

Review article

Role of T cells in drug allergies

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Side-effects to drugs are common. They are usually classified as type A reactions if they are related to the pharmacologic activity of the drug, and type B reactions if unrelated to its pharmacologic activity. Immune-mediated side-effects are type B reactions and account for ~1/7 of all drug-related side-effects (1). However, their frequency is highly dependent on the type of the drug. Some drugs are notorious for their allergic side-effects (i.e., some antibiotics and antiepileptics), while other drugs are seldom related to allergies.

The diagnosis of drug allergy is difficult for various reasons: the *clinical manifestations* of drug allergies are very heterogeneous. Drug-allergic reactions are now the great imitators of diseases, causing symptoms similar to infectious, autoimmune, or superantigen-triggered diseases. When no skin symptoms are present, drug-induced allergic reactions, like hepatitis or interstitial lung diseases, are surely underdiagnosed. Moreover, viral infections, such as those of HIV or Epstein-Barr virus (EBV), may be crucial cofactors in eliciting symptoms (2, 3).

There are no *reliable tests* generally available to diagnose drug allergy and to pinpoint the relevant drug. The great number of different drugs able to elicit side-effects limits the capacity to have standardized tests prepared for each compound, even if one omits metabolites. Skin test systems have been systematically developed for penicillin hypersensitivity only, but they are tailored to detect IgE-mediated allergies, and are not standardized to detect other types of drug-induced immunologic side-effects. Moreover, the presence of minor or more general cross-reactivity limits the relevance of these tests (4).

Finally, the *pathophysiology* of most drug-related side-effects is unknown. Only a few drug allergies

are IgE-mediated. How the sensitization to the drug occurs, to what extent T cells are involved, and how the various disorders are related to the symptoms of drug allergy are still unknown. The classification of drug allergies based on the scheme of Gell & Coombs (5) is helpful for some drug-related side-effects, but the most common side-effect of drugs, exanthema (rash), as well as some of the most severe side-reactions (toxic epidermal necrolysis, Stevens-Johnson syndrome, and hypersensitivity reactions involving internal organs), is not explained by this subclassification.

For the practical approach to a patient with suspected drug allergy, a schematic differentiation between different forms of drug interactions with the immune system is advisable (Table 1). This subdivision of "real" drug allergies, nonallergic hypersensitivities, autoimmune diseases, and pharmacologic interference by drugs with immune cell functions is useful for diagnostic procedures and helpful in advising patients to avoid further symptoms. Thus, in "real" drug allergies, care has to be taken that structurally similar compounds are avoided in case of possible immunologic cross-reactivity. In contrast, in nonallergic hypersensitivity reactions, pharmacologic activities such as inhibition of prostaglandin synthesis, but not structural similarities, have to be taken into account.

Immunogenicity of drugs for T cells

The involvement of drug-specific antibodies in some drug-allergy disorders, such as anaphylaxis, urticaria, angioedema, and hemolytic anemia, is well known. In contrast, the role of drug-specific T cells

Table 1. Interaction of drugs with immune system

	Example
<i>Specific</i>	
Immune reaction to the drug itself ("real" drug allergy)	Penicillins, sulfonamides
Induction of autoimmune response	D Penicillamine, procainamide
<i>Unspecific</i>	
IgE (type I)-like symptoms without evidence of sensitization (nonallergic hypersensitivity)	Acetylsalicylic acid
Interference with immune cell activation, signal transduction	Cyclosporin A

has long been controversial. Two main reasons may explain this neglect of T cells in drug allergy:

- 1) T cells were thought to recognize peptides, but not haptens or drugs. According to the hapten-carrier model, T cells can recognize the carrier molecule, but not the hapten itself, while antibodies are specific to the hapten (6).
- 2) Although ample evidence exists that T-cell infiltrates are present in various allergic skin lesions, the function of these lesional T cells was not understood (7, 8).

However, clinical experience and laboratory data indicate that T cells participate in various drug-allergic reactions (Table 2). Moreover, recent data have convincingly shown that naturally occurring or synthesized, nonpeptidic, low-molecular-weight substances are recognized by T cells (9). Both $\alpha\beta+$ and $\gamma\delta+$ T cells are involved in the recognition of these so-called *nonpeptide antigens*, which are presented by MHC- or MHC-like (CD1) molecules (9–11). These nonpeptide antigens can be subclassified by structure as lipids, prenilypyrophosphates, sugars, metals, or drugs. It is thought that the recognition of some of these nonpeptide antigens is important for the natural immune reaction to pathogens, since prenilypyrophosphates produced by mycobacteria and recognized by $\gamma\delta+$ T cells might steer the immune response toward a Th1-like phenotype (12).

The direct recognition of haptens by T cells has been convincingly shown by the work of Weltzien et al. (13, 14). They directly coupled trinitrophenol (TNP) to immunogenic peptides which are presented by MHC class I or II molecules. These hapten-modified peptides (but not the unmodified peptides) were recognized by TNP-specific T cells obtained from mice sensitized to TNP. The immunogenicity of the hapten depended on its position within the immunogenetic peptide: T-cell clones (TCC) which recognized the hapten in a central position within the immunogenic peptide (i.e., position 5 in a nine-amino-acid [aa]-long peptide) were hapten-specific, and the sequence of

Table 2. Evidence of T-cell participation in drug allergy

Clinical symptoms such as contact dermatitis, exanthema, hepatitis, etc. with no evidence of formation of drug-specific antibodies
Positive lymphocyte transformation and epicutaneous (patch) skin tests
Formation of T-cell-dependent antidrug antibodies (IgE, IgG)
Drug-specific T-cell lines and clones

the immunogenic peptide was irrelevant to T-cell recognition. However, if the hapten bound to an amino acid at the aa positions 1, 2, or 9 of the approx. 9-aa-long peptide, then the T-cell receptor (TCR) corecognized the amino acid of the peptide. In most instances, hapten recognition was MHC-restricted (15, 16).

Chemically reactive and nonreactive drugs

In general, drugs are small compounds and are thought to act immunologically like haptens. Their immunogenicity is thus related to their ability to bind to proteins. Examples of such chemically reactive drugs are β -lactams and sulfonamides, two of the most frequently sensitizing drugs, which are reactive either per se (β -lactams) or after drug metabolism (sulfonamides) (17–22).

Penicillin G (pen G) and its derivatives, as well as the cephalosporins, share the same nuclear structure, the β -lactam ring. Early studies showed that the β -lactam ring spontaneously opens under physiologic conditions so that its carbonyl moiety can form an amide linkage, mainly to the ϵ -amino groups of proteins. Thereby is formed the penicilloyl group, which can act as an immunogen (19–21). Other conjugations occur by degradation of penicillin to penicillenic or penicilloic acid, which forms disulfide bonds with sulfidryl groups of cysteine (minor antigenic determinants) (23).

Penicillins are also recognized by T cells (24, 25). Both CD4+ and CD8+ TCC can be generated by penicillins, and a certain level of cross-reactivity has been demonstrated (26, 27). This cross-reactivity on the T-cell level may explain symptoms to various types of penicillins, even if no antibodies are involved. Recently, it was even shown that *in vitro* synthesized peptides, modified by penicilloyl, are recognized by pen G-specific TCC (28). This underlines the concept elaborated with TNP (13, 14) that drug reactions are mainly directed to hapten-modified peptides.

One has, however, to consider that most drugs are *not chemically* reactive and thus not able to bind *covalently* to proteins. They might gain chemical reactivity only after drug metabolism. Such a pathway is relatively well analyzed with sulfonamides (29–32): a major pathway of sulfamethoxazole (SMX) metabolism is *N*-acetylation of the

aromatic part of the molecule. One responsible enzyme, *N*-acetyltransferase 2 (NAT2), has a polymorphic effect on various substrates, including SMX, with differences in the quantity of the enzyme accounting for "slow" and "fast" acetylator phenotypes (32). An additional metabolic pathway leads to the highly reactive hydroxylamine and nitroso derivatives. As shown by several research groups, these intermediate products are toxic and/or immunogenic (29–32). Persons with a slow acetylator phenotype produce an increased amount of hydroxylamines and nitroso compounds, which are chemically highly reactive and thus able to form new antigens; namely, hapten-carrier complexes. This might explain why the slow acetylator phenotype is a risk factor for the development of SMX hypersensitivity reactions (33).

However, the important role of drug metabolism is hard to reconcile with the low incidence of drug allergies in the liver, the main drug-metabolizing organ in the body. The reason for the low incidence of drug-induced allergic hepatitis is unclear. The liver may represent an immunologically privileged site, as infiltrating T cells may undergo apoptosis (34, 35). Nevertheless, this does not explain why most drug-related symptoms occur in the skin, where the generation of such reactive SMX intermediates has never been shown.

Direct, metabolism-independent drug presentation

We recently elaborated a new model of drug recognition by *already activated* T cells. We call it the direct, metabolism-independent model of T-cell stimulation by drugs. It postulates drug binding to the MHC-peptide complex *and* to the TCR as to other pharmacologic receptors. Thus, no covalent binding is required for presentation. This concept relies on the following findings.

Glutaraldehyde-fixed antigen-presenting cells (APC) can present SMX to specific, CD4+ and CD8+ TCC. Fixation does not interfere with the ability to present (preprocessed) peptides, indicating that the presenting MHC structures are still functional. However, fixation abrogates protein processing, as tetanus toxoid (TT) cannot be presented to TT-specific T-cell lines. The SMX-specific clones proliferate, secrete cytokines, and are even able to kill autologous target cells (36). Recently, we extended these observations by evaluating the kinetics of TCR downregulation after interaction with MHC-matched/unmatched APC and the drug. We found a rapid downregulation of TCR (within 20–30 min) by incubating the drugs with the MHC-matched APC and TCC (37). Moreover, an increment of intracellular Ca^{2+} was seen immediately

after drug addition to APC and TCC. These data demonstrate for the first time a direct involvement of TCR in drug recognition and rule out the possibility that a pharmacologic stimulation of T cells (i.e., via CD2) (38) causes the proliferation. The ability of fixed APC to present the chemically nonreactive drug SMX or lidocaine to TCC, and the rapidity of TCR signaling are strong arguments against the need of antigen processing and drug metabolism for drug recognition by TCC.

Binding of a drug such as SMX or lidocaine to the MHC complex appears to be rather labile, as pulsing of APC (incubation of APC with the drug, followed by a washing step) was not possible. That simple washing could remove the drug from the MHC-peptide complex indicates noncovalent binding. The nature of this unstable drug binding of SMX to the MHC-peptide complex is still unclear. It may be similar to the reversible binding of SMX to its natural substrate, the enzyme dihydropteroyl synthase, which occurs via van der Waals and hydrogen bonds (39).

To some extent, this model of direct, metabolism-independent drug presentation resembles the recognition of gold or NiSO_4 by T cells (40, 41). However, these data on drug-specific recognition were obtained with *activated* T cells. It remains to be determined whether drug recognition is similar for *primary sensitization*. Actually, the association of SMX hypersensitivity with the pharmacogenetic background of the subject (33, 42) makes it likely that drug metabolism and covalent binding are still important. Thus, the following two possible pathways of drug presentation by APC may be outlined (Fig. 1).

Pathway A might always be required to *start* a drug allergy; it relies on covalent binding. Reactive drugs or drugs which become reactive after metabolism in the liver bind covalently to proteins, which are processed and presented as "haptened" (drug-modified) peptides. This model might apply to chemically reactive compounds such as penicillins or to SMX, which is metabolized to a reactive intermediate in the liver.

In *pathway B*, SMX and lidocaine may also interact with the TCR and MHC without prior metabolism or protein binding and processing. These and other chemically nonreactive compounds bind – in a rather labile way – directly to membrane-associated proteins such as TCR *and* MHC (but also to other structures).

Clinical impact of direct, metabolism-independent drug presentation

The direct, metabolism-independent model of drug presentation not only has major implications for

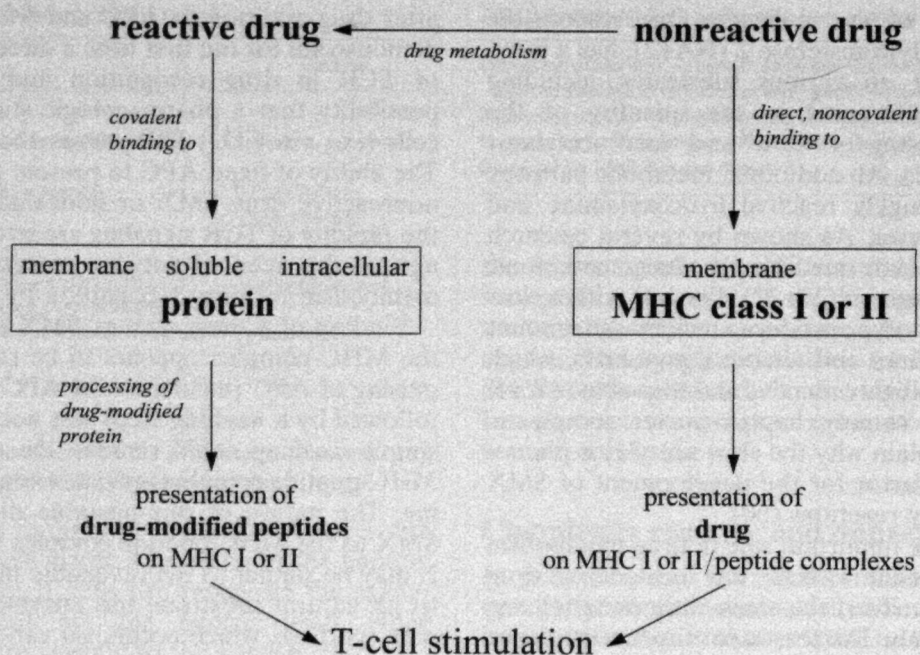


Fig. 1. Schematic presentation of drug-specific recognition. Drugs can be classified into reactive or nonreactive compounds. Nonreactive compounds can become reactive upon drug metabolism. Reactive drugs covalently bind to proteins, which are modified, processed, and presented on MHC class I or II molecules. Direct binding to immunogenic peptide is also possible. Nonreactive drugs may not be metabolized, but may bind directly and noncovalently to MHC class I or II molecules. Preactivated T cells can specifically recognize these drugs together with the restricting MHC molecules. These drug-specific T cells are activated, secrete cytokines, proliferate, and may also have cytotoxic functions.

our understanding of "antigen recognition" by T cells but also has great clinical impact. It may explain the following peculiar features of drug allergy:

- 1) One such feature is the manifestation of drug allergy in organs without active drug metabolism, such as the skin; although some cells in the skin may have a limited ability to metabolize xenobiotics, and some metabolizing enzymes such as myeloperoxidase are found in many cells (43), an activity of the various cytochrome p450 enzymes in the skin has not yet been demonstrated. Only these p450 enzymes, and not the more ubiquitous myeloperoxidase, appear to be relevant to generation of reactive metabolites.
- 2) The disappearance of drug-allergy-related symptoms *rapidly* after stopping drug therapy argues against covalent binding of a drug to its carrier protein, since the modified proteins would be expected to have a longer half-life (i.e., 14 days for albumin), and symptoms should thus persist longer (36). Thus, the rapid resolution of symptoms after stopping drug therapy indicates that noncovalent drug-binding to MHC-peptide complexes and recognition by T cells is relevant to clinical symptoms. Such labile reactions may account for most drug-induced, transitory skin rashes. In contrast, if symptoms persist longer,

recognition of covalently modified proteins may be involved. Indeed, some rare, drug-induced side-effects such as severe hypersensitivity syndromes show a characteristic persistence of symptoms long after stopping therapy (44, 45). In these cases, the immune reaction might be directed to covalently modified proteins. Interestingly enough, these hypersensitivity reactions show liver involvement (hepatitis), implying that the drug is presented in an immunogenic way in the organ where the reactive metabolites are generated. Thus, the rather rare liver involvement in drug allergy might indicate recognition of covalently bound drugs and suggest the presence of a more dangerous and persistent reaction.

- 3) It is well known that certain drug allergies occur more frequently in association with generalized viral infections; in particular, EBV and HIV infections. The reason for this has remained controversial. Enhanced T-cell activation during viral infections and altered drug metabolism in HIV infection have been implicated (46, 47). Our model of direct drug presentation by MHC molecules gives rise to an additional explanation (36, 48). During viral infections, expression of MHC molecules on various cell types in the tissue, i.e., keratinocytes in the skin, is stimulated, probably by elevated interferon-gamma (IFN- γ) levels. This would allow enhanced, direct binding

of drugs to these molecules and thus boost drug presentation. Reactive T cells would be stimulated in the tissue and lead to the allergic symptoms.

- 4) Although a great variety of drugs can cause drug-allergic reactions, only a few are notorious for frequently causing allergies. Given that drug allergies rely on T-cell recognition of the drug, certain features might be elaborated to indicate the sensitizing potential of a drug:
 - Actually, only those drugs might be prone to induce drug allergy that are somehow able to interact with the MHC-peptide complex and the TCR. This might require certain structural features of a drug, features which need to be further elaborated.
 - A further aspect might be a structural similarity between chemically reactive, peptide-bound metabolites and nonmetabolized drugs, presented in a different, noncovalent way, since probably the same T cell reacts with the covalently/noncovalently bound drug.
 - Moreover, since most drug-reactive T cells bear the $\alpha\beta$ -TCR, a similarity to their usual T-cell antigens, namely, amino acids, might aid recognition (compare the structure of penicillins).

Functional properties of drug-specific T cells

In recent years, various groups have succeeded in generating drug-specific TCC. They were specific to β -lactams, SMX, and lidocaine (49–51) and served better to characterize the T-cell immune response to drugs. In many respects, the data showed a similarity between drug- and peptide-specific TCC, but a few findings were peculiar and might be distinguishing features of drug-specific TCC.

Phenotype and restriction

Most drug-specific TCC were CD4⁺; but every cloning procedure revealed also drug-specific CD8⁺ clones. All $\alpha\beta$ ⁺ TCC tested were HLA class I or class II restricted (25, 27, 28, 49, 50). About 5% of the drug-specific CD4⁺ TCC were HLA-DR-restricted, but not allele-restricted. This means that also allogeneic, HLA-DR-mismatched APC could present the drug (16, 52). Interestingly, two $\gamma\delta$ ⁺ TCC specific for lidocaine could be detected as well (50). This illustrates that nonphosphorylated small molecules can also be recognized by $\gamma\delta$ ⁺ T cells and suggests that not only $\alpha\beta$ ⁺ T cells are involved in certain drug allergies.

Oligoclonality

Several infections such as those of HIV, EBV, and mycobacteria have revealed an outgrowth of T cells bearing certain $\alpha\beta$ ⁺ or $\gamma\delta$ ⁺ TCR families (12, 53, 54). However, the specificity of this oligoclonal outgrowth was shown only for a few diseases (12). A stimulation of certain TCR V β families was also detected in drug-stimulated cultures, but not in parallel-analyzed protein (TT)-stimulated PBMC (27, 49, 50). Both SMX and lidocaine triggered an outgrowth of TCR V β 17-bearing cells (27, 50). However, in the case of SMX, cloning did not reveal a majority of drug-specific V β 17⁺ clones (36). In the case of lidocaine, continuous *in vitro* stimulation resulted in a monoclonal outgrowth of one TCRV β 17⁺ clone which was indeed lidocaine-specific (50). Interestingly, V β 17⁺ T cells were also found preferentially in nickel-allergic subjects (55, 56). An outgrowth of certain TCR V β families in penicillin-allergic subjects could be correlated to a limited cross-reactivity of these cells to other β -lactams (27).

Cytokines

Cytokine release in primary cultures of PBMC of drug-allergic subjects was measured 5 days after stimulation with drugs or TT. PBMC activated with SMX and lidocaine, but not pen G, secreted large amounts of interleukin (IL)-5 and little or no detectable IL-2, INF- γ , and IL-4 (49, 50, 57). An upregulation of IL-5 was never seen in TT-driven cultures, but was dominant in various other drug stimulations (e.g., carbamazepine, phenytoin). Cytokine release by drug-specific TCC upon PMA/ionomycin stimulation confirmed the different pattern of SMX/lidocaine- and penicillin-specific clones (25, 50, 57). Pen G-specific clones showed a Th0- or Th1-like cytokine pattern with high amounts of IFN- γ (25). Expression of high IL-5 levels in patients with drug allergy may explain the frequently observed eosinophilia in patients with drug allergy, because IL-5 is the main differentiation factor for eosinophils (58).

Cytotoxicity

Some drug-allergic side-effects, such as hepatitis or bullous exanthema, may reflect a drug-specific cytotoxic T-cell response. CD8⁺ cell lines generated in the skin lesions of subjects with bullous exanthems were cytotoxic upon TCR cross-linking (59, 60). The analysis of TCC of a patient with SMX allergy revealed cytotoxic potential even after drug stimulation: both CD4⁺ and CD8⁺ TCC lysed autologous target cells in an MHC-restricted way

(36). This killing appears to be perforin-mediated (48). Such a cytotoxic mechanism may be dominant in the most common drug-induced side-effect, namely, morbilliform rash (48). It would represent a novel pathway of drug allergy, extending the hitherto used Gell & Coombs (5) classification to a fifth type, namely, drug-induced *T-cell-mediated* cytotoxicity.

Superantigen-like T-cell stimulation by drugs

The type of drug recognition and the characterization of drug-specific T cells are reminiscent of certain features of superantigen presentation (61, 62). Presentation and stimulation by superantigens and drugs share the following features. Both are presented in a processing-independent pathway, as they bind from the outside to the MHC-peptide complex. Both stimulated T cells of the CD4+ and CD8+ phenotype, and certain donors show an oligoclonal outgrowth of T cells bearing certain TCR V β chains. An HLA-DR allele-independent recognition of drugs by TCC, which is typical of superantigens, was found in 5% of our clones (52). Additionally, we detected a high frequency of alloreactivity in drug-specific TCC compared to peptide/protein-specific clones (unpublished data). However, in contrast to superantigens, drugs fail to stimulate PBMC from nonsensitized subjects. Drugs are far smaller compounds than superantigens, and the stimulation is seldom as strong as a superantigen stimulation. Thus, drugs may stimulate T cells in a way intermediate between superantigen and peptide stimulation.

Cross-reactivity of drug-specific TCC

Only limited *in vivo* data are available to determine whether one subject allergic to one drug will tolerate another compound. Antibodies to β -lactams can react with the core structure, resulting in cross-reactivity to several β -lactams; some appear to react preferentially with the β -lactam side-chain, causing cross-reactivity to cephalosporins (4, 63). To investigate the molecular cross-recognition by T cells, we tested T-cell lines (TCL) and TCC specific to various β -lactams from several donors with related substances. We found at least two patterns of drug recognition. On the one hand, we found outgrowth of drug-specific T cells, which react to pen G only, but fail to recognize ampicillin or amoxicillin. They appear to recognize the core structure together with side-chains. On the other hand, certain subjects mount a rather broadly reactive T-cell response, able to react with different β -lactams. These TCL might recognize predominantly the core structure; namely, the β -lactam and

thiazolidine ring structure. None of the TCC tested showed cross-reactivity to cephalosporins (27, 28). Interestingly enough, the rather monospecific TCC stemmed from cultures with a rather oligoclonal TCR V β chain expansion in primary stimulations. Thus, our data suggest that the outgrowth of T cells bearing a certain TCR V β may be a sign of a limited cross-reactivity (27).

In a further study, we tested the ability of clones specific to lidocaine to respond to 20 chemically closely related local anesthetics and their metabolites. We found all clones to be highly specific to the presence of the acid amine, as they did not recognize local ester anesthetics. One clone showed a broader cross-reactivity, allowing us to propose a model of which structural requirements are needed for TCR recognition of local anesthetics (64).

Conclusion

T-cell recognition of drugs plays a decisive role in immunologic and clinical features in drug allergy. This recognition is probably essential in all drug-related side-effects, T cells acting either as helper cells providing essential cytokines (i.e., IL-4 for IgE switch or IL-5 for eosinophilia) or as mediators of symptoms such as rash (i.e., by infiltration of cytotoxic CD4+ T cells in the skin). Future directions in drug-allergy diagnosis and prevention should take into account this long neglected role of drug-specific T cells. New and reliable test systems have to be developed to detect drug-specific T cells in drug allergy. Moreover, since most drug allergies are not mediated by IgE alone, it seems advisable not to focus solely on IgE-mediated allergy, but also to take into account the role of T cells in allergic side-effects during the process of drug development.

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References

1. Hoigné R, Schlumberger HU, Vervloet D, Zoppi M. Epidemiology of allergic reactions. In: Burr M, editor. Epidemiology of clinical allergy. Epidemiology of allergic reactions to drugs. Monographs in Allergy, vol. 31. Basel: Karger, 1993:140-70.
2. Bayard PJ, Berger TG, Jacobson MA. Drug hypersensitivity reactions and human immunodeficiency virus disease. *J Acquir Immune Defic Syndr* 1992;5:1237-57.
3. Geyman JP, Erickson S. The ampicillin rash as a diagnostic and management problem: case report and literature review. *J Fam Pract* 1978;7:493-6.
4. Blanca M, Vega JM, Garcia J, Miranda A, Carmona MJ, Juarez C. New aspects of allergic reactions to betalactams:

- crossreactions and unique specificities. Clin Exp Allergy 1994;24:407-15.
5. Gell PG, Coombs RR, editors. The classification of allergic reactions underlying disease. In: Clinical aspects of immunology. Oxford: Blackwell Scientific, 1963.
6. Katz DH, Benacerraf B. The regulatory influence of activated T cells and B cell responses to antigen. Adv Immunol 1972;15:1-94.
7. Eisen HN, Orris L, Belman S. Elicitation of delayed allergic skin reactions to haptens: the dependence of elicitation on hapten combination with proteins. J Exp Med 1952;95:473-81.
8. 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;167:180-5.
9. Porcelli SA, Morita CT, Modlin RL. T-cell recognition of non-peptide antigens. Curr Opin Immunol 1996;8:510-16.
10. Morita CT, Beckman EM, Bukowski JF, et al. Direct presentation of nonpeptide prenyl pyrophosphate antigens to human $\gamma\delta$ T cells. Immunity 1995;3:495-507.
11. Beckman EM, Porcelli SA, Morita CT, Behar SM, Furlong ST, Brenner MB. Recognition of a lipid antigen by CD1-restricted $\alpha\beta$ T cells. Nature 1994;372:691-4.
12. Tanaka Y, Morita CT, Tanaka Y, Nieves E, Brenner MB, Bloom BR. Nature and synthetic non-peptide antigens recognized by human $\gamma\delta$ T cells. Nature 1995;375:155-8.
13. Martin S, Weltzien HU. T cell recognition of haptens: a molecular view. Int Arch Allergy Immunol 1994;104:10-16.
14. Weltzien HU, Moulon C, Martin S, Padovan E, Hartmann U, Kohler J. T cell immune response to haptens: structural models for allergic and autoimmune reactions. Toxicology 1996;107:141-51.
15. Ortmann B, Martin S, von Bohm A, Schlitz E, Hoschutsky H, Weltzien HU. Synthetic peptides anchor T-cell specific TNP epitopes to MHC antigens. J Immunol 1992;148:1445-50.
16. Köhler J, Hartmann U, Grimm R, Pflugfelder U, Weltzien HU. Carrier-independent hapten recognition and promiscuous MHC restriction by CD4+ T cells induced by trinitrophenylated peptides. J Immunol 1997;158:591-7.
17. Batchelor FR, Janet MD, Gazzard DK. Penicillin allergy: the formation of the penicilloyl determinant. Nature 1965;206:362-4.
18. Sullivan TJ. Drug allergy. In: Middleton E, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, Busse WW, editors. Allergy: principles and practice. St Louis, MO: Mosby Year Book, 1993:1726-46.
19. Levine BB. Immunochemical mechanisms involved in penicillin hypersensitivity in experimental animals and in human beings. Fed Proc 1965;24:45-50.
20. Parker CW. Immunochemical mechanisms in penicillin allergy. Fed Proc 1965;24:51-6.
21. de Weck AL, Schneider CW, Gutersohn J. The role of penicilloylated protein impurities, penicillin polymers and dimers in penicillin allergy. Int Arch Allergy Appl Immunol 1968;33:535-42.
22. Park BK, Coleman JW, Kitteringham NR. Drug disposition and drug hypersensitivity. Biochem Pharmacol 1987;36:581-60.
23. Levine BB, Redmond AP. Minor haptenic determinant-specific reagents of penicillin hypersensitivity in man. Int Arch Allergy Appl Immunol 1969;35:445-9.
24. Koponen M, Pichler WJ, de Weck AL. T cell reactivity to penicillin: phenotypic analysis of *in vitro* activated cell subsets. J Allergy Clin Immunol 1986;78:645-52.
25. Brander C, Mauri-Hellweg D, Bettens F, Rolli H, Goldman M, Pichler WJ. Heterogeneous T cell responses to β -lactam-modified self structures are observed in penicillin allergic individuals. J Immunol 1995;155:2670-8.
26. Padovan E, Mauri-Hellweg D, Pichler WJ, Weltzien HU. T cell recognition of penicillin G: structural features determining antigenic specificity. Eur J Immunol 1996;26:42-8.
27. Mauri-Hellweg D, Zanni MP, Frei E, et al. Cross-reactivity Of T cell lines and clones to β -lactam antibiotics. J Immunol 1996;157:1071-9.
28. Padovan E, Bauer T, Tongio MM, Kalbacher H, Weltzien HU. Penicilloyl peptides are recognized as T cell antigenic determinants in penicillin allergy. Eur J Immunol 1997;27:1303-7.
29. Cribb AE, Spielberg SS. Sulfamethoxazole is metabolized to the hydroxylamine in humans. Clin Pharmacol Ther 1993;51:522-6.
30. Leeder JS, Dosch HM, Spielberg SS. Cellular toxicity of sulfamethoxazole reactive metabolites. Biochem Pharmacol 1990;41:567-73.
31. Grant DM, Morike K, Eichelbaum M, Meyer UA. Acetylation pharmacokinetics. The slow acetylator phenotype is caused by decreased or absent arylamine *N*-acetyltransferase in human liver. J Clin Invest 1990;85:968-72.
32. Rieder MJ, Shear NH, Kanee A, Tang BK, Spielberg SP. Prominence of slow acetylator phenotype among patients with sulfonamide hypersensitivity reactions. Clin Pharmacol Ther 1991;49:13-17.
33. Cribb AE, Nakamura H, Grant DM, Miller MA, Spielberg SP. Role of polymorphic and monomorphic human arylamine *N*-acetyltransferase in determining sulfamethoxazole metabolism. Biochem Pharmacol 1993;45:1277-88.
34. Crispe IN, Mehal WZ. Strange brew: T cells in the liver. Immunol Today 1996;17:522-5.
35. Huang Lin, Soldevila G, Leeker M, Flavell R, Crispe IN. The liver eliminates T cells undergoing antigen-triggered apoptosis *in vivo*. Immunity 1994;1:741-9.
36. Schnyder B, Mauri-Hellweg D, Zanni MP, Bettens F, Pichler WJ. Direct, MHC dependent presentation of the drug sulfamethoxazole to human $\alpha\beta$ T cell clones. J Clin Invest 1997;100:136-40.
37. Zanni MP, von Greyser S, Schnyder B, Vallitutti S, Pichler WJ. Rapid, HLA restricted, processing and metabolism independent recognition of drugs by human $\alpha\beta$ T lymphocytes. J Immunol (submitted).
38. Rhodes J, Chen H, Hall SR, et al. Therapeutic potentiation of the immune system by costimulatory Schiff-base-forming drugs. Nature 1995;376:16-17.
39. Achari A, Somers DO, Chappess JN, Bryant PK, Rosemund J, Stammers DK. Crystal structure of the antibacterial sulfonamide drug target dihydropteroate synthase. Nature Struct Biol 1997;4:490-7.
40. Romagnoli P, Spinas GA, Sinigaglia F. Gold-specific T cells in rheumatoid arthritis patients treated with gold. J Clin Invest 1992;89:254-8.
41. Romagnoli PA, Labhardt M, Sinigaglia F. Selective interaction of Ni with an MHC-bound peptide. EMBO J 1991;10:1303-6.
42. Riley RJ, Leeder JS. *In vitro* analysis of metabolic predisposition to drug hypersensitivity reactions. Clin Exp Immunol 1995;99:1-6.
43. Jiang X, Khursigara G, Rubin RL. Transformation of lupus-inducing drugs to cytotoxic products by activated neutrophils. Science 1995;266:810-13.
44. Vittorio CC, Muglia JJ. Anticonvulsant hypersensitivity syndrome. Arch Intern Med 1995;155:2285-9.
45. De Vriese AS, Philippe J, van Renterghem DM, et al. Carbamazepine hypersensitivity syndrome: report of 4

- cases and review of the literature. *Medicine* (Baltimore) 1995;74:144-51.
46. van der Ven AJ, Koopmans PP, Vree TB, et al. Adverse reactions to co-trimoxazole in HIV infections. *Lancet* 1991;338:431-3.
47. Pichler WJ. Medikamentenallergie. In: Peter HH, Pichler WJ, editors. *Klinische Immunologie*. München: Urban & Schwarzenberg, 1996:718-35.
48. Schnyder B, Frütig K, Mauri-Hellweg D, et al. T cell mediated cytotoxicity in sulfamethoxazole induced skin reactions. *J Clin Invest* (submitted).
49. Mauri-Hellweg D, Bettens F, Mauri D, Brander C, Hunziker T, Pichler WJ. Activation of drug-specific CD4+ and CD8+ T cells in individuals allergic to sulfamethoxazole, phenytoin and carbamazepine. *J Immunol* 1995;155:462-72.
50. Zanni MP, Mauri-Hellweg D, Brander C, et al. Characterization of lidocaine specific T cells. *J Immunol* 1997;158:1139-48.
51. Hertl M, Jugert F, Merk HF. CD8+ dermal T cells from a sulfamethoxazole-induced bullous exanthem proliferate in response to drug-modified liver microsomes. *Br J Dermatol* 1995;132:215-20.
52. Zanni MP, von Greycz S, Schnyder B, Wendland T, Pichler WJ. Drug recognition by specific $\alpha\beta$ + T cell clones in association of multiple HLA-DR alleles. *Immunol Int* (submitted).
53. Pantaleo G, Demarest JF, Soudeyans H, et al. Major expansion of CD8+ T cells with a predominant V β usage during the primary immune response to HIV. *Nature* 1994;370:463-7.
54. Pichler WJ, Mauri-Hellweg D, Baumann K, Bettens F. Selective expression of T cell receptor V β in acute infectious mononucleosis. *Arch Int Med* 1995;55:1555-6.
55. Moulon C, Vollmer J, Weltzien HU. Characterization of processing requirements and metal cross-reactivities in T cell clones from patients with allergic contact dermatitis to nickel. *Eur J Immunol* 1995;25:3308-15.
56. Vollmer J, Fritz M, Doromy A, Weltzien HU, Moulon C. Dominance of the BV17 element in nickel specific human T cell receptors relates to severity of contact sensitivity. *Eur J Immunol* 1997;27:1865-74.
57. Pichler WJ, Zanni M, von Greycz S, Schnyder B, Mauri-Hellweg D, Wendland T. High IL-5 production by drug specific T cell clones. *Int Arch Appl Allergy Immunol* 1997;113:177-80.
58. Dent LA, Strath M, Mellor AL, Anderson CJ. Eosinophilia in transgenic mice expressing interleukin 5. *J Exp Med* 1990;172:1425-31.
59. Merk HF, Hertl M. Immunologic mechanisms of cutaneous drug reactions. *Semin Cutan Med Surg* 1996;15:228-35.
60. Hertl M, Bohlen H, Jugert F, Merk HF. Predominance of epidermal CD8+ T lymphocytes in bullous cutaneous reactions caused by β -lactam antibiotics. *J Invest Dermatol* 1993;101:794-9.
61. Herman A, Labrecque N, Thibodeau J, Marrack P, Kappler JW, Sekaly RP. Identification of the staphylococcal enterotoxin A superantigen binding site in the β 1 domain of the human histocompatibility antigen HLA-DR. *Proc Natl Acad Sci U S A* 1991;88:9954-8.
62. Kappler J, Kotzian B, Herron L, et al. V β -specific stimulation of human T cells by staphylococcal toxins. *Science* 1989;244:811-13.
63. Miranda A, Blanca M, Vega JM, et al. Cross-reactivity between a penicillin and a cephalosporin with the same side chain. *J Allergy Clin Immunol* 1996;98:671-7.
64. Zanni MP, von Greycz S, Schnyder B, Hari Y, Frei E, Pichler WJ. T cell reactivity to local anesthetics: *in vivo* and *in vitro* crossreactivity and identification of a possible core structure for T cell recognition. *J Clin Invest* (submitted).

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