# Idiosyncratic Drug Reactions: Current Understanding

Jack Uetrecht

Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario M5S 2S2, Canada; email: jack.uetrecht@utoronto.ca

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## Key Words

adverse drug reactions, tolerance, reactive metabolites, genetic polymorphism, biomarkers

## Abstract

Clinical characteristics and circumstantial evidence suggest that idiosyncratic drug reactions are caused by reactive metabolites and are immune-mediated; however, there are few definitive data and there are likely exceptions. There are three principal hypotheses for how reactive metabolites might induce an immune-mediated idiosyncratic reaction: the hapten hypothesis, the danger hypothesis, and the PI hypothesis. It has been proposed that some idiosyncratic reactions, especially those involving the liver, represent metabolic idiosyncrasy; however, there are even less data to support this hypothesis. The unpredictable nature of these reactions makes mechanistic studies difficult. There is a very strong association with specific human leukocyte antigen (HLA) genes for certain reactions, but this has only been demonstrated for very few drugs. Animal models represent a very powerful tool for mechanistic studies, but the number of valid models is also limited. There may be biomarkers of risk; however, much more work needs to be done.

## INTRODUCTION

### Definition

**IDR:** idiosyncratic drug reaction

The term idiosyncratic means specific to an individual; thus, an idiosyncratic drug reaction (IDR) is an adverse reaction that does not occur in most people within the range of doses used clinically. In addition, adverse reactions that involve the known pharmacological effects of the drug are often excluded and that is how the term is used in this review. For example, the rare cardiovascular events that have been attributed to cyclooxygenase-2-specific agents presumably involve the inhibition of cyclooxygenase, and, therefore, would not be called idiosyncratic even though they are patient specific. To complicate the matter further, when allergists use the term IDR, they usually exclude adverse reactions that are immune-mediated but not reactions that involve the pharmacological effects of the drug. Other terms that are used with varying degrees of overlap with IDR are type B reactions, hypersensitivity reactions, and allergic reactions. In the absence of a clear mechanistic understanding, it is unlikely that the nomenclature for IDRs will be standardized, but a realization that several different terms can be used for this type of reaction and the term idiosyncratic can be used to mean different things will help to avoid misunderstanding. Thus, IDR here refers specifically to adverse drug reactions that do not occur in most patients and do not involve the known pharmacological effects of a drug.

### Significance

A recent study found that adverse drug reactions in the United Kingdom are responsible for more than 6% of hospital admissions, and the mortality rate was approximately 2% (1). However, only approximately 5% of these adverse reactions were idiosyncratic or type B as defined above, i.e., reactions that do not involve the known pharmacological activity of the drug. The most common serious adverse drug reactions were gastrointestinal or intracranial bleeding owing to nonsteroidal antiinflammatory drugs, renal failure/electrolyte disturbances owing to diuretics, and bleeding owing to warfarin. Other studies have found a somewhat higher fraction of idiosyncratic adverse reactions (2).

Although less common, IDRs are a major issue for drug development. From 1975 to 2000, just over 10% of newly approved drugs in the United States either had to be withdrawn or achieved a black box warning owing to adverse reactions that were not predicted by clinical trials (3). In 1991, the major cause for drug candidate failure was unfavorable pharmacokinetics (4). To a large degree, these problems have been solved, and, presently, a major and increasing cause of candidate failure is toxicity. IDRs are especially difficult to deal with because current testing is not effective in predicting their risk. If a promising new drug causes an unacceptable risk of IDRs, it can lead to the failure of the company involved. Therefore, much effort is expended trying to predict the risk of such reactions and dealing with possible "signals" of a potential IDR during clinical trials and postmarketing surveillance. However, the results are far from satisfactory, and our failure to predict which drug candidates will cause a high incidence of IDRs significantly increases the cost and uncertainty of drug development.

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## CLINICAL CHARACTERISTICS OF IDRs

### Incidence

The defining characteristic of IDRs is that they do not occur in most patients who are treated with a specific drug; however, it would be inappropriate to use some arbitrary incidence cutoff above which an adverse reaction would no longer be considered idiosyncratic because there may be some specific population or circumstance in which the incidence is quite high.

### Time to Onset

A very important characteristic of IDRs is a delay between starting the drug and the onset of the adverse reaction (5). There are rare examples in which an IDR appears to begin within days of the first dose of a drug (6), but this is the exception. In almost all cases, the delay in onset is a week or more on first exposure. The typical delay is different for different types of IDRs and for different drugs. Common maculopapular rashes usually occur after one to two weeks of treatment. Agranulocytosis more commonly occurs after one to three months of therapy. Idiosyncratic drug-induced hepatitis most commonly occurs after a month or two of therapy, but for some drugs, such as troglitazone, the delay is often longer and can occur after a year or more of treatment (7). The syndrome of drug-induced lupus usually occurs after several months of treatment, and a delay of more than a year is not uncommon. In contrast to first exposure, the delay in onset of symptoms on rechallenge of a patient who has previously had an IDR to a drug is often very short, and for anaphylactic reactions, this can occur in minutes. However, sometimes the onset of symptoms on rechallenge is also delayed (8) or the IDR may not even occur (9, 10).

### Dose Dependence

IDRs are often referred to as dose independent; this is incorrect and misleading. It is true that most patients will not have an IDR to a specific drug at any achievable dose, and for these patients it is pointless to talk about a dose-response relationship. There may not be a significant difference in the incidence within the narrow range of doses used clinically; however, it is axiomatic that every biological effect has a dose-response relationship, and a dose can always be found at which no one will have an IDR. Avogadro's number—the number of molecules in one mole of a compound—is $6.023 \times 10^{23}$; therefore, there is a very large number of molecules in the therapeutic dose of a drug even if it is very potent. A good example is the treatment of a patient who is allergic to penicillin. There are some life-threatening infections for which there is no good substitute for penicillin, and if a patient is allergic to penicillin, it is usually possible to give a small dose (about one ten thousandth of the therapeutic dose, but still about $10^{17}$ molecules) and then slowly give increasing doses until the therapeutic dose is achieved. Although many drugs do not show an apparent increase in IDR incidence with increasing dose, there are drugs where a dose-response relationship for an IDR is evident within the therapeutic range (11, 12). In addition, it is an

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empirical observation that IDRs are rare with drugs given at a dose of 10 mg $day^{-1}$ or less (13); conversely, drugs such as procainamide and felbamate, where the dose is often one gram per day or more, are more likely to cause IDRs. This is an important issue for drug development.

## Adaptation/Tolerance

Another characteristic of IDRs is adaptation or tolerance. If a drug causes idiosyncratic liver failure in a small number of patients, it usually causes a much higher incidence (>100-fold) of increased transaminases, generally an indicator of liver injury. However, in most patients this increase in transaminases is transient and returns to normal despite continued treatment with the drug (14). Likewise, drugs that cause a lupus-like syndrome usually cause a much higher incidence of elevated antinuclear antibodies than the incidence of clinically evident autoimmunity; this is not an indication to stop the drug (15). In a similar vein, when patients develop a mild drug-induced rash, the rash often resolves despite continued treatment. I have seen the neutrophil count of a patient return to normal on stopping vesnarinone faster than I believe can easily be explained because it takes time for neutrophil precursors to mature, which suggests that the neutrophil count may have returned to normal even if the vesnarinone had been continued. Thus, adaptation or tolerance appears to be common to various types of IDRs and this has both clinical and mechanistic implications.

## Cross-Reactivity

Although there are patients that believe that they are "allergic" to all drugs, in general, when such patients are tested, it is not true, although there may be a small increase in risk of an IDR to another drug. One exception is the aromatic anticonvulsant syndrome associated with phenytoin, carbamazepine, and phenobarbital. If a patient has an IDR such as rash or hypersensitivity while on one of these drugs, the risk that this patient will also have a similar IDR to the other two drugs is approximately 40%–60% (16, 17). This is probably better termed cross-sensitivity rather than cross-reactivity because if a patient is rechallenged with the same drug, the onset of the IDR is usually very rapid; in contrast, if the patient is started on one of the other two drugs, the onset of the IDR is delayed. This suggests that the mechanisms are related and a major risk factor is common to these three drugs, but the immune recognition (presumably drug-specific T cells) is different. With true cross-reactivity, the T cells would recognize both drugs or whatever the drug generates to which the T cells respond. There may be other examples of such cross-sensitivity, but it does not appear to be common.

## Pathologic Characteristics

Most idiosyncratic adverse effects caused by drugs can also be caused by other agents or be idiopathic, i.e., their cause is unknown. For example, there appear to be more



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cases of liver failure where no cause can be found than those caused by IDRs (18–20), and although the histology can provide clues to the etiology, hepatic IDRs cannot be differentiated from idiopathic liver failure or viral hepatitis on the basis of histology alone (21). Drug-induced hepatic failure has an inflammatory component, usually less pronounced than with viral hepatitis, but it is impossible to know if the inflammation is responsible for hepatic damage or secondary to damage. Some hepatic IDRs are associated with eosinophilia, which is considered evidence of an immune-mediated reaction (21).

**HLA:** human leukocyte antigen

**IL:** interleukin

Drug-induced lupus is, by definition, immune-mediated because it is an autoimmune syndrome. Most lupus is idiopathic and, although drug-induced lupus is usually milder than idiopathic lupus, in any individual case it is not possible to differentiate drug-induced lupus from idiopathic lupus except for the association with a treatment known to cause drug-induced lupus, and resolution of the syndrome when the drug is stopped (15).

Most drug rashes are associated with a leukocytic infiltrate and are presumed to be immune-mediated (22). Most types of drug-induced rashes are indistinguishable from rashes caused by viruses or other agents; however, fixed drug eruptions and probably also toxic epidermal necrolysis are rashes that can only be caused by drugs (23).

## Genetic Associations

Many attempts have been made to find associations between a specific genotype and the risk of a specific IDR. One type of gene that could have an influence on risk are those coding for metabolizing enzymes. A few associations with genetically polymorphic metabolic enzymes have been found. For example, the risk of IDRs caused by isoniazid and sulfonamide antibiotics is greater in slow acetylators (24–26); however, the relative risk is small, and 50% of North Americans are slow acetylators; therefore, this could not represent the factor that makes the IDR idiosyncratic. Most other studies looking for an association between polymorphisms in drug metabolism and the risk of an IDR to a specific drug have been negative (27). It is likely that stronger associations do exist; however, such results suggest that differences in drug metabolism are not the major risk factor responsible for the idiosyncratic nature of IDRs.

If IDRs are immune-mediated, it is likely that there would be associations with specific human leukocyte antigen (HLA) genotypes. Most of the early studies looking for such associations were also either negative or the associations were weak (28–33). One of the stronger associations was between HRB1*1501-DRB5*0101-DQB1*0602 and amoxicillin-clavulanate-induced hepatitis, which was found in 57% of affected patients and only 11.7% of controls, but the incidence of hepatitis is less than 1/1000 and more than 10% of the population carry this genotype, so there must be other risk factors (34). Another risk factor appears to be in genes coding for cytokines. It was found that genes associated with low IL-10 and high IL-4 expression were risk factors for diclofenac-induced hepatotoxicity (35).

In contrast to previous studies, a few very strong associations have been found recently. The first strong association found was between HLA-B*5701 and

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hypersensitivity reactions to abacavir in Australia, where the odds ratio is 960 (36, 37). This led to genotyping of patients in Australia before they are treated with abacavir. In contrast, B*5701 may not be a risk factor for abacavir-induced hypersensitivity reactions in black populations (38, 39).

Very strong associations were also found between HLA-B*1502 and carbamazepine-induced Stevens-Johnson syndrome, with an odds ratio of 895 (100% sensitivity, 97% specificity) in Han Chinese (39). Another study in Han Chinese found an association between HLA-B*5801 and allopurinol-induced Stevens-Johnson/toxic epidermal necrolysis with an odds ratio of 580 (40). There was no association between HLA-B*1502 and carbamazepine-induced generalized hypersensitivity reactions even though there are similarities between Stevens-Johnson syndrome and more generalized hypersensitivity. It is not clear why these strong associations are being found now: Is it because there is something specific about these drugs? Is it because a more specific diagnosis was used, i.e., Stevens-Johnson syndrome is different than generalized hypersensitivity reactions? Is it because more homogeneous populations were studied, or maybe it is because the genotyping is now more specific?

## Other Associations

There are many other factors that have been found to be risk factors for specific IDRs, such as sex, age, weight, and disease state. Women are at increased risk of IDRs caused by some drugs, such as halothane-induced hepatitis (41) and clozapine-induced agranulocytosis (42), but not others. The same is true for idiopathic autoimmune reactions. For example, lupus and autoimmune thyroid disease are much more common in women; however, type I diabetes, although it appears to be autoimmune in nature, is not more common in women. For most drugs that cause liver toxicity, such as isoniazid, acetaminophen, etc., the risk of liver toxicity increases with age; however, it is children who are at increased risk of valproic acid liver toxicity (21). Halothane-induced liver toxicity is more common in obese patients; this is presumably because halothane distributes to fat and it requires a higher dose to achieve the same brain concentrations of halothane in obese patients, therefore exposing obese patients to more drug (41). This likely represents an example of a dose-dependent relationship. It is often assumed that patients with preexisting liver disease are at increased risk of idiosyncratic drug-induced liver disease; however, to quote Hy Zimmerman, "Nevertheless, underlying hepatic disease appears to have no significant effect on most forms of hepatic injury, and there is no evidence that hepatitis, cirrhosis, or carcinoma increases susceptibility to hepatic injury" (21). There are likely exceptions; for example, patients with hepatitis C appear to be at increased risk for veno-occlusive disease after myeloablative treatment (43). Preexisting liver disease can certainly complicate therapy and it is often difficult to determine if there is an increase in risk unless the appropriate control groups are used (44). Some infectious diseases, in particular mononucleosis (45), HIV infections (46), and possibly herpes virus (47), appear to be associated with an increased risk of IDRs. Other types of disease may also affect risk (48).

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## Mechanistic Hints from Clinical Characteristics

We have very little definitive evidence on which to determine the mechanism of IDRs, and therefore we are left to make guesses based on clinical characteristics. The idiosyncratic nature of IDRs is most easily explained by an immune-mechanism; everyone is familiar with the fact that some people are allergic to specific agents, whereas most people are not. However, genetic or environmental factors, either alone or in combination, could be responsible for the idiosyncratic nature of IDRs, and it is likely that some idiosyncratic drug reactions are not immune-mediated.

One clinical observation that supports an immune-mediated mechanism is the delay between starting a drug and the onset of the reaction; it is presumed that this is due to the time it takes to expand the T cell and/or B cell that is specific for a given agent to the point where the immune response is clinically evident. It is possible that a delay in onset could be due to the slow accumulation of some toxic agent or depletion of some vital cell component; however, this would likely result in a similar prolonged time course of recovery, and relatively mild IDRs usually recover very rapidly when the responsible drug is stopped. A very rapid onset on rechallenge is strong evidence for an immune mechanism, but the lack of a rapid onset on rechallenge does not prove that an IDR is not immune-mediated. For example, most heparin-induced thrombocytopenia is mediated by antibodies against the heparin/platelet factor 4 complex and autoantibodies against platelet factor 4. Yet, in most cases, when the heparin was stopped, the antibodies were undetectable within 100 days and rechallenge with heparin not only failed to result in a rapid onset of thrombocytopenia, but in most cases there was no recurrence at all (9). We have also observed this pattern in animal models of propylthiouracil and penicillamine autoimmunity (49, 50). Therefore, the lack of a rapid response on rechallenge does not prove that a reaction is not immune-mediated. This may be a feature of reactions that have an autoimmune component, where the reaction would be expected to continue after the drug is discontinued, and there are probably mechanisms to delete or make autoimmune cells anergic.

The observation that the dose-response relationship for a drug is often different for idiosyncratic drug reactions than for its desired therapeutic effects is to be expected independent of the mechanism. This is because there is no reason why two effects of an agent should share the same dose-response relationship unless the two effects are related, e.g., when the toxicity is simply an extension of the pharmacological effect. However, if the dose response is shifted to the left on rechallenge, it suggests an immune response, but the absence of such an effect does not indicate that a reaction is not immune-mediated. Although the response to rechallenge can be more severe than on first exposure, probably the most common response is a similar adverse reaction, and in many cases there is no adverse reaction; therefore, the lack of a response on rechallenge does not prove that the drug did not cause the previous adverse event (9, 10).

There is considerable selective pressure for organisms to be able to respond to a changing environment, and there are probably as many mechanisms by which organisms adapt/develop tolerance as there are different biochemical pathways. As indicated above, adaptation/tolerance is also a common feature of idiosyncratic

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INF: interferon

reactions. We simply do not know what mechanisms are involved in the observed adaptation/tolerance. One characteristic that suggests that immune tolerance may play an important role in many "adaptive" responses is that the time course for the adverse effect to which adaptation occurs usually has the same delay in onset as clinically evident IDRs. For example, a benign increase in transaminases is usually delayed more than a month after starting a drug (51). Such a delay is more difficult to explain on the basis of direct cytotoxicity or some other type of metabolic effect. If the adaptation involved induction of a protective enzyme after a cytotoxic effect, the onset would be expected to occur earlier.

The pathology of most IDRs, especially skin rashes, is compatible with an immune-mediated reaction. However, the observed histological picture is often also compatible with an immune response to heal a cytotoxic response; therefore, in most cases pathology cannot be used to prove mechanism. The presence of antidrug antibodies suggests an immune-mediated reaction, but they may not be pathogenic. Cells responsible for a cell-mediated immune response are more difficult to detect than antibodies.

One specific example of evidence for an immune-mediated reaction based on response to treatment is drug-induced aplastic anemia. Most aplastic anemia is idiopathic and probably caused by viruses. It is treated by bone marrow transplantation or simply immunosuppression. The fact that it responds to immunosuppression suggests that it is immune-mediated. Furthermore, T cells have been found in patients with aplastic anemia that generate IFN$\gamma$, and recovery correlates with a decrease in these cells (52). Drug-induced aplastic anemia also responds to immunosuppression, which suggests that it is also immune-mediated.

The strong association between specific HLA genotypes and the risk of specific IDRs is strong evidence for an immune mechanism, but this has only been demonstrated in a very limited number of cases. The observation that the risk of an IDR to one drug is usually independent of the risk of an IDR to other drugs suggests that if genetic factors are important, the specific genes involved are different for different drugs. The observations that different genotypes are associated with different IDRs owing to the same drug and different in different ethnic groups suggest a very complex picture, which is more likely to reflect an immune mechanism than differences in metabolic pathways.

In summary, although there are some characteristics that are common to most IDRs, there are also many significant differences, and this likely reflects mechanistic differences. Many of the characteristics, such as the link with HLA polymorphisms, rapid onset on rechallenge, and the presence of antidrug antibodies, suggest an immune mechanism; however, the absence of such characteristics does not prove that an IDR is not immune-mediated. Although agreement may not be universal and exact mechanisms are certainly in dispute, I believe the consensus is that drug-induced autoimmunity, antibody-mediated cytopenias, generalized hypersensitivity reactions, almost all drug-associated skin rashes and hepatitis associated with antidrug antibodies and/or rash and eosinophilia are immune-mediated.

It has been proposed that there are also IDRs based on metabolic idiosyncrasy (21). This applies mainly to drug-induced hepatitis and cytopenias, such as

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agranulocytosis, in which rechallenge does not result in rapid recurrence of the IDR (8). The evidence for this hypothesis is essentially nonexistent except that some IDRs lack characteristics that suggest an immune-mediated reaction. On the other hand, it is likely that some IDRs represent some form of metabolic idiosyncrasy. Unfortunately, the clinical characteristics of IDRs are not sufficient to provide much confidence in the mechanisms of IDRs. Many of our assumptions are likely wrong and we need better ways to perform mechanistic studies.

**APC:** antigen presenting cell

**MHC:** major histocompatability complex

## MECHANISTIC HYPOTHESES

Although the mechanisms of most IDRs are unknown, there is general consensus that many are immune-meditated. Therefore, most of the mechanistic hypotheses have an immune basis. In addition, there is a large amount of circumstantial evidence to suggest that chemically reactive metabolites are responsible for many IDRs (53, 54) and this concept is part of several hypotheses. Reactive metabolite screens are also used to try to avoid drug candidates with a high IDR potential (55). However, it is not known if reactive metabolites are always required nor what role they play in the mechanism of IDRs. In fact, although I believe most IDRs are due to reactive metabolites, I suspect that some, such as those associated with ximelagatran and lamotrigine, are not. Although it is not known whether reactive metabolite screens have significant predictive value for the risk of IDRs, the formation of a large amount of reactive metabolite is considered a significant liability for a drug candidate.

### Hapten Hypothesis

In the hapten hypothesis, a chemically reactive drug (or more likely a reactive metabolite) covalently binds to protein, and this adduct results in an immune response. The classical theory is that the drug-modified proteins are seen as foreign by the immune system and that is what leads to an immune response. This is part of the concept that the immune system learns to differentiate "self" from "nonself" early in development and responds with tolerance to self and mounts an active immune response against anything that is nonself or foreign (56).

The drug-modified protein must be taken up by antigen presenting cells (APCs), processed (hydrolyzed into peptide fragments), and presented in the groove of the major histocompatibility complex (MHC) to T cells. The recognition of this drug-modified peptide by T cell receptors is referred to as signal 1. The hapten hypothesis goes back to the experiments of Landsteiner some 70 years ago (57). He found that small molecules did not elicit an immune response unless they covalently bound to proteins. With today's knowledge, the basis for this observation is presumably because most small molecules do not bind with sufficient affinity to the MHC, and if their interaction with proteins is reversible, such interactions would not survive antigen processing. The hapten hypothesis is illustrated in **Figure 1**.

The IgE-mediated IDRs associated with penicillin are consistent with the hapten hypothesis. Penicillin is chemically reactive because of the ring strain inherent in the β-lactam ring. It binds to proteins, and most of the antibodies associated with

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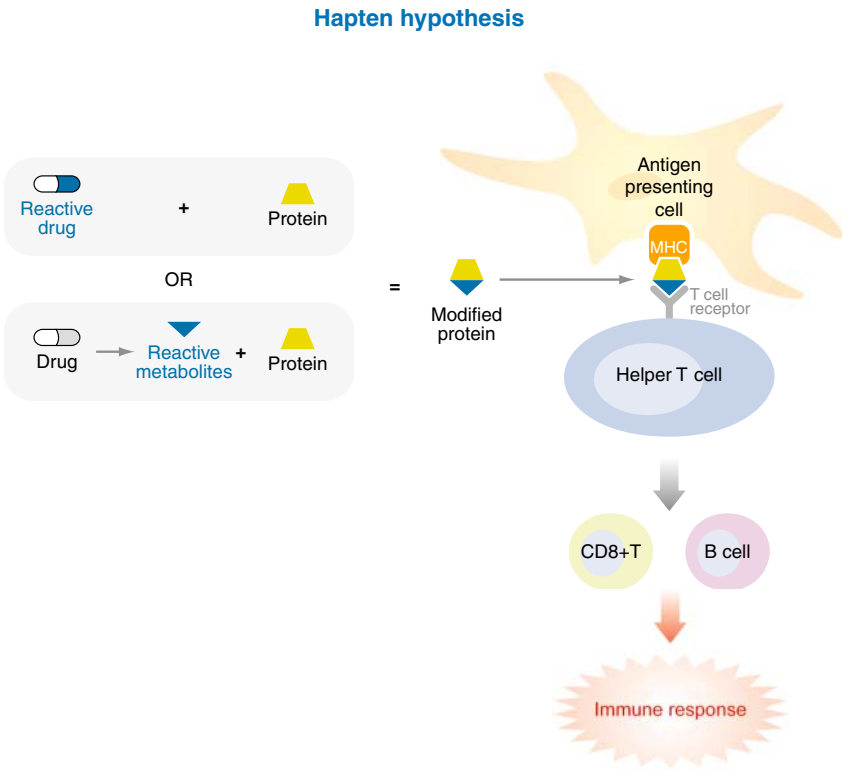
**Figure 1**

Hapten hypothesis. The drug or reactive metabolite binds to protein making it foreign, the modified protein is taken up by antigen presenting cells (APCs), processed, and drug-modified peptides are presented in the context of MHC-II to helper ($CD4^+$) T cells. Recognition of processed antigen by the T cell receptor (TCR) is referred to as signal 1 and leads to an immune response.




penicillin allergies are directed against penicillin-modified proteins (58). IgE antibodies mediate many allergic reactions, such as anaphylaxis, and these antibodies are clearly pathogenic. In the presence of penicillin, the antipenicillin antibodies lead to degranulation of mast cells with the release of histamine, leukotrienes, etc. Several other IDRs are associated with antidrug antibodies, including halothane- and tienilic acid–induced hepatitis (59, 60); however, in these IDRs it is not clear that the antidrug antibodies are pathogenic. In fact, the reactive metabolites associated with these drugs are very reactive and may lead to the formation of intracellular antigens, which would be presented in the context of MHC-I and would result in a predominantly cell-mediated immune response.

Most drugs that are associated with a significant incidence of IDRs are metabolized to reactive metabolites that could bind to proteins and act as haptens. However, not all drugs that are metabolized to reactive metabolites are associated with a significant incidence of IDRs, and it is not clear what determines which drugs will cause IDRs (61). Currently, we do not know enough about what proteins different reactive metabolites bind to, and even if we had that information, we do not have a good way to determine which protein binding, if any, is important to the mechanism of a specific IDR. We do not even have good quantitative data to determine if there is a correlation between the amount of covalent binding and the risk that a drug will cause a relatively high incidence of IDRs. The data that we have requires



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extrapolation from either animals to humans or from in vitro to in vivo, and there is virtually no quantitative data in humans at the target organs of IDRs. We do know that the risk of IDRs is lower for more potent drugs that do not require high daily doses; this suggests that even if the formation of a reactive metabolite is relatively efficient, there is a minimal amount of reactive metabolite required to induce an IDR (13).

## Danger Hypothesis

Polly Matzinger challenged the classical self-nonself hypothesis of immunology (62). She argued that, in general, foreign proteins do not generate a significant immune response in the absence of an adjuvant, which stimulates APCs. There are also proteins that are not expressed until later in development, such as during puberty and pregnancy, and yet they do not invoke an immune response. She also argues that it would be inefficient to respond to something unless it was causing injury or was dangerous to an organism. Her alternative to the self-nonself hypothesis is termed the danger hypothesis, which theorizes that damage to cells causes them to release danger signals that stimulate an immune response. It is known that in addition to signal 1 described above, costimulation of T cells by activated APCs is required for an immune response. This is mediated by interactions between costimulatory molecules, such as B7 on APCs and CD28 on T cells. This is referred to as signal 2, and without signal 2, the response is immune tolerance. In this hypothesis, it is danger signals from stressed cells that stimulate APCs, leading to upregulation of costimulatory molecules. It is not known what these danger signals are, but they are likely to be endogenous and different for different types of cell stress and different types of cells. Thus, a major determinant of the nature of the immune response may be the tissue being affected (63).

Extending this hypothesis to IDRs, it may be that some reactive metabolites cause cell damage, which generates a danger signal (13, 64, 65). Therefore, the apparent association between reactive metabolites and IDRs could be due to their ability to act as danger signals rather than as haptens, or both effects may be important. Likewise, it is possible that the reason that some drugs form reactive metabolites but do not cause a significant incidence of IDRs is that their reactive metabolites do not cause cell damage. The danger hypothesis applied to IDRs does not address the issue of signal 1; in principle, it could be provided by the drug, a drug-modified peptide, or an autoantigen. Any complete hypothesis must address the origin of signal 2. The danger hypothesis applied to IDRs is illustrated in **Figure 2**.

If the danger hypothesis is correct, other types of injuries or infections could increase the incidence of IDRs. As mentioned above, some viral infections do increase the risk of IDRs, yet this is not a universal effect. Not all viral infections affect the immune system in the same way; in addition, there is a big difference between the effect on the immune system of an acute infection and a chronic infection.

## Pharmacological Interaction Hypothesis

Pichler generated clones of T cells from patients with a history of IDRs to specific drugs and found that these T cells proliferated in the presence of drug involved

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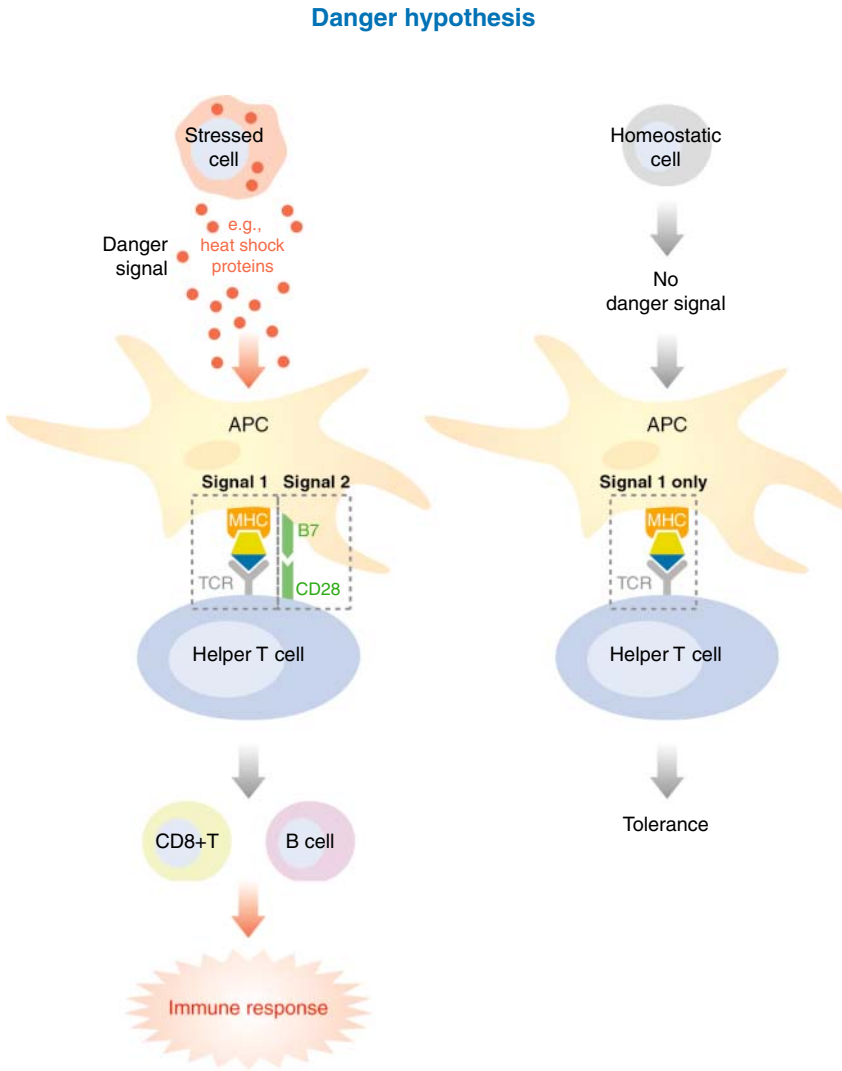


**Figure 2**

Danger hypothesis. Stressed cells produce danger signals such as heat shock proteins that activate APCs, leading to the upregulation of costimulatory molecules such as B7. The exact nature of these danger signals is unknown and is likely different for different types of cell stress. The costimulation of T cells by interactions between APCs and T cells, such as between B7 and CD28, is referred to as signal 2. In the absence of signal 2, the response is tolerance. In principle, the immune response can be to drug, drug-modified proteins, or autoantigens; this hypothesis does not address the issue of signal 1. It is known that signal 2 is required for an immune response, and this has to be incorporated into any complete hypothesis; what is different about the danger hypothesis is what causes activation of APCs and upregulation of costimulatory molecules.

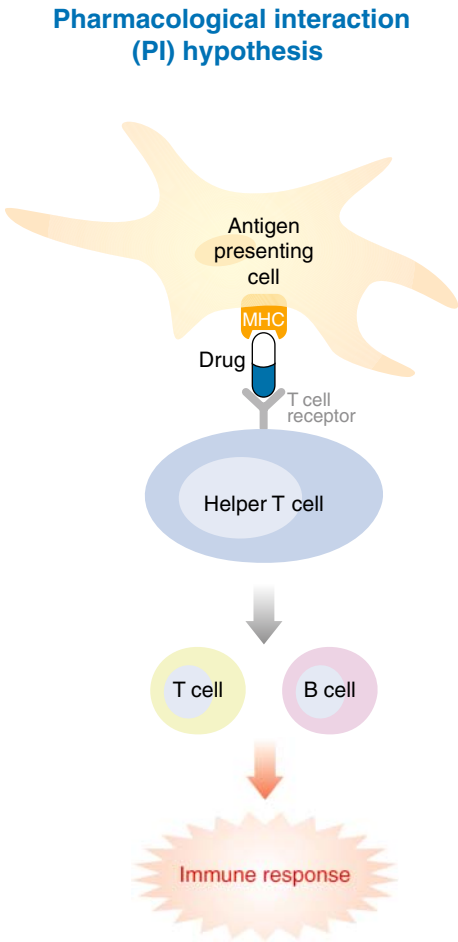


**Figure 3**

Pharmacological interaction (PI) hypothesis. The drug binds directly to the MHC-TCR complex, leading to signal 1 and an immune response to the parent drug. This hypothesis does not address the issue of signal 2.

in the IDR in the absence of metabolism (66). He proposed that many drugs bind reversibly to the MHC–T cell receptor complex, much like a superantigen, and this can stimulate an immune response, in some cases leading to an IDR. He referred to this as the pharmacological interaction (PI) hypothesis (67), which is illustrated in **Figure 3**. This hypothesis addresses the issue of signal 1, but like the hapten hypothesis, it does not address the issue of signal 2.

It is known that several metals, such as nickel (68) and beryllium (69), bind to the MHC and cause allergic reactions, which could be used as an example of a similar mechanism. However, the binding of these metals to protein is stronger than binding of most small organic molecules is likely to be. Sulfamethoxazole was the major drug

**PI:** pharmacological interaction

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NK: natural killer

involved in the studies that led to the PI hypothesis. It is a primary aromatic amine and virtually all primary aromatic amine drugs given at a dose of 10 mg $day^{-1}$ or more are associated with a significant incidence of IDRs independent of the rest of the structure (70). It is likely that this association is due to the oxidation of primary aromatic amines to reactive metabolites; however, it is possible the association of primary aromatic amine reactive metabolites and IDRs is due to their activity as danger signals rather than acting as a hapten.

Another aspect of the finding that T cell clones proliferated in the absence of reactive metabolite is that the generation of these clones involves incubation of T cells from the patients in the presence of drug. This exerts selective pressure so that it is more likely that T cells that proliferate in the presence of drug will be cloned. It is quite plausible that it is the reactive metabolite of sulfamethoxazole that is responsible for the induction of an immune response, but in a significant IDR the immune response widens (epitope spreading) to include recognition of the parent drug. The reactive nitroso metabolite of sulfamethoxazole is more immunogenic than the parent drug and it—but not the parent drug—also induces the production of interleukin 5 (IL-5), which is a characteristic of the T cells associated with sulfamethoxazole-induced rashes (71, 72). There is no way to determine from these clones what actually induced the original immune response.

## Nonimmune Hypotheses

There is substantive evidence that many IDRs are immune-mediated, and the major characteristics of IDRs are most compatible with an immune mechanism. However, it is likely that some IDRs are not immune-mediated and it is currently impossible to know what fraction of IDRs are immune-mediated. In fact, a clear separation may not be possible because a cytotoxic agent may cause cell damage that provokes an immune response, and the immune response may contribute to the damage caused by a cytotoxic agent. For example, there is evidence that the immune system (Kupffer cells, NK T cells, and cytokines) is involved even in the toxicity of drugs such as acetaminophen that are considered directly cytotoxic (73–76).

As mentioned above, some IDRs, especially those involving the liver, are referred to as representing metabolic idiosyncrasy based on a lack of fever and rash and/or lack of immediate onset on rechallenge. However, there is no clear picture of what metabolic pathways might be responsible for the idiosyncratic nature of these reactions, and these characteristics are not very strong evidence against an immune-mediated mechanism. One example of an IDR that is considered to represent metabolic idiosyncrasy is troglitazone-induced liver failure. Various studies have suggested that this IDR is mediated by oxidative stress, mitochondrial damage, inhibition of bile salt transport, and drug-induced apoptosis; however, none of the studies are convincing, nor do they explain the idiosyncratic nature of the reaction (77). On the other hand, some hepatic IDRs, such as valproate-induced hepatotoxicity, do have markers of mitochondrial dysfunction such as microvesicular steatosis, and mitochondrial toxicity presumably does play a role in some IDRs (78). It does not explain the idiosyncratic nature of these reactions, although mitochondrial

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diseases appear to be a risk factor for valproate-induced hepatotoxicity (79). Roth has suggested that the idiosyncratic nature of many hepatic IDRs is due to coincident exposure to a drug and some "inflammagen" such as lipopolysaccharide (LPS) (80). An animal model involving this hypothesis is discussed in the next section.

**LPS:** lipopolysaccharide

### Summary

Currently, these mechanistic hypotheses are simply working hypotheses, and firm evidence for any one hypothesis is lacking for virtually all IDRs. The hypotheses are not mutually exclusive; for example, a reactive metabolite may act as both a hapten and a danger signal, or it may be that T cells recognize the parent drug, but a reactive metabolite is required to stimulate an immune response. Furthermore, the immune system may play a role in the damage caused by agents that are mostly cytotoxic. It is likely that the mechanisms of different IDRs are different and different elements of several hypotheses may be involved in a specific IDR. Although clinical characteristics provide important clues, we need better ways to rigorously test these hypotheses.

## ANIMAL MODELS

Given the difficulty in trying to test mechanistic hypotheses in humans and the impossibility of reproducing such reactions in vitro, as in most biomedical research, animal models represent an important tool for mechanistic studies (81). The difficulty is that IDRs are also idiosyncratic in animals, therefore finding a practical model is very difficult. For example, dogs, especially large breed dogs such as the Doberman Pinscher, have IDRs to sulfonamides that are similar to those that occur in humans, but the incidence is only on the order of 1% and Doberman Pinschers are not easy animals to work with (82). In addition, because what we are really interested in is IDRs in humans, it is essential that the mechanism in the animal model represent the mechanism of the IDR in humans. This criterion is made more complex by the fact that different patients have different IDRs to the same drug; therefore, an animal model may be a good model for one patient but not for another.

### LPS-Potentiated Liver Cytotoxicity

Roth has found that cotreatment with LPS potentiates the hepatotoxicity of ranitidine. The toxicity occurs within hours and it appears to be mediated by neutrophils (83). Ranitidine is available without a prescription and is rarely associated with significant toxicity. In addition, the time course of this reaction is quite different than typically observed with IDRs, so I do not believe that this represents a common mechanism of IDRs. However, there are likely many mechanisms for IDRs and this may represent one.

### Halothane-Induced Liver Injury in the Guinea Pig

As discussed earlier, halothane-induced hepatitis has several characteristics that suggest that it is immune-mediated. Several attempts have been made to reproduce this

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IDR in animals but none have been successful in producing toxicity that is similar to that observed in humans. The most interesting studies involve the treatment of guinea pigs with halothane, which results in an immune response but it does not lead to a persistent immune response or liver failure (84). This result suggests that the usual response of most animals and people to a drug that causes a relatively high incidence of immune-mediated IDRs is immune tolerance.

**BN:** Brown Norway

**TGF-β:** transforming growth factor beta

## Penicillamine-Induced Autoimmunity in Brown Norway Rats

Penicillamine therapy in humans is associated with a relatively high incidence of various autoimmune syndromes, including a lupus-like syndrome and myasthenia gravis (85). It also causes an autoimmune syndrome in Brown Norway (BN) rats (86, 87). The syndrome in BN rats includes a rash, antinuclear antibodies, hepatic necrosis, arthritis, and weight loss. Like IDRs in humans, there is a delay between starting the drug and the onset of the autoimmune syndrome (in this case about 3 weeks), and it is idiosyncratic in that it only occurs in BN rats. Furthermore, even though this is a highly inbred strain, it only occurs in 50%–80% of treated animals. The dose-response relationship is unusual; specifically, it requires 20 mg $day^{-1}$ to induce the syndrome, but increasing the dose to 50 mg $day^{-1}$ does not increase the incidence. However, the incidence at a dose of 10 mg $day^{-1}$ is 0, and after 2 weeks of treatment at this dose, animals are tolerant to a dose of 20 mg $day^{-1}$. This is immune tolerance because it can be transferred to naïve animals with spleen cells from a tolerant animal (88). The major cell involved in this tolerance appears to be $CD4^+$ T cells; when tolerized animals are treated with 20 mg $day^{-1}$, their $CD4^+$ T cells express increased levels of IL-10 and transforming growth factor beta (TGF-β) mRNA (88). This is not observed when naïve animals are treated with doses of 10 or 20 mg $day^{-1}$, and suggests that tolerance is mediated by regulatory $CD4^+$ T cells; however, it appears that other cells also play a role (89). As mentioned before, if the penicillamine is stopped and the animal is allowed to recover and then rechallenged with penicillamine, the autoimmune syndrome recurs with the same time course as on initial exposure.

Penicillamine-induced autoimmunity in the BN rat is increased in incidence and severity by one dose of poly-IC (a synthetic polymer of inosine and cytosine), which mimics viral RNA and stimulates macrophages through toll-like receptor 3 (90). The syndrome is prevented by one dose of misoprostol (a prostaglandin E analog). Treatment of tolerized animals with a combination of poly-IC and penicillamine partially overcomes tolerance, and it also appears that depletion of macrophages during tolerance induction partially prevents the induction of tolerance. LPS, which stimulates macrophages through toll-like receptor 4, has a similar effect as poly-IC, although the effect is less (88). Thus the incidence of autoimmunity can be influenced by manipulation of the immune system. However, treatment of Lewis rats with a combination of penicillamine and poly-IC does not lead to autoimmunity; thus, the syndrome is very strain dependent, and simply stimulating the immune system while giving an animal a drug that causes an immune-mediated IDR in humans is not sufficient to produce an animal model.

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Penicillamine is chemically reactive without metabolism; it can react with protein disulfides to form mixed disulfides and it reacts with aldehydes to form a thiazolidine ring (91). One of the signaling pathways between macrophages and T cells involves reaction of an aldehyde on macrophages with an amine on T cells with the formation of a reversible imine linkage (92). The irreversible reaction of penicillamine with the aldehyde groups on macrophages could lead to activation of the macrophages, and in some cases this could lead to a generalized autoimmune syndrome (93), a hypothesis that we are currently testing.

## Nevirapine-Induced Skin Rash in Rats

Nevirapine (**Figure 4**), a nonnucleoside reverse transcriptase inhibitor, causes a high incidence of skin rash, some of which are severe, and it can also cause liver toxicity (94). The incidence is higher in women, and patients with a low $CD4^+$ T cell count are partially protected (95). We discovered that nevirapine also causes a skin rash in rats, but it does not cause significant liver toxicity (96). The rash is strain and sex dependent, with a 0% incidence in all male animals treated and a 20%–100% incidence in female Sprague-Dawley and BN rats, respectively. Like the rash in humans, there is a 2–3 week delay between starting the drug and the onset of rash in BN rats. Unlike penicillamine-induced autoimmunity, if nevirapine is discontinued and the rash is allowed to resolve, rechallenge results in an accelerated and more severe reaction, with red ears in approximately 8 h. This sensitivity can be transferred to naïve animals with spleen cells. As in humans, $CD4^+$ T cells appear to be essential in the rat model, and their depletion is partially protective; in contrast, depletion of $CD8^+$ T cells is not protective, and even appears to make the rash worse (97). Unlike the

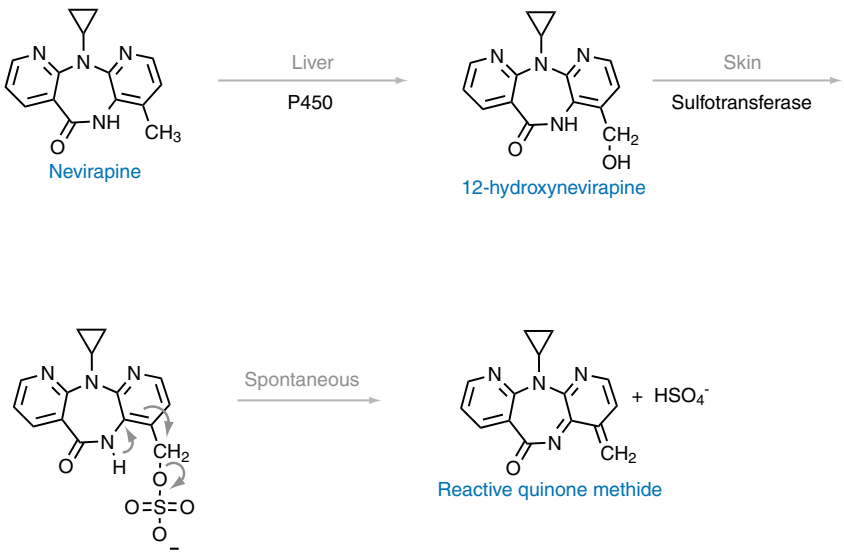


**Figure 4**

Postulated reactive metabolite of nevirapine.

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penicillamine model, poly-IC and misoprostol had no effect on the incidence or severity of nevirapine-induced rash in rats. Nevirapine-induced skin rash in the rat is clearly immune-mediated and, because its characteristics are very similar to those of the rash in humans, the mechanism is likely very similar. In both humans and the rat model, $CD4^+$ T cells appear to play a key role.

As in humans (98), low-dose nevirapine pretreatment of rats resulted in tolerance to high-dose nevirapine treatment (97). However, unlike the penicillamine model, in which the tolerance is immune tolerance, the major mechanism in the nevirapine model is metabolic. The tolerance is not transferable with spleen cells, it is not long lasting, and it can be overcome by aminobenzotriazole, which is a cytochrome P450 inhibitor. Nevirapine causes enzyme induction, and when tolerized animals are treated with high-dose nevirapine, the blood levels of the drug are significantly lower than when a naïve animal is treated (J. Chen & J. Uetrecht, unpublished observations). The sex and strain dependence is also largely due to metabolic differences: Given the same per weight dose, the blood level of nevirapine is much lower in male animals than female animals and is lower in Lewis rats than BN rats.

It is not yet clear whether nevirapine or a reactive metabolite is responsible for the rash. The major metabolic pathways of nevirapine are 2, 3, and 12 hydroxylation (99). There is a nitrogen para to the 2 and 3 position; therefore, oxidation at these positions has the potential to form a quinoneimine-type reactive metabolite. However, aminobenzotriazole inhibits 2 and 3 hydroxylation and yet leads to a rash at a lower dose of nevirapine than occurs with nevirapine alone (J. Chen & J. Uetrecht, unpublished observations). Therefore, these pathways must not be responsible for the rash. It is possible that a one-electron oxidation of the cyclopropyl amine would lead to a reactive metabolite, because of ring strain, that leads to a rearrangement with the formation of a more reactive carbon-centered free radical. However, treatment of a sensitized animal with a nevirapine analog in which the cyclopropyl group is replaced by an ethyl group led to a rash; therefore, the cyclopropyl group must not be essential for the induction of rash. Although aminobenzotriazole markedly inhibits 2 and 3 hydroxylation, it does not inhibit 12 hydroxylation (J. Chen & J. Uetrecht, unpublished observation). Sulfation of 12-hydroxynevirapine followed by loss of $HSO_4^-$ would lead to a reactive quinone methide, as illustrated in **Figure 4**. Sulfotransferases are present in the skin, so this could explain why the skin is a target organ (100). Painting of small amounts of either nevirapine or 12-hydroxynevirapine on the ear of a sensitized animal leads to a rash, which suggests that there are T cells in sensitized animals that recognize the parent drug because there is unlikely to be significant oxidation of nevirapine to the 12-hydroxy metabolite in the ear. In addition, in a version of the lymphocyte transformation test, T cells from animals that have been rechallenged with nevirapine, when incubated with nevirapine, produce interferon-$\gamma$ (IFN-$\gamma$), although there is unlikely to be any reactive metabolite generated in this in vitro system (M. Popovic & J. Uetrecht, unpublished observations). This is consistent with the PI hypothesis; however, it does not mean that it is the parent drug that induced the immune-mediated rash in the first place. It is quite conceivable that it is a reactive metabolite that induces the immune response, but once induced, T cells are generated that also respond to the parent drug. We have observed



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that treatment of animals with 12-hydroxynevirapine also causes a rash (J. Chen & J. Uetrecht, unpublished observation). This model should make it possible to test the PI hypothesis by studying the induction phase of the immune response. I cannot think of any other way to rigorously test this type of mechanistic hypothesis.

## Lessons from Animal Models

We have two animal models—penicillamine-induced autoimmunity in the BN rat and nevirapine-induced rash in the rat—that we believe represent the mechanism of the similar IDR that occurs in humans, yet in these two models the findings are very different. Specifically, although both are immune-mediated, penicillamine-induced autoimmunity is potentiated by immune stimulation with poly-IC, whereas nevirapine-induced skin rash is not. The penicillamine model appears to be quite specific to the BN rat, whereas nevirapine induces skin rash in several rat strains. This is a bit surprising because the penicillamine model seems to represent more of a generalized autoimmune syndrome, possibly owing to generalized macrophage activation, as suggested above, and as such might be less dependent on antigen presentation by a specific MHC molecule. In contrast, the nevirapine might be expected to involve antigen presentation and be more MHC and strain specific. Low-dose treatment for two weeks produces tolerance in both models, but in the penicillamine model it is immune tolerance, whereas in the nevirapine model it is mostly metabolic tolerance. In the nevirapine model, rechallenge results in a very rapid onset and a more severe syndrome, whereas in the penicillamine model, rechallenge leads to a response that is indistinguishable from the initial response. With such differences in these two models, it is difficult to make any generalizations that would apply to most human IDRs and more models are needed. However, we still have a lot to learn from these two models.

Valid animal models represent a very important tool for mechanistic studies of IDRs, and yet most attempts to develop new models have failed (81). This probably reflects our mechanistic ignorance because if the existing hypotheses were correct, it should be possible to produce models by inducing reactive metabolite formation, inhibiting detoxication pathways, and/or stimulating the immune system to prevent the development of tolerance. We have tried these strategies without success. It may be that, as seen with carbamazepine-induced Stevens-Johnson syndrome, a specific MHC is required and the nevirapine model is an exception. Using genetically modified animals, such as IL-10 knockouts, may help, but it is not clear yet what would likely result in an animal model. A better understanding of tolerance, especially immune tolerance, is also likely to be important (101).

## The Role of mRNA Profiles, Proteomics, and Metabonomics in the Study of IDRs

Although drugs that are associated with IDRs do not cause toxicity in most people who take the drug, it is likely that they do cause biochemical changes that are the precursor to the IDR but the individual responds with tolerance/adaptation. In theory, such changes could be monitored using mRNA microarrays, proteomics, and

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metabonomics to see if there are patterns that predict a drug's propensity to cause IDRs. It would be difficult to perform such studies in humans, especially if it involved sampling tissue such as the liver, and in most cases, the metabolic and biochemical pathways are sufficiently similar between humans and animals that it should be possible to perform these studies in animals. However, it is likely that in some cases there would be significant differences and the results in animals would be misleading; thus, confirmation in humans where possible would be very desirable.

Given the importance of finding a screening method that predicts the risk that a drug candidate would cause IDRs, it would seem that the pharmaceutical industry would have performed extensive studies to try to find patterns of changes that reflect IDR risk. However, if such studies have been performed, no major studies have been published. Most of the studies that have been reported at scientific meetings involve agents that cause predictable types of toxicity. We have performed limited studies with microarrays, most of which have not been published yet, and my impression from these limited studies is that, although drugs associated with IDRs do cause changes in mRNA expression that represent a stress response, it is more complex than one might have hoped. If there are patterns that predict IDR risk, there probably are a large number of different patterns, and simple screens may not be sufficiently accurate to be of benefit. However, the stakes are high and it is important that extensive studies be performed and published. Such studies should also provide mechanistic clues.

## CONCLUSIONS

IDRs are now a major factor contributing to the cost and uncertainty of drug development. They are very difficult to study and little is known with certainty about their mechanisms. It is possible that there are patterns of biochemical changes that will make it possible to better predict which drug candidates are likely to be associated with a high incidence of IDRs, but from what we have seen to date in animal models and with limited studies using microarrays, I suspect that there are several mechanisms for IDRs and even greater numbers of biochemical patterns associated with IDRs. A better basic mechanistic understanding is essential for dealing with the problem. I believe that animal models represent the best way to answer the basic questions of whether it is the parent drug or a reactive metabolite that is responsible for a specific IDR, and further, how the drug or its reactive metabolite induces an IDR. The recent successes in finding specific genotypes that are very strongly associated with specific IDRs are also quite encouraging; however, these relationships may also be very complex. Such genetic relationships probably do not exist for all IDRs, and they appear to be different for different ethnic populations and different for different IDRs associated with the same drug.

### SUMMARY POINTS

1. Mechanistic understanding of IDRs is superficial and it is likely that there are many mechanisms.

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2. Most IDRs appear to be due to reactive metabolites and be immune-mediated; however, the evidence is circumstantial and there are probably many exceptions.
3. It is not clear what makes such reactions idiosyncratic; however, there are a few examples where very strong HLA associations have been demonstrated.
4. IDRs are often said to be dose independent; this is misleading and drugs given at low doses are less likely to cause such reactions.
5. Animal models represent an important tool for mechanistic studies, but few valid animal models have been found.
6. Screening for reactive metabolites may provide an indication of IDR risk, but that has not been demonstrated. Other biomarkers that predict the risk that a drug candidate will cause IDRs may exist, but the complexity of such reactions may preclude a simple biomarker screen.

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**Errata**

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