

Mechanistic perspectives on sulfonamide-induced cutaneous drug reactions

Timothy P. Reilly and Cynthia Ju

Purpose of review

Idiosyncratic drug reactions continue to limit the therapeutic utility of sulfonamide drugs because of their associated morbidity and mortality. Cutaneous reactions are the predominant reasons for withdrawal of such drugs from use in patients. As a consequence of the recognized metabolic and immunologic capability of the skin, an understanding of the pathogenic role of this tissue in the development of sulfonamide-induced cutaneous drug reactions may provide insight into the mechanisms and risk factors for these and other adverse drug events.

Recent findings

In the present review we discuss currently available mechanistic information, including issues related to drug bioactivation and adduct formation, immunoresponsiveness, and immune dysregulation, for the development of sulfonamide-induced (delayed-type) cutaneous drug reactions. The potential application of findings from several related areas of research are also discussed within the context of the pathogenesis of these cutaneous reactions.

Summary

Despite progress, numerous unresolved issues support the testing of novel hypotheses, the search for additional risk factors, and the need for a global approach, including links between laboratory and clinical paradigms. These issues must be addressed if we are to gain an understanding of the mechanistic bases for these cutaneous drug reactions.

Keywords

cutaneous drug reactions, idiosyncratic drug toxicity, keratinocytes, skin, sulfonamides

Curr Opin Allergy Clin Immunol 2:307–315. © 2002 Lippincott Williams & Wilkins.

Molecular and Cellular Toxicology Section, Laboratory of Molecular Immunology, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA

Correspondence to Tim Reilly, PhD, Molecular and Cellular Toxicology Section, Laboratory of Molecular Immunology, NHLBI, NIH, 9000 Rockville Pike, Building 10, Room 8N110, Bethesda, MD 20892-1760, USA
Tel: +1 301 402 7323; fax: +1 301 480 4852; e-mail: ReillyT@nhlbi.nih.gov

Current Opinion in Allergy and Clinical Immunology 2002, 2:307–315

Abbreviations

CDR	cutaneous drug reaction
HLA	human leukocyte antigen
MHC	major histocompatibility complex
SMX-NO	sulfamethoxazole nitroso metabolite
SMX-NOH	sulfamethoxazole hydroxylamine metabolite
TNF	tumor necrosis factor

Introduction

The therapeutic utility of sulfonamides, particularly sulfamethoxazole, has been limited by their propensity to cause adverse reactions with significant morbidity and mortality [1]. Although clinical presentation and severity may vary [1], the most frequent manifestations of toxicity involve the skin [2•].

Sulfonamide-induced cutaneous drug reactions (CDRs) occur in approximately two to four out of every 100 individuals taking sulfonamides, but are dramatically more common (reportedly in the 40–60% range) in HIV-infected patients (for review [2•]). Such CDRs encompass a wide array of clinical/pathological diagnoses that include urticaria, macular exanthemas, eczematous and fixed drug eruptions, and erythema multiforme, as well as severe and life-threatening manifestations such as Stevens–Johnson syndrome and toxic epidermal necrolysis [1,2•]. The clinical onset of many sulfonamide-induced CDRs, often occurring at least 7 days after drug initiation, suggests a delayed-type, idiosyncratic reaction (for review [2•]). Histopathological studies of patient samples have demonstrated significant infiltration of immune cells [3–7,8•,9•], as well as induction of proinflammatory cytokines [7,8•,10] and adhesion molecules [5] within the affected areas of skin. Moreover, Hertl *et al.* [11] identified sulfamethoxazole-specific T cells within lesions of a patient during a sulfonamide-induced CDR. Those observations provide compelling but still circumstantial evidence to support a cellular immune-mediated component of many sulfonamide-induced CDRs. However, the varied clinical phenomena also suggest a complexity of ‘cause’ and ‘effect’ responses, making definitive mechanistic studies extremely difficult. The present review addresses the proposed mechanistic models for these idiosyncratic (delayed-type) cutaneous reactions, including recent studies that suggest important but controversial ideas regarding the pathogenesis of sulfonamide-induced CDRs.

A mechanistic framework: integrating cutaneous reactions with the hapten and danger hypotheses

The hapten hypothesis is a useful model to explain how many low-molecular-weight drugs such as sulfonamides trigger an immune-mediated CDR (for recent review [2•]). Although sulfamethoxazole is believed to be too small and chemically inert for recognition by immune cells, it is bioactivated to a reactive hydroxylamine

[sulfamethoxazole hydroxylamine metabolite (SMX-NOH)] [12], which spontaneously oxidizes to a nitroso species [sulfamethoxazole nitroso metabolite (SMX-NO)] that binds cellular proteins and is cytotoxic [13–15]. In contrast to drug or metabolite alone, metabolite–protein adducts are believed to be immunogenic, acting as ‘neoantigenic’ initiators of an immune response when presented in the context of major histocompatibility complexes (MHCs). Identification of sulfamethoxazole–protein conjugates in human sera [16], recognition of sulfamethoxazole-bound proteins by antibodies from patients with a previous sulfonamide-induced CDR [17], and the unique immunogenic potential of SMX-NO in rats [18] support this hypothesis. Moreover, the association between clinical toxicity and decreased capabilities of sulfonamide detoxification pathways, as in slow acetylators phenotypic individuals [19], suggests that the generation of reactive metabolites may be a critical determinant of toxicity.

One problematic issue in relating this hypothesis to sulfonamide-induced CDRs has been the inability to readily equate hepatic activation of sulfonamides with cutaneous toxicity [2•]. Some have questioned the extent to which hepatocyte-generated reactive metabolites may survive transit from the liver to peripheral sites such as skin [2•,20–22]. Although phagocyte-mediated oxidative activity may be an extrahepatic metabolic source (for review [22]), Reilly *et al.* [21] proposed an alternative mechanism in which epidermal keratinocytes might directly generate reactive drug species within the skin. Using an *in-vitro* system, they showed that human epidermal keratinocytes can metabolize sulfamethoxazole and the sulfone drug dapsone to reactive hydroxylamines; that these reactive species covalently bound to keratinocyte proteins; and that there was a unique dependence of SMX-NOH-mediated binding and cytotoxicity on cellular glutathione levels. The latter data may help to explain the increased incidence of sulfonamide-induced CDRs in HIV-infected individuals [2•] who have a reported deficiency in glutathione [23] and a decreased capacity to detoxify SMX-NO [24]. This is also an intriguing model because, apart from their metabolic potential [25•,26], keratinocytes represent the predominant cell type within the skin and possess a range of immunologic activities [27,28] that include expressing MHCs [29] and adhesion molecules [30,31] on their cell surface, as well as the capacity to release cytokines [30,32] and chemokines [33,34•]. Induced expression of MHC, adhesion, cytokine, and chemokine molecules by keratinocytes is a common but varied histopathological observation in patients with sulfonamide-induced CDRs [6,9•,35•].

In addition to their potential to present drug-bound antigens directly to T cells [36–38], keratinocytes may

also activate nearby professional antigen-presenting cells in the skin, particularly Langerhans cells, by releasing drug–protein ‘neoantigens’ or stimulatory signals [39]. Langerhans cells are critical in the development of cutaneous immune responses to allergens and model haptens, and have been shown to be depleted in drug-induced lesional skin [4,40].

Although this model [21] still requires experimental validation, it suggests that the general hallmarks of the hapten hypothesis (i.e. bioactivation, protein binding, and presentation of drug–protein ‘neoantigens’ to immune cells) might all occur directly within the cutaneous environment and may contribute significantly to the development of sulfonamide-induced CDRs.

Other data have emerged that challenge the necessity for bioactivation and covalently linked ‘neoantigens’ as a primary stimulant for immune activation. Pichler and coworkers [41–43] showed that T-cell clones from patients with previous reactions to sulfonamides, as well as to lidocaine, proliferate *in vitro* in the presence of the offending drug in an MHC-dependent, but metabolism- and antigen processing-independent, manner. These data suggest that sulfamethoxazole can associate with MHCs in a noncovalent manner sufficient to stimulate sulfamethoxazole-specific T cells. However, whereas specificity has been demonstrated for the parent drug in many cases [44], T-cell proliferation can also be selective for protein-bound SMX-NO [11,44], which is inhibited by glutathione [45•]. These data suggest that drug-specific T-cell activation may occur through a variety of different mechanisms, although the pathological role and preponderance of each remain to be determined *in vivo*.

Importantly, the model presented by Pichler and coworkers of reversible sulfamethoxazole–MHC interaction need not negate the relevance of bioactivation because reactive drug species may still be critical in initiating an immune response. As discussed in an earlier report [20], although drug–peptide–MHC complexes provide the first antigenic signal for T-cell activation through the T-cell receptor, a second costimulatory signal is required to establish an effective immune reaction [46•]. The toxic effects of metabolites might provide this costimulation via the generation of ‘danger’ signals, as proposed by Matzinger [47]. The argument that ‘bad’ (necrotic) death or cellular stress mediators [47], including possibly heat shock proteins [48,49•], are ‘danger’ signals that result in costimulation fits with the cytotoxic or stressful effects of reactive drug species. Others have shown, for example, that cutaneous irritants can stimulate keratinocyte expression of costimulatory molecules including CD80 (B7.1) [50] and CD40 [46•,51]. Although this ‘danger hypothesis’ continues to be a subject of debate [52,53], it

has gained recent experimental support [54,55] and maintains the a-priori necessity of bioactivation. Moreover, a combination of the hapten and danger hypotheses provides a workable framework for understanding how sulfonamides and other drugs might initiate a CDR.

Recent developments, continued controversy, and new questions

Whereas much data favors a role for bioactivation, it has yet to be proven that elevations in reactive metabolites lead to sulfonamide-induced CDRs. Past studies have failed to find an association with polymorphisms in oxidative capability [56] or glutathione processing [57], and have shown the association with slow acetylation (NAT2) to be less than absolute [58]. More recently, studies have failed to correlate the increased incidence of sulfonamide-induced CDRs in HIV-positive patients with metabolic polymorphisms [59] and have found the combination of slow acetylation and glutathione S-transferase M1 null genotype to be less than expected, given the importance of detoxification pathways [60]. One interesting development is the demonstration that bacterial lipopolysaccharide can decrease metabolic inactivation of SMX-NOH [61•]. Those data provide limited support for the hypothesis that concomitant infections may increase susceptibility to sulfonamide-induced CDRs secondary to increased metabolite levels. What remains to be determined is how much of a metabolic alteration might significantly alter susceptibility, whether there is a 'threshold' [21] difference between patients in terms of their cellular ability to withstand the toxic effects of reactive species, and whether induction of metabolic changes alone is sufficient for development of sulfonamide-induced CDRs.

Aside from questions regarding the absolute effect of metabolic polymorphisms, however, the hypothesis that bioactivation is required for initiation of sulfonamide-induced CDRs has gained strong support from two recent studies [62•,63•]. Using a delayed-type hypersensitivity model, Choquet-Kastylevsky *et al.* [62•] showed that hypersensitivity could only be induced upon treatment of mice with sulfamethoxazole and an S9 bioactivating system. This supports a reactive metabolite as the initiating hapten *in vivo*. Moreover, splenocyte proliferation could be induced from sulfamethoxazole- or sulfamethoxazole/S9-initiated mice, but only with drug and the bioactivating system. This suggests that sulfamethoxazole treatment can induce cellular activation but that in-vivo responsiveness (i.e. hypersensitivity) requires a higher concentration of reactive metabolites within the cutaneous environment than might normally be produced *in vivo*.

Naisbitt *et al.* [63•] extended these ideas, demonstrating that sulfamethoxazole-specific T cells could be gener-

ated in rats in an SMX-NO-specific manner. Those investigators showed in-vivo labeling of keratinocytes and peripheral blood cells when rats were injected with SMX-NO, and to a lesser degree with SMX-NOH, and correlated covalent labeling with an ability to induce T-cell activation. Their data suggest that, in addition to whatever cutaneous metabolism occurs [21], reactive sulfonamide species can also survive transit to the skin and covalently bind cellular proteins to initiate an in-vivo response [63•]. Moreover, in combination with immune-enhancing adjuvant, in-vivo injection of sulfamethoxazole induced proliferation *ex vivo*, but only when restimulated with SMX-NO (sulfamethoxazole and SMX-NOH were ineffective). Although that study cannot be construed as an in-vivo model of sulfonamide-induced CDRs, it does strongly argue that production of protein adduct-forming metabolites are necessary for a systemic immune response to sulfamethoxazole. The ultimate ability to promote a sulfonamide-induced CDR may be secondary to alterations in additional pathways, including cutaneous increases in interferon- γ or other events [63•].

In contrast to the aforementioned evidence for the role of bioactivation, Pichler and coworkers presented further data that support a unique reactivity of drug-specific T cells to noncovalently linked parent drugs. Interestingly, they found significant allogeneity and divergence in drug-specific T-cell responses [64•], which suggests a heterogeneous T-cell response that may vary with the type of CDR [35•] as well as between individuals [9•]. They have elegantly demonstrated that sulfamethoxazole-specific (and other drug-specific) clones can be both MHC allele-restricted and unrestricted, and that the propensity of T-cell receptors that are specific for self-MHC-peptide-drug complexes to cross-react with non-self-MHC-peptide complexes is significantly higher than that of most common, peptide-specific T-cell receptors [64•], suggesting a possible inclination toward autoimmune-type reactions initiated by drugs. The finding that certain human leukocyte antigen (HLA) types, namely HLA-DRB1*07 [35•] and HLA-A30 B13 Cw6 [65•], are associated with different types of sulfonamide-induced CDRs further supports the suggestion of heterogeneous T-cell responses, possibly through preferential interactions of drugs with certain MHC molecules [35•], leading to varied clinical phenomena. Intriguingly, a correlation between CD8⁺ T-cell activation in CDRs and the development of hepatic injury was also observed [9•]. An obvious question that arises, therefore, is whether the activation of a particular type of T cell with specific phenotypic characteristics (e.g. cytokine profile or HLA specificity) might be more or less likely to lead to a particular type of adverse reaction. Moreover, what links drug-specific T cells, particularly those found in peripheral blood, with the apparent tissue

specificity of CDRs? Are there additional skin homing factors [34•,66,67] that are also altered in patients who are prone to sulfonamide-induced CDRs, or might it be related to factors such as redistribution of immune cells to cutaneous regions by acute stress [68]?

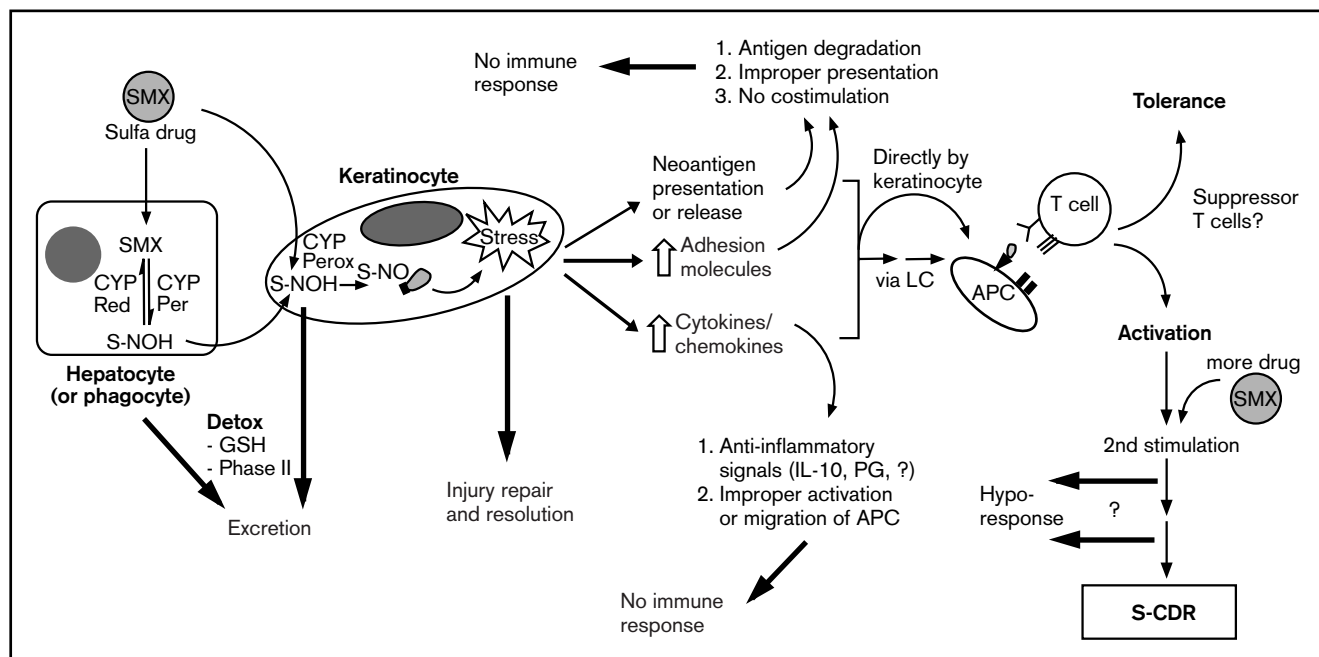
Thus, it seems reasonable to speculate that molecular events within keratinocytes and/or Langerhans cells may be critical points of sulfonamide-induced CDR initiation. Might drugs (or their metabolites) induce cytokine [e.g. tumor necrosis factor (TNF)- α , interleukin-1] or chemokine responses within the skin, as has been shown for drugs such as acetaminophen in the liver (for references [69•])? Might other factors, such as concomitant bacterial or viral infection, induce such initiating events? Interferon-inducible protein-10, which is upregulated in response to interferon- γ , has been shown to be high in CDRs [70], as has interleukin-5 [7,8•,71] and interleukin-8 [7,35•]. Do these chemoattract more infiltrating cells for immunosurveillance, or might the increased incidence of skin reactions simply be related to the simplicity of their observation clinically? Alternatively, could the skin be a default site for toxicity as a consequence of the fact that the liver (the primary site

of drug bioactivation) has significant detoxification and tolerogenic capabilities [72] that resist drug toxic events more effectively than do corresponding mechanisms within the skin [52,73]? With regard to the latter point, studies of acetaminophen-induced liver injury suggest that, metabolic activation and covalent binding being the same, immunoregulatory factors including interleukin-10 [69•] and cyclooxygenase-2-derived mediators [74•] exist to counterbalance the degree of drug-induced injury, and their perturbation significantly affects susceptibility. Although increased proinflammatory and decreased anti-inflammatory mediator levels have been noted as contributing to other skin conditions, including psoriasis [75], their role in susceptibility to sulfonamide-induced CDRs is unknown.

Alternative hypotheses, suggested risk factors, and new approaches

Despite recent progress, we still do not understand how and why sulfonamide-induced CDRs and other drug reactions occur only in certain individuals. Significant variation in the time until toxicity and the clinical/pathological sequelae [1,2•] support the existence of a multitude of factors. As illustrated in Figure 1, a cascade

Figure 1. The complexity of sulfonamide-induced cutaneous drug reactions



Although events such as drug bioactivation to reactive species, covalent binding to cellular proteins, and immunostimulation might favor the development of a sulfonamide-induced cutaneous drug reaction (S-CDR), there also appear to be competing mechanisms that can counteract each of these proinjurious events. In the average individual, protective or anti-inflammatory mechanisms (thick arrows) push the mass balance against the development of toxicity. However, in certain susceptible individuals, genetically or environmentally induced deficiencies occur in one or more of these protective/detoxification mechanisms, allowing for progression along a cascade of events that ultimately results in an S-CDR. APC, antigen-presenting cell; CYP, cytochrome P450; GSH, glutathione; IL, interleukin; LC, Langerhans cell; Per(ox), peroxidase(s); PG, prostaglandin(s); Red, reductase; SMX, sulfamethoxazole; S-NO, sulfamethoxazole nitroso metabolite(s); S-NOH, sulfamethoxazole hydroxylamine metabolite(s). Significantly altered from Reilly *et al.* [21].

of events, including bioactivation, keratinocyte stress secondary to reactive drug species, and immunostimulation, probably links sulfonamide use with cutaneous toxicity. At the same time, regulatory mechanisms also exist to combat these events (Fig. 1). The dynamic interactions between metabolic, detoxification and repair, and anti-inflammatory and proinflammatory mechanisms may well determine the probability of a CDR and its pathological development. Thus, it seems prudent that we continue to explore alternative hypotheses and consider the application of new approaches to gain an understanding of sulfonamide-induced CDRs and the risk factors most likely to be targets for clinical intervention.

Hess *et al.* [76•] recently showed that SMX-NOH may interfere with cell-signaling events within peripheral blood mononuclear cells. At sublethal, therapeutically achievable concentrations, SMX-NOH disrupted interleukin-2 receptor signaling through interference with Janus kinase-STAT (signal transducer and activator of transcription) pathways. The result was a shift toward higher levels of interferon- γ , which favors cell-mediated responsiveness [76•]. Goodman *et al.* [77] suggested that keratinocyte-mediated T-cell activation in the skin causes an 'immune deviation' associated with minimal interferon- γ production, the result being an active, but nonpathogenic immunological tolerance [52]. If SMX-NOH can also cause comparable alterations in signaling cascades or changes in cytokine production within keratinocytes (or Langerhans cells), might the result be a pathogenic immune response as in sulfonamide-induced CDRs? The hydroxylamine metabolite of procainamide has recently been shown to disrupt the induction of central T-cell tolerance, resulting in drug-induced autoimmune-like pathology [78]. Despite the apparent differences in toxicity between procainamide and sulfonamides, those data provide limited support for the potentially important immunomodulatory effect of hydroxylamine metabolites at the cellular and molecular level.

As noted above, a variety of protective mechanisms also exist to prevent the potential development of a drug-specific, immune-mediated, sulfonamide-induced CDR (Fig. 1). Anti-inflammatory cytokines, for instance, may help to resist a 'slippery slope' toward immune reactivity by repressing costimulatory signals, preventing proper activation and migration of antigen-presenting cells, or inducing tolerance, 'immune deviation' [52], or hyporesponsiveness (Fig. 1). What if these protective factors were not regulated properly secondary to genetic or environmental defects? Polymorphisms in interleukin-10, for instance, have been associated with the development of diclofenac and ethanol-induced hepatitis [79,80] and with cutaneous inflammatory diseases (e.g. psoriasis)

[81]. Other investigators have shown that cyclooxygenase-2-derived mediators are tolerogenic, such that their inhibition with cyclooxygenase-2 inhibitory drugs could conceivably increase immune reactivity or drug injury (for references [74•]) subsequent to loss of this protective mechanism. On the other hand, recent data suggest that increases in TNF- α secondary to a polymorphism in its promoter region are associated with carbamazepine-induced CDRs [82•].

In searching for mechanistic explanations for sulfonamide-induced CDRs, no better model exists than the vastly increased incidence of sulfonamide-induced CDRs in HIV-positive patients. Does this clinical observation provide insight into the mechanisms of sulfonamide-induced CDRs? For instance, HIV has been suggested to modify heat shock protein expression by keratinocytes [83], which may in turn accelerate antigen-specific interferon- γ production [84•]. Could similar changes with HIV infection provide mechanistic clues? HIV infection induces secretion of TNF- α , interleukin-1, interleukin-6, and interferon [85–87]. These cytokines are critical in the activation of keratinocytes, migration of Langerhans cells to lymph nodes, and stimulation of T-cell responses, suggesting that their alteration could play some role in enhancing susceptibility. Schnyder *et al.* [88] have recently demonstrated a pathogenic role for sulfamethoxazole-specific T cells in the destruction of MHC-expressing keratinocytes incubated with sulfamethoxazole. This mechanism was interferon- γ dependent, suggesting another possible mechanism for the increased susceptibility of HIV-infected individuals who have elevated interferon- γ levels. The perforin-mediated apoptotic mechanism of keratinocyte killing also correlates with the in-vivo importance of perforin in patients with CDRs [8•] and other skin diseases, as well as the hypothesized involvement of apoptotic death in the pathogenesis of drug-induced toxic epidermal necrolysis [89].

CD4⁺ T cells from HIV-positive patients also produce abnormally low levels of interleukin-2 in response to mitogen and antigen stimulation [90]. This observation is interesting because interleukin-2 is multifunctional, having a redundant mitogenic role that can be fulfilled by interleukin-4, -7, -9, or -15 [91]. A compensatory increase in interleukin-15 in a state of reduced interleukin-2 therefore might promote monocyte differentiation into Langerhans-like cells [92]. Interleukin-2 is also critical at limiting immune responses to foreign or self-antigens, as evidenced by the increased cellular proliferation and autoimmune diseases seen in interleukin-2-deficient mice [91,93]. These data suggest that HIV and its associated reduction in interleukin-2 may impair T-cell homeostasis, and, although lacking experi-

mental support, this altered immune homeostasis may favor the development of sulfonamide-induced CDRs.

An association between sulfonamide-induced CDRs and alterations in gross CD4⁺/CD8⁺ T-cell subsets in HIV-infected patients has been reported [94]. However, HIV is also associated with changes in other cellular subsets that include an altered $\gamma\delta$ T-cell distribution in peripheral blood and a significant increase in V δ 1 CD3⁺ T cells (approximately 12% in AIDS versus <1% in control individuals) [95]. The $\gamma\delta$ T cells are believed to be important in cutaneous immune surveillance and tissue repair [96], and V δ 1 T cells are continuously stimulated throughout the course of HIV infection to produce interferon- γ [95]. High levels of interferon- γ can stimulate MHC expression on keratinocyte surfaces [29,51] and can perturb important regulatory events within the skin [30,39]. The selective CD4⁺ T-cell depletion in HIV-infected individuals might also lead to the loss of tolerogenic control normally provided by CD4⁺CD25⁺ regulatory T cells [97], although their relation to susceptibility to sulfonamide-induced CDR is unknown.

It might also be possible to address a number of questions relevant to the pathogenesis of sulfonamide-induced CDRs using animal models of viral infection, whether they be animal equivalents of HIV or alternatives (e.g. infectious mononucleosis or herpesvirus-6) that are associated with increased incidences of CDR [98,99]. The response of mice, for instance, to many drugs during acute and chronic infection with viruses, parasites, and bacteria is uncharted territory for investigation. Because viral infection has been shown to abrogate CD8⁺ deletion [100], one might imagine that a loss of deletional mechanisms could support the stimulation of drug-specific T cells that are otherwise targets of tolerance induction. More recently, Buchweitz *et al.* [101••] showed that the clinical and histopathological properties of liver injury caused by the antipsychotic drug chlorpromazine in patients can be reproduced in rats following low-dose treatment with bacterial lipopolysaccharide. Although the application of this model to CDRs is unknown, signaling of lipopolysaccharide through CD14 might alter the cutaneous cytokine milieu or increase the number of dermal Langerhans cells [102] that are able to properly initiate CDRs.

Conclusion

The substantial morbidity and mortality associated with sulfonamide-induced CDRs provides a strong impetus to explain how and why particular drugs cause toxicity in individual patients. Although we hope to uncover general mechanisms, it is more likely that there are a large array of factors that contribute to the initiation and development of toxicity, and others that protect against these mechan-

isms (Fig. 1). If we are to better understand such diverse pathogenesises, it is imperative that we bridge the gap between basic laboratory and clinical research paradigms. The continued search for animal models of idiosyncratic toxicity [62••,63••,69••,74•,101••,103] is one such approach, particularly if it leads to the elucidation of hypotheses (and risk factors) that can be evaluated in patients. Alternatively, if pharmacovigilance techniques can be improved, then skin biopsy samples might be utilized in conjunction with genomic and proteomic applications to uncover new and exciting areas for study. If ethical and logistical issues can be rectified, then genomic information might be gathered from each and every person that develops a CDR, and genome-wide analyses performed in order to search for genetic risk factors. Together, these and other approaches should facilitate an enhanced level of comprehension of the complex pathophysiological mechanism(s) of sulfonamide-induced CDRs.

Acknowledgements

Special thanks to Dr Craig K. Svensson (Department of Pharmaceutical Sciences, Wayne State University, Detroit, Michigan, USA) and Dr Lance R. Pohl (National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA) for their critical reading of the manuscript and insightful comments prior to submission.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

- 1 Cribb AE, Lee BL, Trepanier LA, Spielberg SP. Adverse reactions to sulphonamide and sulphonamide-trimethoprim antimicrobials: clinical syndromes and pathogenesis. *Adverse Drug React Toxicol Rev* 1996; 15:9–50.
- 2 Svensson CK, Cowen EW, Gaspari AA. Cutaneous drug reactions. *Pharmacol Rev* 2001; 53:357–379.
This is a recent, comprehensive review of the many issues related to CDRs.
- 3 Correia O, Delgado L, Ramos JP, *et al.* Cutaneous T-cell recruitment in toxic epidermal necrolysis. Further evidence of CD8⁺ lymphocyte involvement. *Arch Dermatol* 1993; 129:466–468.
- 4 Carr A, Vasak E, Munro V, *et al.* Immunohistological assessment of cutaneous drug hypersensitivity in patients with HIV infection. *Clin Exp Immunol* 1994; 97:260–265.
- 5 Barbaud AM, Bene MC, Reichert-Penetrat S, *et al.* Immunocompetent cells and adhesion molecules in 14 cases of cutaneous drug reactions induced with the use of antibiotics. *Arch Dermatol* 1998; 134:1040–1041.
- 6 Yawalkar N, Egli F, Hari Y, *et al.* Infiltration of cytotoxic T cells in drug-induced cutaneous eruptions. *Clin Exp Allergy* 2000; 30:847–855.
- 7 Yawalkar N, Shrikhande M, Hari Y, *et al.* Evidence for a role for IL-5 and eotaxin in activating and recruiting eosinophils in drug-induced cutaneous eruptions. *J Allergy Clin Immunol* 2000; 106:1171–1176.
- 8 Yawalkar N, Pichler WJ. Pathogenesis of drug-induced exanthema. *Int Arch Allergy Immunol* 2001; 124:336–338.
This work expands on previous in-vitro studies showing that infiltrating T cells during a CDR have cytotoxic potential and produce significantly higher amounts of interleukin-5 and interferon- γ .

- 9 Hari Y, Frutig-Schnyder K, Hurni M, *et al*. T cell involvement in cutaneous drug eruptions. *Clin Exp Allergy* 2001; 31:1398–1408.
This study suggests an important correlation between the predominant activation of particular T-cell classes (CD4 versus CD8) and the type of drug reaction. Most interesting are the findings that HLA expression is increased in patients with bullous and hepatic involvement, and that CD8+ T-cell predominance correlates with the noted development of hepatic injury.
- 10 Choquet-Kastylevsky G, Intrator L, Chenal C, *et al*. Increased levels of interleukin 5 are associated with the generation of eosinophilia in drug-induced hypersensitivity syndrome. *Br J Dermatol* 1998; 139:1026–1032.
- 11 Hertl M, Jugert F, Merk HF. CD8+ dermal T cells from a sulphamethoxazole-induced bullous exanthem proliferate in response to drug-modified liver microsomes. *Br J Dermatol* 1995; 132:215–220.
- 12 Cribb AE, Spielberg SP, Griffin GP. N4-hydroxylation of sulfamethoxazole by cytochrome P450 of the cytochrome P450C subfamily and reduction of sulfamethoxazole hydroxylamine in human and rat hepatic microsomes. *Drug Metab Dispos* 1995; 23:406–414.
- 13 Rieder MJ, Uetrecht J, Shear NH, Spielberg SP. Synthesis and in vitro toxicity of hydroxylamine metabolites of sulfonamides. *J Pharmacol Exp Ther* 1988; 244:724–728.
- 14 Cribb AE, Nuss CE, Alberts DW, *et al*. Covalent binding of sulfamethoxazole reactive metabolites to human and rat liver subcellular fractions assessed by immunochemical detection. *Chem Res Toxicol* 1996; 9:500–507.
- 15 Naisbitt DJ, Hough SJ, Gill HJ, *et al*. Cellular disposition of sulphamethoxazole and its metabolites: implications for hypersensitivity. *Br J Pharmacol* 1999; 126:1393–1407.
- 16 Meekins CV, Sullivan TJ, Gruchalla RS. Immunochemical analysis of sulfonamide drug allergy: identification of sulfamethoxazole-substituted human serum proteins. *J Allergy Clin Immunol* 1994; 94:1017–1024.
- 17 Daftarian MP, Filion LG, Cameron W, *et al*. Immune response to sulfamethoxazole in patients with AIDS. *Clin Diagn Lab Immunol* 1995; 2:199–204.
- 18 Gill HJ, Hough SJ, Naisbitt DJ, *et al*. The relationship between the disposition and immunogenicity of sulfamethoxazole in the rat. *J Pharmacol Exp Ther* 1997; 282:795–801.
- 19 Shear NH, Spielberg SP, Grant DM, *et al*. Differences in metabolism of sulfonamides predisposing to idiosyncratic toxicity. *Ann Intern Med* 1986; 105:179–184.
- 20 Uetrecht JP. New concepts in immunology relevant to idiosyncratic drug reactions: the 'danger hypothesis' and innate immune system. *Chem Res Toxicol* 1999; 12:387–395.
- 21 Reilly TP, Lash LH, Doll MA, *et al*. A role for bioactivation and covalent binding within epidermal keratinocytes in sulfonamide-induced cutaneous drug reactions. *J Invest Dermatol* 2000; 114:1164–1173.
- 22 Rubin RL, Kretz-Rommel A. Phagocyte-mediated oxidation in idiosyncratic adverse drug reactions. *Curr Opin Hematol* 2001; 8:34–40.
- 23 Buhl R, Jaffe HA, Holroyd KJ, *et al*. Systemic glutathione deficiency in symptom-free HIV-seropositive individuals. *Lancet* 1989; 2:1294–1298.
- 24 Naisbitt DJ, Vilar FJ, Stalford AC, *et al*. Plasma cysteine deficiency and decreased reduction of nitrososulfamethoxazole with HIV infection. *AIDS Res Hum Retroviruses* 2000; 16:1929–1938.
- 25 Baron JM, Holler D, Schiffer R, *et al*. Expression of multiple cytochrome p450 enzymes and multidrug resistance-associated transport proteins in human skin keratinocytes. *J Invest Dermatol* 2001; 116:541–548.
Together with [26], these studies provide the most recent analyses of the expression of a variety of drug-metabolizing enzymes and drug transporters in human keratinocytes.
- 26 Janmohamed A, Dolphin CT, Phillips IR, Shephard EA. Quantification and cellular localization of expression in human skin of genes encoding flavin-containing monooxygenases and cytochromes P450. *Biochem Pharmacol* 2001; 62:777–786.
- 27 Barker JN, Mitra RS, Griffiths CE, *et al*. Keratinocytes as initiators of inflammation. *Lancet* 1991; 337:211–214.
- 28 Stoof FJ, Boersma DM, Nickoloff BJ. Keratinocytes and immunological cytokines. In: Leigh L, Lane E, Watt F, editors. *The keratinocyte handbook*. Cambridge, UK: Cambridge University Press; 1994. pp. 365–399.
- 29 Albanesi C, Cavani A, Girolomoni G. Interferon-gamma-stimulated human keratinocytes express the genes necessary for the production of peptide-loaded MHC class II molecules. *J Invest Dermatol* 1998; 110:138–142.
- 30 Barker JN, Sarma V, Mitra RS, *et al*. Marked synergism between tumor necrosis factor-alpha and interferon-gamma in regulation of keratinocyte-derived adhesion molecules and chemotactic factors. *J Clin Invest* 1990; 85:605–608.
- 31 Teraki Y, Moriya N, Shiohara T. Drug-induced expression of intercellular adhesion molecule-1 on lesional keratinocytes in fixed drug eruption. *Am J Pathol* 1994; 145:550–560.
- 32 Haas J, Lipkow T, Mohamadadeh M, *et al*. Induction of inflammatory cytokines in murine keratinocytes upon in vivo stimulation with contact sensitizers and tolerizing analogues. *Exp Dermatol* 1992; 1:76–83.
- 33 Barker JN, Jones ML, Mitra RS, *et al*. Modulation of keratinocyte-derived interleukin-8 which is chemotactic for neutrophils and T lymphocytes. *Am J Pathol* 1991; 139:869–876.
- 34 Homey B, Alenius H, Muller A, *et al*. CCL27–CCR10 interactions regulate T cell-mediated skin inflammation. *Nat Med* 2002; 8:157–165.
This study demonstrates that keratinocytes from patients with various cutaneous inflammatory diseases produce increased amounts of the chemokine CCL27, which can be induced by TNF- α and interleukin-1 β . CCL27 then binds to CCR10 on circulating T cells, therein providing a homing mechanism for T cells to enter the cutaneous compartment.
- 35 Britschgi M, Steiner UC, Schmid S, *et al*. T-cell involvement in drug-induced acute generalized exanthematous pustulosis. *J Clin Invest* 2001; 107:1433–1441.
This study shows the heterogeneous distribution of drug-specific CD4/CD8 phenotypes, T-cell receptor expression, and cytokine/chemokine profiles from patients with various CDRs. Interestingly, the data suggest that these varied characteristics may translate into different clinical manifestations of CDR.
- 36 Nickoloff BJ, Mitra RS, Green J, *et al*. Activated keratinocytes present bacterial-derived superantigens to T lymphocytes: relevance to psoriasis. *J Dermatol Sci* 1993; 6:127–133.
- 37 Huber H, Descossy P, van Brandwijk R, Knop J. Activation of murine epidermal TCR-gamma delta+ T cells by keratinocytes treated with contact sensitizers. *J Immunol* 1995; 155:2888–2894.
- 38 Nakano Y. Antigen-presenting cell function of epidermal cells activated by hapten application. *Br J Dermatol* 1998; 138:786–794.
- 39 Ansel J, Perry P, Brown J, *et al*. Cytokine modulation of keratinocyte cytokines. *J Invest Dermatol* 1990; 94(Suppl):101S–107S.
- 40 Villada G, Roujeau JC, Clerici T, *et al*. Immunopathology of toxic epidermal necrolysis. Keratinocytes, HLA-DR expression, Langerhans cells, and mononuclear cells: an immunopathologic study of five cases. *Arch Dermatol* 1992; 128:50–53.
- 41 Schnyder B, Mauri-Hellweg D, Zanni M, *et al*. Direct, MHC-dependent presentation of the drug sulfamethoxazole to human alphabeta T cell clones. *J Clin Invest* 1997; 100:136–141.
- 42 Zanni MP, von Greysen S, Schnyder B, *et al*. HLA-restricted, processing- and metabolism-independent pathway of drug recognition by human alpha beta T lymphocytes. *J Clin Invest* 1998; 102:1591–1598.
- 43 von Greysen S, Zanni MP, Frutig K, *et al*. Interaction of sulfonamide derivatives with the TCR of sulfamethoxazole-specific human alpha beta+ T cell clones. *J Immunol* 1999; 162:595–602.
- 44 Schnyder B, Burkhart C, Schnyder-Frutig K, *et al*. Recognition of sulfamethoxazole and its reactive metabolites by drug-specific CD4+ T cells from allergic individuals. *J Immunol* 2000; 164:6647–6654.
- 45 Burkhart C, von Greysen S, Depta JP, *et al*. Influence of reduced glutathione on the proliferative response of sulfamethoxazole-specific and sulfamethoxazole-metabolite-specific human CD4+ T-cells. *Br J Pharmacol* 2001; 132:623–630.
These experiments demonstrate a unique specificity of individual T-cell clones from patients with a previous sulfonamide-induced CDR to sulfamethoxazole or its chemically reactive metabolite SMX-NO. The ability of glutathione to significantly inhibit T-cell reactivity to SMX-NO supports its unique detoxifying role.
- 46 Frauwirth KA, Thompson CB. Activation and inhibition of lymphocytes by costimulation. *J Clin Invest* 2002; 109:295–299.
A recent review of costimulation and its effects on immune responsiveness.
- 47 Matzinger P. Essay 1: the Danger model in its historical context. *Scand J Immunol* 2001; 54:4–9.
- 48 Todryk SM, Melcher AA, Dalgleish AG, Vile RG. Heat shock proteins refine the danger theory. *Immunology* 2000; 99:334–337.
- 49 Li Z, Menoret A, Srivastava P. Roles of heat-shock proteins in antigen presentation and cross-presentation. *Curr Opin Immunol* 2002; 14:45–51.
This is a recent overview of the critical immunological functions of heat shock proteins.
- 50 Wakem P, Burns Jr RP, Ramirez F, *et al*. Allergens and irritants transcriptionally upregulate CD80 gene expression in human keratinocytes. *J Invest Dermatol* 2000; 114:1085–1092.

- 51 Nickoloff BJ, Mitra RS, Green J, *et al.* Accessory cell function of keratinocytes for superantigens. Dependence on lymphocyte function-associated antigen-1/intercellular adhesion molecule-1 interaction. *J Immunol* 1993; 150:2148–2159.
 - 52 Nickoloff BJ, Turka LA. Keratinocytes and the danger model. *Science* 1996; 273:1479–1480.
 - 53 Vance RE. Cutting edge: cutting edge commentary: a Copernican revolution? Doubts about the danger theory. *J Immunol* 2000; 165:1725–1728.
 - 54 Gallucci S, Lolkema M, Matzinger P. Natural adjuvants: endogenous activators of dendritic cells. *Nat Med* 1999; 5:1249–1255.
 - 55 Shi Y, Zheng W, Rock KL. Cell injury releases endogenous adjuvants that stimulate cytotoxic T cell responses. *Proc Natl Acad Sci USA* 2000; 97:14590–14595.
 - 56 Gill HJ, Tjia JF, Kitteringham NR, *et al.* The effect of genetic polymorphisms in CYP2C9 on sulphamethoxazole N-hydroxylation. *Pharmacogenetics* 1999; 9:43–53.
 - 57 Riley RJ, Cribb AE, Spielberg SP. Glutathione transferase mu deficiency is not a marker for predisposition to sulphonamide toxicity. *Biochem Pharmacol* 1991; 42:696–698.
 - 58 Zielinska E, Niewiarowski W, Bodalski J, *et al.* Genotyping of the arylamine N-acetyltransferase polymorphism in the prediction of idiosyncratic reactions to trimethoprim-sulfamethoxazole in infants. *Pharm World Sci* 1998; 20:123–130.
 - 59 Pirmohamed M, Alfrevic A, Vilar J, *et al.* Association analysis of drug metabolizing enzyme gene polymorphisms in HIV-positive patients with cotrimoxazole hypersensitivity. *Pharmacogenetics* 2000; 10:705–713.
 - 60 Wolkenstein P, Liorot MA, Aractingi S, *et al.* Prospective evaluation of detoxification pathways as markers of cutaneous adverse reactions to sulphonamides in AIDS. *Pharmacogenetics* 2000; 10:821–828.
 - 61 Cribb AE, McQuaid T, Renton KW. Effect of lipopolysaccharide (LPS)-evoked host defense activation on hepatic microsomal formation and reduction of sulfamethoxazole hydroxylamine in the rat. *Biochem Pharmacol* 2001; 62:457–459.
- These data suggest a unique mechanism by which bacterial infection may decrease detoxification capability, and therein potentially increase susceptibility to sulfamethoxazole-induced adverse drug reactions.
- 62 Choquet-Kastylevsky G, Santolaria N, Tedone R, *et al.* Induction of delayed-type hypersensitivity to sulfamethoxazole in mice: role of metabolites. *Toxicol Lett* 2001; 119:183–192.
- This is the first in-vivo demonstration of an immune-mediated reaction to sulfonamides. These data, along with those presented by Naisbitt *et al.* [63••], provide important support for the critical role of reactive metabolite formation in the development of cutaneous toxicity.
- 63 Naisbitt DJ, Gordon SF, Pirmohamed M, *et al.* Antigenicity and immunogenicity of sulphamethoxazole: demonstration of metabolism-dependent haptenation and T-cell proliferation in vivo. *Br J Pharmacol* 2001; 133:295–305.
- Together with [62], this study provides strong evidence to support the dependence of cellular immune reactivity *in vivo* on reactive metabolite formation and haptenation of cellular proteins. It also suggests the existence of other critical factors that seem to be necessary for the development of toxicity.
- 64 von Greyl S, Bultmann G, Schnyder K, *et al.* Degeneracy and additional alloreactivity of drug-specific human alpha beta(+) T cell clones. *Int Immunol* 2001; 13:877–885.
- This report shows a wide diversity of drug-specific T cells, and suggests a unique autoimmune-type reactivity of drug-specific T cells based on their unusually high cross-reactivity with non-self-MHC-peptide complexes.
- 65 Ozkaya-Bayazit E, Akar U. Fixed drug eruption induced by trimethoprim-sulfamethoxazole: evidence for a link to HLA-A30 B13 Cw6 haplotype. *J Am Acad Dermatol* 2001; 45:712–717.
- This paper provides the first evidence linking sulfonamide-induced CDRs with a particular HLA haplotype.
- 66 Blanca M, Posadas S, Torres MJ, *et al.* Expression of the skin-homing receptor in peripheral blood lymphocytes from subjects with nonimmediate cutaneous allergic drug reactions. *Allergy* 2000; 55:998–1004.
 - 67 Reiss Y, Proudfoot AE, Power CA, *et al.* CC chemokine receptor (CCR)4 and the CCR10 ligand cutaneous T cell-attracting chemokine (CTACK) in lymphocyte trafficking to inflamed skin. *J Exp Med* 2001; 194:1541–1547.
 - 68 Dhabhar FS, Satoskar AR, Bluethmann H, *et al.* Stress-induced enhancement of skin immune function: a role for gamma interferon. *Proc Natl Acad Sci USA* 2000; 97:2846–2851.
 - 69 Bourdi M, Masubuchi Y, Reilly TP, *et al.* Protection against acetaminophen-induced liver injury and lethality by interleukin 10: role of inducible nitric oxide synthase. *Hepatology* 2002; 35:289–298.
- This study demonstrates a key role for the endogenously produced, anti-inflammatory cytokine interleukin-10 in limiting drug-induced liver injury. The data suggest that polymorphisms in interleukin-10 and other protective factors may serve as susceptibility factors for drug toxicity.
- 70 Smoller BR, Krueger J. Detection of cytokine-induced protein gamma-immune protein-10 (gamma-IP10) in atypical melanocytic proliferations. *J Am Acad Dermatol* 1991; 25:627–631.
 - 71 Pichler WJ, Zanni M, von Greyl S, *et al.* High IL-5 production by human drug-specific T cell clones. *Int Arch Allergy Immunol* 1997; 113:177–180.
 - 72 Knolle PA, Gerken G. Local control of the immune response in the liver. *Immunol Rev* 2000; 174:21–34.
 - 73 Nickoloff BJ, Turka LA. Immunological functions of non-professional antigen-presenting cells: new insights from studies of T-cell interactions with keratinocytes. *Immunol Today* 1994; 15:464–469.
 - 74 Reilly TP, Brady JN, Marchick MR, *et al.* A protective role for cyclooxygenase-2 in drug-induced liver injury in mice. *Chem Res Toxicol* 2001; 14:1620–1628.
- Comparable to the overall theme of [69••], this study demonstrates an important protective function of endogenously produced mediators, in this case cyclooxygenase-2 derived mediators, that respond to drug-induced tissue injury to limit the extent of damage.
- 75 Craven NM, Jackson CW, Kirby B, *et al.* Cytokine gene polymorphisms in psoriasis. *Br J Dermatol* 2001; 144:849–853.
 - 76 Hess DA, O'Leary EF, Lee JT, *et al.* Inhibition of cytokine production and interference in IL-2 receptor-mediated Jak-Stat signaling by the hydroxylamine metabolite of sulfamethoxazole. *FASEB J* 2001; 15:1855–1857.
- This article provides evidence to support the immunomodulatory effects of SMX-NOH, with implications for immune-based drug reactions *in vivo* that are secondary to alterations in normal immune function.
- 77 Goodman RE, Nestle F, Naidu YM, *et al.* Keratinocyte-derived T cell costimulation induces preferential production of IL-2 and IL-4 but not IFN-gamma. *J Immunol* 1994; 152:5189–5198.
 - 78 Rubin RL, Kretz-Rommel A. A nondeletional mechanism for central T-cell tolerance. *Crit Rev Immunol* 2001; 21:29–40.
 - 79 Aithal PG, Daly AK, Chen Y, Day CP. Promoter polymorphism of IL-10 and IL-4 predict risk of diclofenac-induced hepatitis [Abstract]. *Gastroenterology* 2000; 118:1071.
 - 80 Grove J, Daly AK, Bassendine MF, *et al.* Interleukin 10 promoter region polymorphisms and susceptibility to advanced alcoholic liver disease. *Gut* 2000; 46:540–545.
 - 81 Asadullah K, Eskdale J, Wiese A, *et al.* Interleukin-10 promoter polymorphism in psoriasis. *J Invest Dermatol* 2001; 116:975–978.
 - 82 Pirmohamed M, Lin K, Chadwick D, Park BK. TNFalpha promoter region gene polymorphisms in carbamazepine-hypersensitive patients. *Neurology* 2001; 56:890–896.
- This is the first study to demonstrate an association between CDRs and polymorphic expression of inflammatory mediators.
- 83 Puig L, Fernandez-Figueras MT, Ferrandiz C, *et al.* Epidermal expression of 65 and 72 kd heat shock proteins in psoriasis and AIDS-associated psoriasiform dermatitis. *J Am Acad Dermatol* 1995; 33:985–989.
 - 84 Breloer M, Dorner B, More SH, *et al.* Heat shock proteins as 'danger signals': eukaryotic Hsp60 enhances and accelerates antigen-specific IFN-gamma production in T cells. *Eur J Immunol* 2001; 31:2051–2059.
- This is one of the more recent studies showing that heat shock proteins, which themselves can be induced by the stress of reactive drug species, can enhance immune responsiveness.
- 85 Merrill JE, Koyanagi Y, Chen IS. Interleukin-1 and tumor necrosis factor alpha can be induced from mononuclear phagocytes by human immunodeficiency virus type 1 binding to the CD4 receptor. *J Virol* 1989; 63:4404–4408.
 - 86 von Sydow M, Sonnerborg A, Gaines H, Strannegard O. Interferon-alpha and tumor necrosis factor-alpha in serum of patients in various stages of HIV-1 infection. *AIDS Res Hum Retroviruses* 1991; 7:375–380.
 - 87 Rautonen J, Rautonen N, Martin NL, *et al.* Serum interleukin-6 concentrations are elevated and associated with elevated tumor necrosis factor-alpha and immunoglobulin G and A concentrations in children with HIV infection. *AIDS* 1991; 5:1319–1325.
 - 88 Schnyder B, Frutig K, Mauri-Hellweg D, *et al.* T-cell-mediated cytotoxicity against keratinocytes in sulfamethoxazole-induced skin reaction. *Clin Exp Allergy* 1998; 28:1412–1417.

- 89 Paul C, Wolkenstein P, Adle H, *et al.* Apoptosis as a mechanism of keratinocyte death in toxic epidermal necrolysis. *Br J Dermatol* 1996; 134:710–714.
- 90 Graziosi C, Pantaleo G, Fauci AS. Comparative analysis of constitutive cytokine expression in peripheral blood and lymph nodes of HIV-infected individuals. *Res Immunol* 1994; 145:602–605.
- 91 Dai Z, Konieczny BT, Baddoura FK, Lakkis FG. Impaired alloantigen-mediated T cell apoptosis and failure to induce long-term allograft survival in IL-2-deficient mice. *J Immunol* 1998; 161:1659–1663.
- 92 Mohamadzadeh M, Berard F, Essert G, *et al.* Interleukin 15 skews monocyte differentiation into dendritic cells with features of Langerhans cells. *J Exp Med* 2001; 194:1013–1020.
- 93 Sadlack B, Lohler J, Schorle H, *et al.* Generalized autoimmune disease in interleukin-2-deficient mice is triggered by an uncontrolled activation and proliferation of CD4+ T cells. *Eur J Immunol* 1995; 25:3053–3059.
- 94 Carr A, Swanson C, Penny R, Cooper DA. Clinical and laboratory markers of hypersensitivity to trimethoprim-sulfamethoxazole in patients with *Pneumocystis carinii* pneumonia and AIDS. *J Infect Dis* 1993; 167:180–185.
- 95 Gougeon ML, Poccia F, Boullier S. Human gamma delta T lymphocytes in HIV disease: effector functions and control by natural killer cell receptors. *Springer Semin Immunopathol* 2000; 22:251–263.
- 96 Boismenu R, Havran WL. An innate view of gamma delta T cells. *Curr Opin Immunol* 1997; 9:57–63.
- 97 Shevach EM. Regulatory T cells in autoimmunity. *Annu Rev Immunol* 2000; 18:423–449.
- 98 Pullen H, Wright N, Murdoch JM. Hypersensitivity reactions to antibacterial drugs in infectious mononucleosis. *Lancet* 1967; 2:1176–1178.
- 99 Suzuki Y, Inagi R, Aono T, *et al.* Human herpesvirus 6 infection as a risk factor for the development of severe drug-induced hypersensitivity syndrome. *Arch Dermatol* 1998; 134:1108–1112.
- 100 Turgeon NA, Iwakoshi NN, Phillips NE, *et al.* Viral infection abrogates CD8(+) T-cell deletion induced by costimulation blockade. *J Surg Res* 2000; 93:63–69.
- 101 Buchweitz JP, Ganey PE, Bursian SJ, Roth RA. Underlying endotoxemia •• augments toxic responses to chlorpromazine: is there a relationship to drug idiosyncrasy? *J Pharmacol Exp Ther* 2002; 300:460–467.
This is the first in-vivo demonstration, in an experimental setting, that nontoxic doses of a drug can be made toxic in combination with underlying endotoxemia. The data provide important support for the assertion that concomitant infection may increase susceptibility to adverse drug events.
- 102 Larregina AT, Morelli AE, Spencer LA, *et al.* Dermal-resident CD14+ cells differentiate into Langerhans cells. *Nat Immunol* 2001; 2:1151–1158.
- 103 Sayeh E, Uetrecht JP. Factors that modify penicillamine-induced autoimmunity in Brown Norway rats: failure of the Th1/Th2 paradigm. *Toxicology* 2001; 163:195–211.