinol
Antithyroid drugs	Carbimazole, thiamazole, thiouracils
Anticonvulsants	Phenytoin, carbamazepine, felbamate
Psychotropic drugs	Phenothiazines, dothiepin, clozapine, mianserin
Cardiovascular drugs	Methyldopa, captopril, lisinopril, ticlopidine
Other drugs	Tolbutamide, acetazolamide, interferon-alpha

13.6.5.2 Aplastic Anemia

Quinacrine is an antimalarial drug that has proven correlation between drug administration and aplastic anemia. Used widely as a prophylactic against malaria infection during WWII, enough patients were studied to provide statistical significance to clinical observations. Although the incidence of aplastic anemia was approximately one to two cases per 100,000 in soldiers stationed in the European theater, the incidence increased to two to 28 cases per 100,000 troops treated with quinacrine. The actual mechanism of aplastic anemia appears to be immunologically related as quinacrine appears to serve as a hapten that induces antibody production. Surprisingly this antibody is directed toward bone marrow stem cells and prevents normal bone function.

Chloramphenicol is a broad spectrum antibiotic that has direct effects on the bone marrow, probably related to the drug's inhibitory effects on the mitochondria. This reversible depression of marrow function is considered to be a type A ADR and is not the same toxicity as chloramphenicol-induced aplastic anemia. Chloramphenicol-induced aplastic anemia occurs weeks to months following drug treatment and does not appear to be related to dose or length of treatment. The oral route of administration most commonly is associated with the development of aplastic anemia, leading some investigators to speculate that a nitrosylated derivative formed by intestinal bacterial metabolism is the causative agent for aplastic anemia. This hypothesis has been supported recently by clinical studies with topically administered drug, particularly ocular use of the drug to treat conjunctivitis in which no increase in the incidence of aplastic anemia above control populations were observed. Although chloramphenicol does cause aplastic anemia the actual mechanism remains unknown.

13.6.5.3 Agranulocytosis

In addition to aplastic anemia, more bone marrow selective drug-induced hypoplasias have been reported. For example, clozapine-induced agranulocytosis occurs in

approximately 1% of the patients receiving this drug. Clozapine is an important psychotropic drug used to treat schizophrenia. The major advantage of this drug is its low propensity to cause the extrapyramidal effects commonly associated with long-term use of earlier antipsychotics.

The mechanism of clozapine-induced agranulocytosis has been under intensive investigation but has yet to be conclusively identified. It appears likely that activation of clozapine, to norclozapine and/or a further metabolite, clozapine N-oxide, to electrophilic nitrenium ions is the initial step in the events leading to neutropenia/agranulocytosis. Oxidation of clozapine by neutrophil-generated hypochlorous acid (HOCl) via the NADPH oxidase/myeloperoxidase system has been demonstrated, which could then lead to granulocyte death.

Antineutrophil antibodies, possibly generated by reaction of nitrenium ions with neutrophil proteins resulting in hapten formation, may also be involved in the etiology of clozapine-induced neutropenia. There is likely to be an immune component since the reaction occurs more quickly and is more severe on rechallenge of patients who have developed clozapine-induced neutropenia.

It should be noted that other chemically related antipsychotic drugs such as olanzepine and quetiapine have the potential to undergo similar metabolic pathways and cause agranulocytosis, but the incidence of these ADRs is less than that of clozapine. Given the importance of clozapine in long-term management of patients it is possible that a patient could be rechallenged with the drug. In such cases, only about 60% of the patients will be able to continue clozapine following rechallenge. Switching to one of the less toxic drugs such as olanzepine may provide benefit, but once a patient has developed clozapine-induced neutropenia or agranaulocytosis, the risk of a repeat toxic event using a drug such as olanzapine appears to be significantly increased.

13.6.5.4 Sideroblastic Anemia

Sideroblastic anemia is characterized by a pattern of morphological marrow abnormalities in which there is an accumulation of perinuclear granules in nucleated red blood cell precursors. These granules, referred to as siderotic granules, are a result of disordered hemoglobin synthesis. The antitubercular drugs such as isoniazid and cycloserine can cause such dysplasias. The extent of damage is exacerbated in patients with underlying vitamin B6 deficiency.

Why isoniazid causes this type of anemia is not well understood but it is well established that the toxic effects of long-term isoniazid therapy of tuberculosis can be significantly diminished by coadministration of Vitamin B6. This is somewhat surprising since the primary anti-TB mechanism of action for isoniazid appears to be the inhibition of mycolic acid, an important substituent in Mycobacteria cell walls, which is not Vitamin B6 dependent. However, Vitamin B6 does play an important role in heme synthesis. Since the administration of Vitamin B6 with isoniazid can reverse the formation of sideroblastic anemia it seems likely that isoniazid affects Vitamin B6 in a number of important metabolic pathways.

13.6.6 Idiosyncratic Hepatotoxicity

This form of type B ADR is again difficult to study as it is a rare event and it is human specific. This type of toxicity results from a series of multiple discrete events that eventually is expressed as hepatoxicity. The key determinant events are the chemical in question, type and length of exposure, and environmental and genetic factors. The chemical properties critical to idiosyncratic drug toxicity are identified via a review of the common properties of drugs that cause idiosyncratic liver toxicity. These properties include:

- Formation of reactive metabolites
- Metabolism by P450 isoforms
- Preponderance of P450 inducers
- Occurrence of clinically significant pharmacokinetic interactions with coadministered drugs

Although idiosyncratic hepatotoxicity is a relatively rare event, a number of drugs have the potential of inducing such a toxicity (Table 13.5).

As can be seen from Table 13.5, a number of drugs used to treat a wide variety of diseases are included. Recognize that other drugs can also affect liver function in an idiosyncratic manner; the drugs listed in Table 13.5 are but examples of drugs with the greatest potential of inducing idiosyncratic hepatotoxicity. Again, discussion of each of these drugs is beyond the scope of this chapter. Rather, we will discus diclofenac as a representative of drugs capable of inducing idiosyncratic hepatotoxicity.

Of the drugs listed, 25 are capable of undergoing hepatic metabolism, generating reactive metabolites that can form protein adducts. The enzymes responsible for these metabolic processes are primarily cytochrome P450 isoforms and the UDP glucuronosyltransferase isoforms. It is possible that the adducted proteins could serve as neoantigens leading to autoimmune diseases of the liver. Of the drugs listed in Table 13.5, 15 can induce the cytochrome P450 enzymes. Although there is no evidence as yet that enzyme induction can lead to hepatotoxicity, enzyme induction does cause altered gene expression. As toxicogenomics, the study of gene expression and toxicity, increases as a research tool, the role of enzyme induction in drug toxicity may become better understood. In its most simplistic terms it is not unreasonable to hypothesize that the induction of these metabolic enzymes leads to more reactive metabolites and hence increased neoantigen formation.

An interesting correlation between drug and dose is noted from Table 13.5. Most of the drugs listed in that table could be thought of as high-dose drugs administered according to prolonged regimens. This continued exposure to high levels of drug and metabolites could enhance the likelihood of hepatotoxicity. Perhaps the development of low-dose drug equivalents may lower the risk of idiosyncratic hepatotoxicities.

13.6.6.1 Diclofenac as a Model of Idiosyncratic Hepatotoxicity

Diclofenac is an NSAID widely used in the treatment of rheumatoid diseases such as osteoarthritis, rheumatoid

Table 13.5 Drugs Known To Be Associated with Idiosyncratic Hepatotoxicity

Drug	Purpose
Acetaminophen	Antipyretic analgesic
Alpidem	Antianxiety
Amineptine	Antidepressant
Amodiaquine	Antimalarial
Bromfenac	Analgesic
Carbamazepine	Anticonvulsant
Combination	Anti-HIV therapy
Cyproterone acetate	Androgen antagonist
Diclofenac	NSAID
Dideoxyinosine	Anti-HIV
Dihydralazine	Antihypertensive
Ebrotidine	H2-receptor antagonist
Enalapril	Antihypertension
Felbamate	Antiepileptic
Flutamide	Nonsteroidal antiandrogen
Halothane	Anesthetic
Isoniazid	Anticonvulsant 300
Ketoconazole	Antifungal
Methotrexate	Anticancer/antipsoriatic
Methoxyflurane	Anesthetic
Minocycline	Antibiotic
Nefazodone	Antidepressant
Phenobarbital	Anticonvulsant
Phenprocoumon	Anticoagulant
Phenytoin	Antiepileptic
Procainamide	Antiarrhythmic
Pyrazinamide	Antibacterial
Rifampicin	Antimicrobial
Salicylate	Analgesic
Sulfasalazine	Crohn's disease
Tacrine	Alzheimer's disease
Tienilic acid	Diuretic
Troglitazone	Diabetes
Valproate	Anticonvulsant

arthritis, and alkylosing spondylitis. Although the incidence of idiosyncratic hepatotoxicity is rare on a per patient basis, given the large numbers of patients being treated with the drug the absolute number of patients developing this toxicity is quite impressive. Obtaining exact numbers of patients developing this toxicity is very difficult as there is significant underreporting, a problem addressed earlier in the chapter.

The symptomatology of this toxicity is similar to other idiosyncratic drug toxicities in that the onset is delayed, usually after four to six weeks of treatment and may be accompanied by rashes, fever, and/or eosinophilia. Further, blood tests reveal that alterations in serum enzymes such as aminotransferase rise slightly and remain elevated in about 25% of the patients developing this toxicity. Taken together diclofenac-induced idiosyncratic hepatotoxicity is not an acute toxicity but appears to be a result of multiple insults that once a threshold level of damage is reached liver toxicity occurs rapidly primarily to the hepatobiliary region of the liver.

Diclofenac is extensively metabolized by the cytochrome P450 3A4 and 2C8 isoforms to generate reactive metabolites capable of interacting with protein and nonprotein –SH groups.

Diclofenac can also undergo glucuronidation to form diclofenac 1-acyl-glucuronide, which then attacks nucleophilic sites on proteins to form yet another class of protein adducts. These adducts could result in the formation of neoantigens, thus inducing an autoimmunity as described earlier, or in fact could inhibit the CYP enzymes and enhance significantly the risk of drug–drug interactions. Yet another potential role for diclofenac metabolism in idiosyncratic hepatotoxicity is the generation of free radicals during drug metabolism and the subsequent effect of these free radicals on

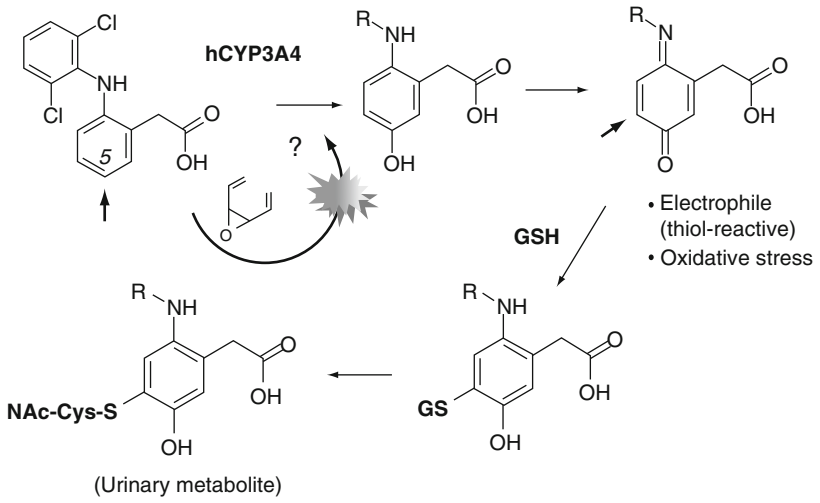

Figure 13.5 Liver metabolism of diclofenac.

mitochondrial function. This latter hypothesis is supported by experimental data demonstrating that diclofenac can decrease ATP production by 20 to 40%. Further, drug-induced ROS have been reported to alter mitochondrial membrane function in other ways such as elimination of the inner transmembrane potential.

Although much has been learned regarding this toxicity much still remains unknown. We do not understand the role of the genetic makeup of the patient, the role of the environment regarding sensitivity of this toxicity, nor the actual mechanism of the toxicity. Until the mechanism of toxicity and relevant factors affecting susceptibility to the toxicity are known, prevention of the toxicity will remain on an individual basis. Again, the role of genotoxicity and pharmacogenomics could very well play a pivotal role in unraveling this and many other idiosyncratic toxicities.

13.6.7 Idiosyncratic Cardiotoxicity

The list of drugs known to cause idiosyncratic cardiotoxicity is significantly smaller than that of drugs known to cause idiosyncratic hepatotoxicity. The reason for this may rest in the fact that many drug metabolites are responsible for the unexpected toxicities, and the liver is the primary site of drug metabolism. Thus the concentration of these reactive metabolites is highest in the liver. Be that as it may, the list in Table 13.6 clearly demonstrates that a number of noncardiac drugs are capable of inducing or worsening cardiomyopathies. Note that there are at least four major ways in which drugs cause this type of type B ADR.

Table 13.6 Noncardiac Drugs Known to Induce or Worsen Heart Damage

Cardiomyopathy	
Cytotoxic drugs	Doxorubicin, epirubicin, and other anthracyclines, mitoxantrone, cyclophosphamide, 5-fluorouracil, capecitabine, gleevec, sunitinib
Immunomodulating drugs/antibodies	Trastuzumab, interferon-α-2, interleukin-2, infliximab, etanercept
Antifungal drugs	Itraconazole, amphotericin B
Antipsychotic drugs	Clozapine
Pulmonary Hypertension	
Antimigraine drugs	Methysergide, ergotamine
Appetite suppressants	Fenfluramine, dexfenfluramine, phentermine
Heart-valve Abnormalities	
Antimigraine drugs	Methysergide, ergotamine
Appetite suppressants	Fenfluramine, dexfenfluramine, phentermine
Antiparkinsonian drugs	Pergolide
Fluid Overload	
NSAIDs	All
Antidiabetic drugs	Rosiglitazone, pioglitazone, troglitazone
Glucocorticoids	All

13.6.7.1 Anthracycline Cardiotoxicity

The anthracyclines have been by far the most studied of all cardiotoxic drugs and doxorubicin is by far the most studied of the anthracyclines. Doxorubicin is a microbial derived natural product that has proven clinical activity in a wide array of tumors. The mechanism of action ascribed to this drug is the inhibition of topoisomerase II following DNA intercalation, thus interfering with cell division. Not surprisingly this drug causes reversible marrow suppression and GI disturbances. However, once entered into the clinic a disturbing pattern of cardiotoxicity was observed in cancer patients.

These toxicities are not related to the mechanism of antitumor activity and in point of fact are not completely understood. What is known is that patients treated with doxorubicin can display an acute type of cardiac alteration and/or a chronic type of cardiac toxicity. The acute toxicities are most often expressed as myocardial arrhythmias and decreased left ventricular ejection fraction. Both effects are reversible once drug administration stops and are not considered to be a reason to discontinue the use of doxorubicin. Whether there is a correlation between these acute events and subsequent chronic cardiac toxicity is not known since individuals who never displayed acute toxicities ultimately developed chronic toxicities including fatal congestive heart failure. A reversible and nontreatment-limiting pericarditis is also observed within weeks of doxorubicin administration.

The most severe cardiotoxic effect of doxorubicin is chronic and dose-related cardiomyopathy. Because of the progressive nature of this toxicity is it recommended that no patient receive a cumulative dose of drug exceeding 450 to 550 mg/m^2. Once this total dose is reached the risk of drug-induced digitalis nonresponsive congestive heart failure (with a fatality rate approaching 50%) becomes too great and further treatment with doxorubicin is ceased. Morphological changes include loss of mitochondrial structure integrity, loss of myofibrils, and altered cellular shapes all detected by electron microscopy. At present a great deal of effort is being placed on developing noninvasive clinical methods such as echocardiograms and radionuclide cineographic techniques to predict the development of these cardiomyopathies.

Given the importance of this drug, if the toxicity could be prevented the patient could receive the benefit of this drug for longer periods of time. A number of chemical analogs have been tested either preclinically or clinically but unfortunately no approved drug has proven to be a significant step forward in

diminishing this dangerous ADR. Liposome encapsulation of doxorubicin appears to decrease the cardiac toxicity of doxorubicin but it is still early to state confidently that this approach has obviated the concern of doxorubicin-induced cardiac toxicity.

The exact mechanism of doxorubicin-induced cardiomyopathy remains unknown but there is a considerable body of evidence supporting the hypothesis that doxorubicin-induced free radicals may play an important role. The current working hypothesis is that the drug is distributed to tissues throughout the body. The drug can generate reactive oxygen species (ROS) through redox recycling of the drug. Further, doxorubicin can bind iron and deliver the iron to DNA through intercalation, and this iron can undergo its own redox recycling further generating ROS. Both pathways are shown in Figure 13.6.

Why is the heart selectively damaged if the drug is distributed widely in the body? Studies have clearly demonstrated that the heart is far less capable of protecting itself from ROS than are other tissues in the body and is therefore far more sensitive to drug-induced ROS. This sensitivity of heart tissue to drug-induced ROS is substantiated through a number of experimental studies. First, at least in nonclinical studies, antioxidants such as cytochrome Q10, vitamin E, and the flavinoids have protected the heart for some of doxorubicin-induced cardiotoxicity. One free-radical scavenger, dexrazoxane, has been shown clinically to reduce the cardiotoxic risk of doxorubicin and is currently undergoing broad clinical testing to establish its efficacy.

In summary, doxorubicin, an important anticancer drug, causes a dose-limiting toxicity to an organ that we would not predict to be a target for toxicity with this drug. The mechanism of toxicity is different from the mechanism of antitumor activity, and this toxicity was totally unexpected. Although the toxicity is fairly common in cancer patients, it does not truly fit into the type A ADR and is therefore included in the type B ADR.

13.6.7.2 NSAIDs and Cardiotoxicity

Another unexpected cardiotoxicity following drug administration is the increased risk of myocardial infarction in patients taking one of the COX-2 (cyclooxygenase-2) selective NSAIDs for rheumatoid arthritis. NSAIDs have been a long-standing class of drugs to help treat inflammation, pain, and fevers. Until recently, all NSAIDs inhibited both COX-1 and COX-2. A problem with these drugs is the potential for GI complications, including gastric mucosal ulceration, hemorrhage, or perforation. The mechanism of this toxicity is most commonly ascribed to the inhibition of COX-1, which has an important role in the production of prostaglandins needed to provide GI protection. Thus the search for a COX-2 selective NSAID was a major undertaking for the pharmaceutical industry.

Several years ago a new family of NSAIDs, the coxibs, were developed and were the desired COX-2 selective drugs. This class of drugs has been discussed previously but in this section we focus on the perplexing problem of NSAID-induced myocardial damage. Clinical trials have demonstrated that these new drugs provide equivalent analgesic and anti-inflammatory effect but with fewer GI complications. However, recent studies have reported an association been coxib use and increased cardiovascular disease. This association is strongest between rofecoxib and cardiovascular disease. When administered 50 mg/day for nine months and comparing the results to patients receiving 500 mg naproxen (a nonselective COX inhibitor) for nine months, a higher incidence of myocardial infarction was noted in the rofecoxib group.

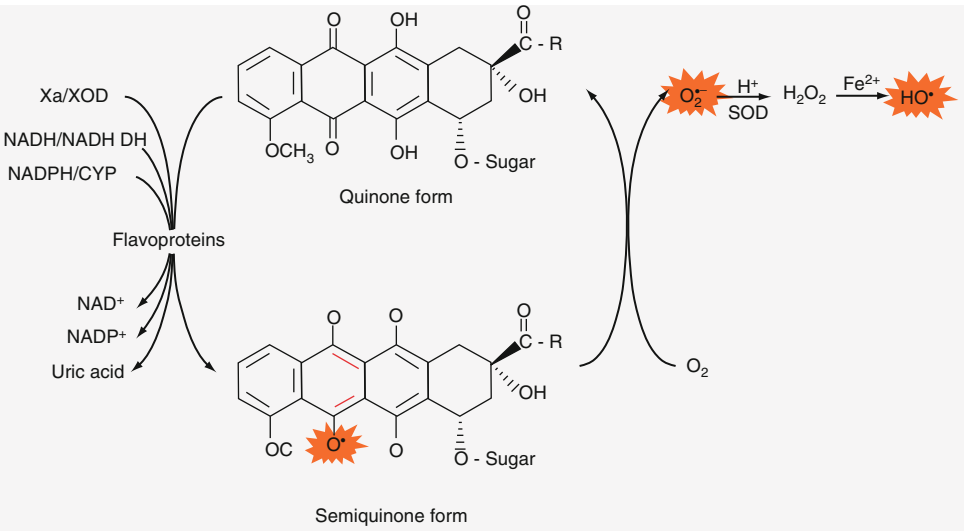

Figure 13.6 Redox cycling of doxorubicin.

Initially this increased risk of myocardial infarction was attributed to the myocardial protective properties of the nonselective COX inhibitors. COX-2 selective inhibitors may lack this protective capability. Later meta analysis suggested that the degree of myoprotection associated with naproxen could not account for the difference in the incidence of myocardial infarction. Merck, the maker of rofecoxib, withdrew the drug from the market because of this association. The other two coxibs, celecoxib and lumiracoxib, remain on the market as no similar increase in myocardial infarction has been associated with these drugs. It must be stated here that there is controversy regarding this issue and only time will provide the ultimate answer regarding the cardiotoxic potential of these two coxibs.

Another potential use for these drugs was to prevent the formation of adenomatous polyps in patients with a history of colorectal adenomas. Rofecoxib and celecoxib were both tested in this disease. It was the results of this test that prompted Merck to withdraw their drug from the market since this study clearly established the increased risk of cardiovascular events when rofecoxib is used. The results were sufficiently strong to have the safety monitoring board reevaluate the data for a similar trial with celecoxib. On the basis of these data the study with celecoxib was also terminated. Interestingly, another study in which celecoxib was used to prevent polyp formation resulted in no increase in cardiovascular events. The only difference between the two studies was that in the latter case celecoxib was given once a day whereas in the prior study celecoxib was administered at the same dose but twice a day. How this difference in treatment schedules affected the toxic outcomes is unknown at the present time.

Why these drugs apparently increase the risk of cardiovascular problems in patients remains unknown. One interesting hypothesis rests on the fact that COX-1 and COX-2 both metabolize arachadonic acid to protanoinds, protacyclins, and thromboxane A2. Prostacyclins help prevent platelet aggregation and induce vasodilation and are produced primarily in the vascular endothelial cells via COX-2, whereas thromboxane A2, which promotes platelet aggregation and vasoconstriction, is the product almost exclusively of COX-1 activity in the platelets. Thus, nonselective COX inhibitors lower the production of both the prostacyclins and thromboxane A2, whereas the COX-2 selective NSAID diminish prostacyclin production but leave thromboxane A2 production unabated. This imbalance promotes platelet aggregation and vasoconstriction. There remain a number of questions to be answered regarding this phenomenon including whether the nonselective NSAIDs cause increased cardiovascular problems, how the NSAIDs cause this toxicity, what the risk factors are regarding this toxicity, and whether there is a therapeutic benefit in using one type of NSAID compared to another. It is amazing given the extensive use of NSAIDs over the years that such toxicities are now being considered and so many questions remain. But of course that is the nature of the beast when evaluating type B ADRs.

13.6.8 Idiosyncratic Pulmonary Damage

The number of drugs with a demonstrated propensity to cause an idiosyncratic lung disease are far fewer than either hepatotoxicity or cardiotoxicity. One such drug is yet another anticancer drug called bleomycin. This drug is a natural product of microbial origin that intercalates DNA and causes DNA damage through free-radical generation. There are two important regions to this molecule, shown in Figure 13.7.

A metal binding site is on left-hand side of the molecule and a spermidine tail on the right-hand side of the molecule. The metal binding site traps the metal (iron or cobalt have been the two commonly cited metals) and provides the ROS generation site for the molecule. The spermidine tail enables the drug to interact with DNA through intercalation and delivers the metal to the DNA to maximize ROS-induced DNA damage. Loss of either portion of the molecule results in complete loss of antitumor activity.

As with doxorubicin we might ask why the lung is particularly affected when the drug is distributed throughout the body. Further, if bleomycin kills cells through ROS production then why isn't a significant amount of cardiotoxicity seen in patients treated with bleomycin since we just established that doxorubicin-induced cardiotoxicity results from insufficient ROS protection in the heart? The reason rests in the fact that most tissues are endowed with an enzyme bleomycin hydrolase, which forms a metabolite lacking the metal binding site and the loss of ROS production. In contrast, the lung lacks sufficient quantities of the enzyme to protect it from ROS damage. Thus, the duration of exposure to the ROS producing bleomycin is significantly longer than it is in almost any other tissue in the body. Interestingly, another organ with limiting amounts of the enzyme is the skin, which is also susceptible to bleomycin-induced ROS damage.

Bleomycin-induced lung damage begins as a pneumonitis that can either be resolved or progress to a far more serious pulmonary fibrosis. This toxicity is seen in as many as 5% of patients treated with bleomycin and has a 10% mortality rate. Age, underlying lung damage, and thoracic radiation can increase the risk and severity of this treatment-limiting toxicity. Once a patient develops this toxicity, regardless of the severity of the toxicity, the patient can no longer receive bleomycin. Unlike doxorubicin-induced cardiotoxicity, there is no cumulative toxicity and therefore there is no total cumulative dose that can be used to predict an increasing likelihood of pulmonary toxicity.

Including this toxicity in the area of idiosyncratic toxicity is justified since the lung is not thought of a typical target for cytotoxic chemotherapy. Rather, the toxicity results from an unexpected organ differential that results in an unexpected but not rare toxicity. Further, there are few indicators that will provide insight into if and when this toxicity will be encountered.

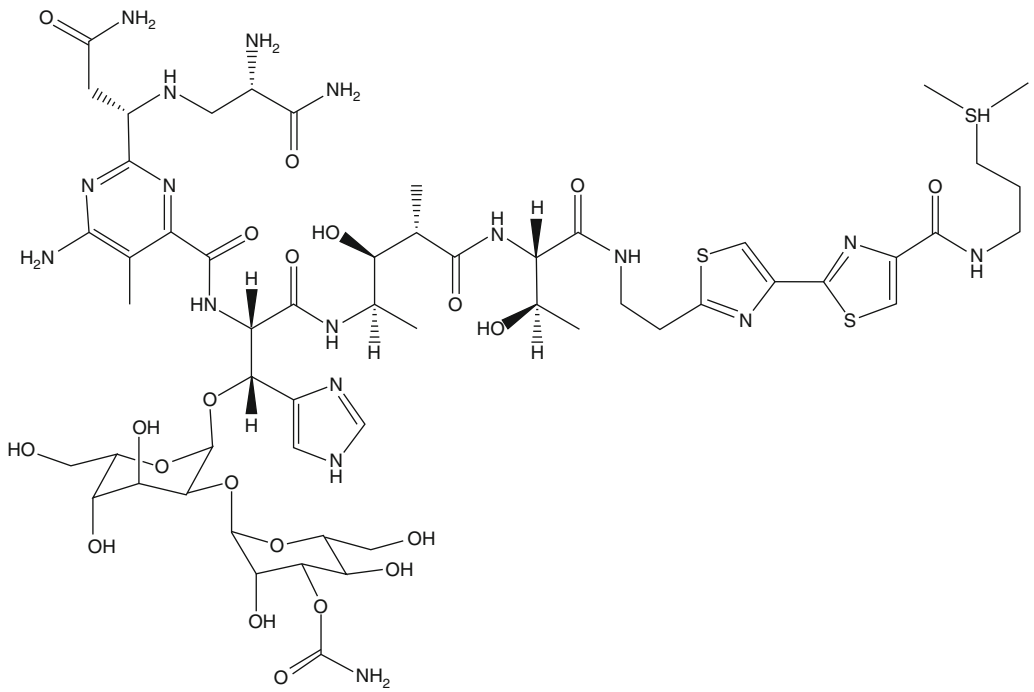

Figure 13.7 Chemical structure of bleomycin.

13.6.9 Idiosyncratic Renal Toxicity

To address this organ-directed idiosyncratic toxicity we will highlight two drugs, cisplatin and streptomycin, which are chemically distinct (see structure in Figure 13.8) yet have an intriguing similarity of spectrum of activities.

13.6.9.1 Cisplatin-induced Renal Toxicity

Cisplatin, as described earlier, is a heavy metal-based anticancer drug with absolutely no chemical features, mechanism of action, or spectrum of activity in common with streptomycin, yet both drugs cause loss of hearing, peripheral neuropathies, and renal toxicities.

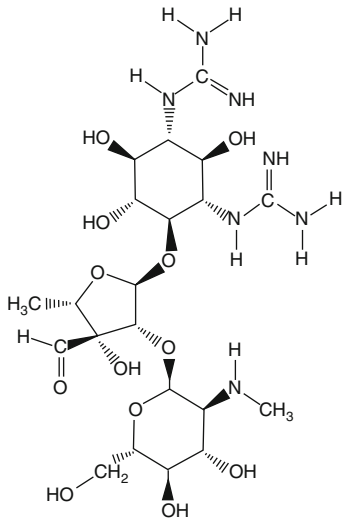

Figure 13.8 Chemical structure of streptomycin.

Approximately 25% of patients treated with cisplatin would develop a renal toxicity primarily of the proximal convoluted tubules when cisplatin was first used clinically. As with doxorubicin and bleomycin, once a patient developed tubular nephritis, no further cisplatin could be administered, regardless of the responsiveness of the tumor to cisplatin. The toxicity is associated with hypomagnesemia, loss of urinary concentration, loss of electrolyte control, and proteinuria. Cisplatin administration is associated with increases in creatinine and BUN levels, two indicators of renal toxicity. In addition, histopathology revealed that the damage was primarily to the epithelial cells lining the tubules and included mitochondrial damage, nuclear damage, and major alterations of epithelial morphology. Although many of these drug-induced changes in renal morphology and function are apparently reversible, a patient remains much more susceptible to platinum toxicity.

The toxicity is thought to be related to other heavy metal renal toxicity. In spite of the clinical importance and the relative frequency of this toxicity the mechanism of the toxicity remains unknown. A number of hypotheses have been put forward including altered mitochondrial function, activation of cisplatin, and inappropriate cellular binding, concentration of the heavy metal in the kidney, induction of apoptosis in

tubular epithelial cells, but as yet no clear-cut mechanism has been identified.

In spite of the lack of understanding of the mechanism of toxicity, treatment regimens have been developed that have diminished renal toxicity associated with cisplatin. Briefly, patients are infused with hypertonic saline solutions prior to administration and hydration and elevated urine output maintained during cisplatin administration. The mechanism of protection is not completely understood but it is believed that the hypertonic saline slows the activation of cispatin in the renal tubules, which lowers inappropriate cellular binding. The increased urine output is thought to lower cisplatin accumulation in the kidneys. Whatever the mechanism, cisplatin-induced nephrotoxicity has decreased significantly following the introduction of this protective clinical protocol.

More recently, the clinical introduction of the cisplatin analog, carboplatin, appears to be far less renal damaging that its precursor yet maintains equivalent antitumor activity. Why this is so is under investigation. Encouraging data further demonstrate that this newer platinum anticancer drug is far less nauseating and far less neurotoxic than cisplatin. This is very important since cisplatin is considered to be the most nauseating drug ever given to humans. Further, continued therapy with cisplatin results in an ever-increasing likelihood of a potentially significant and even paralyzing neurotoxicity.

This story of the development of carboplatin in an attempt to develop a less toxic platinum-based drug demonstrates clearly the importance of continued drug development. Remember that one of the most important considerations in the use of a drug is its therapeutic index and risk versus benefit. The smaller the TI the greater the risk of using a given drug. When treating a headache or common cold, we would not accept a high risk since the benefit is low. In contrast when treating cancer, we accept a much higher risk since the potential benefit is much greater. In spite of this, the development of a drug with an increased TI is the goal of even anticancer drug discovery. We can increase the TI of a drug by increasing efficacy, decreasing toxicity, or both. Carboplatin is an improved drug because it has a lowered toxicity potential and can be used much more safely than cisplatin. We must keep this concept in mind when involved in drug discovery; improvements come not only from developing a more active analog but also by developing a less toxic analog.

13.6.9.2 Streptomycin-induced Renal Toxicity

The class of antibiotics called the aminoglycosides, of which streptomycin is a member, was an important addition to our arsenal of drugs to treat infectious diseases. First used to treat TB, the drugs soon expanded in importance and spectrum of activity. The use of these drugs has decreased dramatically in the Western nations as they have been replaced by safer and more effective drugs. Worldwide, however, the use of aminoglycosides remains important because these drugs are relatively inexpensive when compared to many of the newer less toxic antibiotics.

This continued use of the aminoglycosides warrants a discussion of the toxicities associated with their use. Surprisingly, many of the toxicities of the aminoglycosides are similar to those ascribed to cisplatin, that being nephrotoxicity, neurotoxicity, and hearing loss. Why these two disparate classes of drugs cause similar toxicities is unknown.

After only a few days of administration, streptomycin induces characteristic changes in lysosomes of proximal tubular cells consistent with the accumulation of polar lipids (myeloid bodies). These changes are preceded and accompanied by signs of tubular dysfunctions or alterations (release of brush-border and lysosomal enzymes; decreased reabsorption of filtered proteins; wasting of K^+, Mg^{2+}, Ca^{2+}, and glucose; phospholipiduria; and cast excretion). In humans, the occurrence of these signs may be followed by the development of overt renal failure characterized mainly by a nonoliguric and even often polyuric hypoosmotic fall in creatinine clearance. Progression to oliguric or anuric renal failure is infrequent, and recovery upon drug discontinuation is most often observed. Occasionally, a Fanconi's syndrome or a Bartter's-like syndrome has been observed. A correlation between the development of these clinical signs and the severity or rate of progression of the subclinical alterations remains difficult to establish, mainly because of large interpatient variations. Consequently, the usefulness of monitoring the subclinical changes to detect individuals at risk has remained questionable. In animals, tubular alterations have clearly been associated with the development of focal necroses and apoptoses in the tubular epithelium, together with an extensive tubular and peritubular cell proliferation, without an apparent change in kidney function.

As with platinum complexes a great deal of effort has gone into preventing this toxicity. Streptomycin is concentrated in lysosomes and Golgi bodies. Decreasing or preventing streptomycin accumulation by the kidneys would represent one of the most simple approaches to reduce streptomycin-induced nephrotoxicity. Streptomycin accumulation could be reduced either by impairing drug uptake or by enhancing its excretion. Two strategies have been used to reduce drug uptake: (1) to complex the drug extracellularly, and (2) to compete with or decrease drug binding to the brush-border membrane. Unfortunately, these approaches could not be translated into clinical applications because of a lack of efficacy and/or because of intrinsic toxicity. Another approach has been to develop ways to minimize lysosomal concentration of the drug either by the use of lysosomotropic drugs or by structural modification of the aminoglycoside to lower lysosomic trapping. Again, neither approach has met with significant clinical success.

Significant effort has been expended in an attempt to develop less toxic analogs of the initial aminoglycosides with the focus on two properties of the aminoglycosides. The first was described earlier—lowered

potential to accumulation on the lysosomes. At present it must be concluded that this approach has met with some success but not significant success. A lowered nephrotoxic potential of such drugs has been reported but the impact has been relatively small in clinical trials. The other approach has been to develop drugs with less ability to bind renal phospholipids, a proposed mechanism of streptomycin nephrotoxicity. Several compounds have undergone clinical trials but unfortunately none has shown to be a breakthrough drug. Thus, the search goes on to prevent or at least decrease the nephrotoxic potential of the aminoglycosides. Unfortunately, this search has not met with the same success as the platinum story. Given the importance of these drugs this search will continue and hopefully someday the efforts will bear fruit for this important class of drugs.

13.7 SUMMARY

In summary, ADRs remain a very significant problem in pharmacology. It seems as though every day a new problem is identified that has raised concerns about the safety of drugs that we take. As discussed in this chapter there are a number reasons why this is so. With type A ADRs the concern is that during the development of the drug, both preclinical and clinical, we must maintain a rigorous pharmacovigilance to insure these toxicities are identified early to limit the risk of untoward effects in large numbers of individuals taking the drug. Careful reporting, recording, and analyses of all type A ADRs must occur. These toxicities are far more predictable than type B ADRs, and it is incumbent upon our health delivery system to prevent or at least minimize the incidence of these effects. Type B ADRs are far more difficult to predict and prevent because they are rare and/or idiosyncratic in nature. The identification of these types of toxicities rely even more heavily on careful observations and record keeping. As can be seen from the examples presented in this chapter, ADRs represent a significant problem in pharmacology but also provide a vast array of research opportunities for the experimentalist.

REVIEW QUESTIONS

1. Discuss the differences between type A and type B ADRs.
2. What is pharmacovigilance?
3. Discuss potential difficulties in identifying ADRs and assuring that these ADRs in fact are related to the drug under testing.
4. A drug that is being developed to lower blood pressure is in Phase 1 clinical trials. While the subject is taking the drug, a calcium channel blocker, you note the following symptoms: decreased cardiac output, significant vasodilation, and a weakening of skeletal muscle strength. In addition as the study is continued a worrisome elevation of SGPT and SGOT are noted. Which of these would you ascribe to type A and which to type B ADRs? Defend your decisions.
5. Why is it that a drug may progress to postmarketing clinical trials before certain toxicities are identified?
6. What is the difference between a hypersensitivity response and a hypersensitive individual?
7. What is the therapeutic index and how does it come into play in the drug discovery process? Weave the concept of risk versus benefit in your answer.
8. How might drug metabolism play a role in both type A and type B ADRs? How might pharmacogenomics come to play a role in this process?
9. What is the concept of a rechallenge in a hypersensitive patient? What are potential risks involved in such a process?
10. Discuss how a small molecular weight molecule such as a typical drug induce an immunological response.
11. How might a drug induce a hypersensitive response without induced IgE antibody production? What role could IgE play in a hypersensitive response?

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