Drug Hypersensitivity Reactions: Pathomechanism and Clinical Symptoms

Werner J. Pichler, MD²,³, Jaqueline Adam, MS¹, Barbara Daubner, MSc¹, Thomas Gentinetta, MSc², Monika Keller, PhD², Daniel Yerly, PhD²

The immune system has developed to combat infections, which it achieves by a sophisticated interplay between the innate and adaptive immune systems. People are exposed to many infectious agents, but also encounter many (new) chemicals, mostly in very small amounts. Some chemicals, such as drugs, are given consistently and in comparatively high doses. These chemicals can interfere with the immune system in various ways and may lead to somewhat neglected, phenotypically unusual consequences, which are a potential cause of allergic diseases.

Drug-induced adverse reactions are often classified as type A and type B reactions: Type A represent predictable side effects due to a pharmacologic action of the drug, whereas type B reactions are assumed not to be predictable. They comprise so-called idiosyncratic reactions due to some individual predisposition (eg, an enzyme defect), and hypersensitivity reactions.¹ About 1 in 6 adverse drug reactions represents drug hypersensitivity, and are allergic or non–immune-mediated (pseudoallergic) reactions. The latter are common causes of side effects to nonsteroidal antiinflammatory drugs (NSAIDs) (see the article by Mario Sánchez-Borges elsewhere in this issue for further exploration of this topic). It is rare for drugs to cause autoimmunity or immunodeficiency. Such abnormal immune reactions to a drug are a substantial cause of

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¹ Gell and Coombs classification
² Specific IgE
³ Type IV reactions
⁴ Exanthema
⁵ Multiple drug hypersensitivity
⁶ Flare-up reactions

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¹ Division of Allergology, Clinic for Rheumatology and Clinical Immunology/Allergology, Inselspital, University of Bern, CH-3010 Bern, Switzerland
² ADR-AC GmbH, Holligenstr 91, Bern CH-3008, Switzerland
³ Corresponding author. Division of Allergology, Clinic for Rheumatology and Clinical Immunology/Allergology, Inselspital, University of Bern, CH-3010 Bern, Switzerland.

E-mail address: werner.pichler@insel.ch

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morbidity, and even mortality, and deserve special attention by the medical community because they represent iatrogenic diseases.

The clinical symptoms and diseases of drug hypersensitivity reactions are heterogeneous and can imitate many different diseases, which often delays a correct diagnosis. Some side effects are mild, but others are severe and even fatal.\textsuperscript{2,3} Many allergic reactions affect the skin and can cause a variety of different exanthems. Most common is a maculopapular rash, which is observed in about 2\% to 3\% of hospitalized patients.\textsuperscript{4,5} However, drug hypersensitivity reactions can also affect various internal organs, causing hepatitis, nephritis, carditis, pneumonitis, and so forth.

Any drug is assumed to be able to elicit hypersensitivity reactions. However, the frequency differs widely. Antibiotics and antiepileptics are the most prevalent causes. The risk of sensitization and the severity of clinical symptoms depend on the state of immune activation of the individual, the dose, the duration of treatment, sex (more frequent in women), and the immunogenetic predisposition (in particular human leukocyte antigen B [HLA-B] alleles), whereas a pharmacogenetic predisposition has rarely been detected.

Epicutaneous application of a drug clearly increases the chance of sensitization compared with oral or parental treatments. It may be due to the high density of dendritic cells (DCs) in the skin. Atopy (defined as the genetic predisposition to mount an immunoglobulin E [IgE] response to inhaled or ingested innocuous proteins) is normally not associated with a higher risk of drug hypersensitivity. However, an atopic predisposition may prolong the persistence of drug-specific IgE in the serum,\textsuperscript{6} and an ongoing IgE-mediated allergic inflammation such as asthma may aggravate the symptoms of an IgE-mediated drug hypersensitivity reaction.

\section*{HOW DO SMALL MOLECULES STIMULATE THE IMMUNE SYSTEM?}

\textit{Hapten and Prohapten Concepts}

Small chemical compounds, usually less than 1000 Da, are not immunogenic per se. These compounds are normally degraded, metabolized, and eliminated without stimulating an immune response. However, if the chemical is reactive and able to bind covalently to proteins, DNA, and so forth, a new antigenic determinant arises that can produce a new immune response. This modification can, theoretically, affect any kind of autologous protein, such as soluble extracellular proteins (eg, albumin), membrane proteins (eg, an integrin), and intracellular proteins (eg, enzymes). It can even bind directly to the peptide embedded in the major histocompatibility complex (MHC) molecule itself. The hapten modification may also affect essential proteins or the DNA, which may result in a dose-dependent toxicity (Fig. 1A).

A certain toxic effect may also be important for inducing an immune response: the toxicity is sensed by the innate immune system as a danger, and DCs react to so-called danger signals by upregulating costimulatory molecules and cytokines. These danger signals can be generated by a toxic effect on cells, which are then sensed by DCs; or it may occur by activating DCs themselves.

Simultaneously, this drug-protein complex generates new antigenic determinants, which may be recognized by antigen-specific receptors of the immune system. This combined stimulation of innate (DCs and other cells) and adaptive immunity (T and B cells) results in a new, antigen-specific immune response, which is based on T cells and antibody production, both specific to the drug-protein complex (ie, hapten-carrier complex). The ensuing immune response is variable, because it uses against the drug
**Fig. 1.** Hapten and prohapten concepts and the noncovalent drug presentation to T cells. (A) Haptons. Drugs are haptons if they can bind covalently to soluble or cell-bound molecules (eg, penicillin G). They can bind directly to the immunogenic major histocompatibility complex (MHC)/peptide complex on antigen-presenting cells (APC); to the embedded peptide or to the MHC molecule itself. Thus, the chemical reactivity of haptons leads to the formation of many distinct antigenic epitopes that can elicit simultaneous humoral and cellular immune responses. Some examples of B- or T-cell–mediated immune responses are listed on the right of the figure. (B) Prohaptons. Other drugs are prohaptons, requiring metabolic activation to become haptons (ie, chemically reactive). The metabolism leads to the formation of a chemically reactive compound (eg, from sulfamethoxazole [SMX] to the chemically reactive form SMX-NO). The resulting intake may lead to modification of cell-bound or soluble proteins by the chemically reactive metabolite, similar to a hapten. (C) The p-i concept (pharmacologic interaction with immune receptors). Drugs are often designed to fit into certain proteins/enzymes to block their function. Some drugs may also bind to some of the available T-cell receptors (TCR) or MHC molecules (plus or minus embedded peptide). Under certain conditions (see text) this drug interaction with the TCR or MHC molecule may lead to an immune response of the T cell. For a full T-cell stimulation by such an inert drug, an interaction with a particular TCR is required, or the drug interacts with the MHC molecule that is stimulating the TCR/T cells. This p-i type of drug stimulation results in an exclusive T-cell stimulation. (From Pichler WJ. Drug hypersensitivity: classification and relationship to T-cell activation. In: Pichler WJ, editor. Drug hypersensitivity. Basel (Switzerland): Karger; 2007. p. 168–89; with permission.)

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<tr>
<th>Table 1</th>
<th>Drug Hypersensitivity Reactions</th>
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<tr>
<td><strong>Clinic: “everything”:</strong></td>
<td>1 &amp; 2 (binding to cell-bound and soluble proteins)</td>
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<td>T-cell reaction with exanthem, hepatitis, interstitial lung disease, contact dermatitis, AGEP, TEN...</td>
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<tr>
<td><strong>Clinic: “everything”:</strong></td>
<td>3: MHC class I and II modification</td>
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<td>Immunogenicity and clinical manifestation might be restricted to the liver (hepatitis) or kidney (interstitial nephritis), where metabolism occurs</td>
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<tr>
<td><strong>Clinic: only T cells</strong></td>
<td>an exclusive T-cell response might develop with exanthems, hepatitis, etc.</td>
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<td></td>
<td>Whether B cells (by drug binding to Ig) can similarly be stimulated, remains unclear.</td>
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all of the tools generated to eliminate infectious agents. Consequently the clinical situation is variable.

Many drugs are not chemically reactive but are still able to elicit immune-mediated side effects. The prohapten hypothesis tries to reconcile this phenomenon with the hapten hypothesis by stating that a chemically inert drug may become reactive on metabolism. Sulfamethoxazole (SMX) is a prototype prohapten. It is not chemically reactive but gains reactivity, and thus antigenicity, by intracellular metabolism. A cytochrome P450–dependent metabolism (CYP2C9) in the liver leads to
sulfamethoxazole-hydroxylamine (SMX-NHOH), which can be found in the urine and which is easily converted to sulfamethoxazole-nitroso by oxidation. The latter is highly chemically reactive and easily binds to intracellular proteins, creating neoantigenic determinants.\(^9\) Toxic effects of SMX occur when it exceeds a threshold level. Thus, SMX seems to have indirect antigenic and immunogenic features (see Fig. 1B).

**The p-i Concept**

A new possibility of drug interaction with immune receptors has recently been developed by our group: It is called the p-i concept (pharmacologic interactions of drugs with immune receptors). It is a simple concept that postulates that drugs may directly interact with immune receptors, as they do with other receptors, and that this interaction may stimulate the immune cells: This concept contradicts the original belief that the immune-stimulatory capacity of most chemicals and drugs is based on covalent binding and may be predicted by their protein reactivity.\(^{10-12}\) According to the p-i concept, chemically inert drugs, unable to covalently bind to peptides or proteins, can nevertheless activate certain T cells if they fit with a sufficient affinity into some of the many different T-cell receptors (TCR) or MHC molecules. This reversible interaction is similar to that of a drug ligand to its receptor, and is not based on covalent interaction but only on reversible van der Waals interactions. In vivo, p-i–activated T cells expand and subsequently infiltrate the skin and other organs, resulting in a T-cell–orchestrated inflammation.

Evidence for the p-i mechanism lies in various experimental data:

1. Aldehyde-fixed antigen-presenting cells (APC; unable to process antigen or to convert a prohapten to a hapten) are still able to activate specific terminal complement complex (TCC) if incubated together with the (inert) drug
2. The drug binding to proteins is more labile than the covalent interactions of hapten and can be washed away
3. Calcium influx in TCC happens within seconds after the addition of the drug; before drug uptake, metabolism, and processing can occur.

**Second (danger) signal in the p-i concept**

To initiate an immune response, in addition to the antigenic feature (signal 1, sensed by specific TCR), DCs provide costimulatory signals after having been activated. This response may be toll-like receptor signaling, or other danger signaling, connected to the antigen presented. This stimulation of DCs is transmitted by many means, and is well documented for hapten, contact sensitizers, and so forth.

In contrast to hapten, p-i–acting drugs do not covalently interact with proteins or with intracellular proteins: thus, these drugs are less toxic. There are 3 hypotheses to explain how the second (danger) signal, which is believed to be essential to starting an immune response, is delivered by p-i–acting drugs (these may also work in combination):

1. The p-i–stimulating drugs are not proinflammatory, and the innate immune system may not be stimulated.\(^{13}\) Consequently, it is assumed that no generation of an own drug (hapten)-specific immune response occurs. The p-i–stimulated T cells would not arise from naive T cells, but from previously primed effector-memory T cells, which were primed by some prior peptide contact. Consequently, p-i–stimulated T cells have an additional (peptide) specificity. Effector-memory cells have a substantially lower threshold for activation than naive T cells. Thus, only preactivated T cells may be susceptible for the p-i stimulations, which may explain why
concomitantly occurring massive immune stimulations of T cells, as occur during
generalized herpes or human immunodeficiency virus infections, are well-known
risk factors for drug hypersensitivity reactions. Exacerbations of autoimmune
diseases or an ongoing drug hypersensitivity (see later discussion) may represent
risk factors for further drug hypersensitivities. Such immune processes correspond
with high cytokine levels (eg, interleukin 2 [IL-2], interferon γ [IFNγ]) in the circulation
and in the tissues, and an increased expression of MHC and costimulatory
molecules in cells of the immune system. Consequently, T cells of patients with
generalized immune activations due to virus infections, ongoing autoimmunity, or
drug allergies are already preactivated and able to react to a minor signal such
as the binding of a small drug to a certain TCR. This theory would explain the
high occurrence of drug hypersensitivities in these diseases.

2. The p-i–stimulating drugs have an additional intrinsic activity that somehow acti-
vates DCs; for example, some drugs may bind to toll-like receptors (eg, imiquimod
and TLR8); others may bind to other receptors linked to cell activation. Such
intrinsic activity of a drug, which occurs aside of the normal target structure, may
substitute for other danger signals and thus provide the necessary second signal
for T-cell activation.

3. Although the p-i concept has been documented for many drugs (SMX, lidocain, la-
motrigine, carbamazepine, p-phenylendiamine, radiocontrast media),11,14–17
metabolites of these drugs are also implicated in hypersensitivities to these drugs.
Detailed analysis of affected patients shows that many T-cell clones react to the
parent compound, but others react to metabolites. Thus, hapten and p-i responses
occur together. A cross-reactivity can occasionally be observed, indicating that the
T-cell clone reacts via p-i and hapten recognition. The common occurrence raises
the question of whether the hapten characteristic of a drug (with its immune-stim-
ulatory consequences on innate immunity, as described earlier) is a prerequisite for
p-i stimulations to (also) occur. In this scheme, the danger signal may come from
the processed, haptenlike drug.

**p-i for CD4+ and CD8+ T cells**

Full T-cell activation by the drug (measured by immediate Ca^{2+} influx into specific T
cells, and cytokine synthesis or proliferation) requires the interaction of the TCR
with MHC on APC.11,18 This finding raises the question of whether the drug binds first
to the MHC molecule, modifying its structure, which is sensed by the TCR, and thus
leading to specific TCR activation, or whether the drug binds primarily to specific
TCR, rendering the MHC interaction only a supplementing signal.

Both concepts are possible: initial data with drug-specific, CD4+ T-cell clones
suggest that the interaction of the drug happens first with the TCR, because the
MHC-bound peptide could be exchanged or removed without affecting CD4+ T-
cell activation (see Fig. 1B).18 Some TCC reacted to the drug even if presented by allo-
geneic MHC molecules, indicating that no strict HLA restriction for drug presentation
exists.19 However, this may be different for the less well-analyzed CD8+ TCC. Some
severe drug hypersensitivity reactions caused by certain drugs have a high HLA-B-
allele association.20–26 In the case of abacavir hypersensitivity (a drug hypersensitivity
syndrome strongly associated with the HLA-B*5701 allele23,24) key interacting resi-
dues in the HLA-B*5701 peptide-binding cleft could be identified, which allow the
formation of noncovalent interactions with the drug abacavir.24 Recent in silico data
published by Yang and colleagues25 suggest that drugs could also fit in empty,
non–peptide-bearing MHC class I molecules. Thus, the strong MHC allele; drug spec-
ificity can be explained by a steric complementarity together with other strong
noncovalent interactions between the drug molecule and the antigen presentation groove. It is tempting to speculate that the interaction of abacavir with empty MHC class I molecules may stabilize these MHC molecules, because MHC molecules without peptides are unstable.

This and other strong MHC class I–associated drug hypersensitivity reactions were among the first examples of personalized medicine; nowadays HLA-B*5701 typing is regularly done before abacavir is prescribed, which has almost eliminated severe abacavir-related drug hypersensitivity reactions. Similarly, among Han Chinese, HLA-B*1502 typing greatly reduces the incidence of Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) in carbamazepin-treated patients.

Based on these findings, 2 types of p-i mechanism may occur. In the case of MHC class I restricted drug hypersensitivity reactions, the drug may first bind to the MHC class I molecules, and subsequently elicit a strong (CD8+ T cell) immune response. Whether this drug binding affects empty MHC I molecules, or whether the MHC-embedded peptide could influence the interaction, is still not clear. Nevertheless, the direct binding of the drug to the MHC molecule itself (and not to the peptide) could explain the extremely strong association with the MHC class I molecule (see Fig. 1C), and that eluting peptides from the MHC molecule failed to identify (covalently) drug-peptide complexes.26

Alternatively, a more polymorphic CD4+ T-cell response would occur if the drug interacts primarily with the TCR. Full stimulation of these CD4 cells would still require an interaction with the MHC class II molecules; however, probably just by binding to common determinants of the MHC structure, as various MHC class II molecules do, seems to be sufficient to provide T-cell stimulation. Therefore, in CD4 cell reactions, no MHC-associations have been found for these clinically mostly mild reactions (mainly maculopapular exanthems, rarely drug rash with eosinophilia and systemic symptoms [DRESS]). Some clinical features of the p-i concept are as follows:

- Positive skin test reactions to inert drugs, although no cutaneous metabolism of this peculiar drug is known
- Immune reactivity at the first encounter, without time of sensitization.7 In this case, the drug may already interact with many T cells.
- Generalized reaction to a drug without local danger signs
- Fulminant course of a T-cell–mediated hypersensitivity (as with superantigen stimulations)7,27
- Flare-up reactions to a novel drug (?)
- It reflects an abnormal T-cell stimulation with massive/fatal self-destruction as seen in SJS/TEN and DRESS/drug-induced hypersensitivity syndrome (DiHS) (?)

The p-i concept represents a new way to explain drug-induced hypersensitivity reactions. It suggests that certain drug hypersensitivities are also pharmacologic reactions, because the drug interacts not only with the target for which it is designed but also with some immune receptors. The enormous diversity of immune receptors facilitates this possibility of additional drug interactions outside the original scope. The dogma that small chemicals are not full antigens is still valid and must not be rejected, but drugs are able to interfere with the human immune system in additional ways. Related to this finding of pharmacologic stimulation of the immune system by drugs is the development that some of the so-called unpredictable type B drug reactions become the most predictable drug reactions and a paradigm for personalized medicine. It seems that the belief that type B reactions are bizarre reactions is becoming outdated.
CLASSIFICATION OF DRUG HYPERSENSITIVITY REACTIONS

Coombs and Gell\textsuperscript{28} classified drug hypersensitivity, as well as other immune reactions, into 4 categories termed type I-IV reactions: This classification relies on the formation of IgE antibodies that bind to high-affinity IgE receptors on mast cells and basophilic leukocytes, on complement-fixing antibodies, and in T-cell reactions. Because recent immunologic data reveal that T cells orchestrate different forms of inflammation, which may result in different symptoms, the classification of Coombs and Gell\textsuperscript{28} has been refined\textsuperscript{7} into IVa, IVb, IVc, and IVd reactions, to better accommodate this heterogeneity of T-cell functions.

The extended Coombs and Gell\textsuperscript{28} classification is a simplification of complex events occurring in vivo. The immune system combines different approaches to defend against a real or presumed pathogen, even if the pathogen is not dangerous, as in allergy. Nevertheless, a certain type of immune reaction may dominate the clinical situation: for example, in anaphylaxis to β-lactam antibiotics, there may not only be drug-specific IgE but also a T-cell reaction to the drug. However, the formation of drug-specific IgE is the relevant clinical event. In patients with an exanthem and hepatitis, an eosinophilic infiltrate may be found in the skin biopsy, but the liver cell destruction by cytotoxic T cells may be the more dangerous event. For the diagnosis of a drug allergy, the skin event may be sufficient.

Type I (IgE-mediated) Allergies

The IgE system reacts to small amounts of antigen. It achieves this sensitivity by the ubiquitous presence of mast cells armed with high-affinity fragment crystallizable IgE receptors (Fc-IgE RI), to which allergen- or drug-specific IgE is bound. On cross-linking the Fc-IgE RI, various mediators (histamine, tryptase, leukotriens, prostaglandins, TNF\textsubscript{α}, and so forth) are released, which cause the immediate symptoms and may start and facilitate late-appearing allergic inflammations.

IgE-mediated reactions to drugs are believed usually to depend on the prior development of an immune response to a hapten/carrier complex: B cells, able to interact via their surface Ig receptors with the hapten-carrier complex, mature into IgE-secreting plasma cells. This maturation is helped by hapten-carrier complex–specific T cells, which interact with B cells (ie, via CD40-CD40L interaction) and which release IL-4/IL-13, which are switch factors for IgE synthesis. This sensitization phase is normally asymptomatic. On renewed contact with the drug, a hapten-carrier complex is formed again, which then cross-links preformed drug-specific IgE on mast cells and causes mast cell degranulation and immediate allergic symptoms (Fig. 2).

Peculiar features of IgE-mediated reactions to drugs

IgE-mediated reactions to drugs have some features that need to be considered to better understand these reactions:

1. Very small amounts of a drug seem to be sufficient to allow interaction and cross-linking of receptor-bound IgE molecules. Even intradermal (ID) skin tests with drugs may elicit systemic reactions, and fatal reactions to ID testing have been described.\textsuperscript{29} What is the difference to protein-specific reactions? Why are drug-induced anaphylactic reactions often so severe?

The drug itself is normally too small to cross-link 2 adjacent IgE molecules, and it needs to bind covalently to proteins to cross-link specific IgE bound to Fc-IgE receptors (see Fig. 2). If a protein does not consist of repetitive determinants, it needs at least 2 distinct IgE-binding sites (epitopes) that can bind and cross-link 2 distinct
IgE molecules. If the protein contains only 1 epitope, no cross-linking can occur, because the IgE molecules can only bind to a single epitope, making cross–linking impossible.30

The situation is different for haptens. A hapten may modify a protein at various positions. Consequently, different new epitopes arise (see Fig. 2, position A, B, and so forth). If these new epitopes are spatially distinct enough to allow binding of distinct IgE molecules, at least 2 or more IgE could bind. Even IgE with the same hapten specificity could bind, and cross-linking Fc–IgE receptors would no longer depend on the proximity of at least 2 distinct IgE molecules. Consequently, hapten formation is the main facilitator of IgE cross-linking, as a single hapten-modified protein can cross-link IgE molecules with the same (or different) specificity. This enhanced cross-linking ability may result in rapid and fulminant mast cell degranulations, and may explain the severity of drug-induced anaphylaxis (see schematic representation in Fig. 2).

2. A second feature of drug-induced anaphylaxis is that 50% or more of patients with immediate reactions to various drugs deny any prior contact with the drug; 4/5 of the patients with lethal anaphylaxis had no prior contact with the drug.31 This was previously interpreted as sign of a non–immune-mediated anaphylaxis (pseudoallergy), because prior contact with the drug was believed to be essential for specific IgE formation. However, IgE specific to neuromuscular blocking agents (NMBAs) could be detected in perioperative anaphylaxis by skin tests and by serology even at the first encounter with these drugs,32 and, similarly, a substantial proportion of patients with radiocontrast media–elicited anaphylaxis had positive immediate skin tests.33

This raised the question that perhaps other chemical compounds had sensitized these patients. Observation of the distinct use of the antitussive drug pholcodein in Norway and Sweden may have shed some light on this issue: peripoerative...

Fig. 2. IgE cross-linking is facilitated by hapten binding to proteins. A protein usually contains a few different epitopes, to which IgEs with the appropriate specificities bind. These IgEs are cross-linked by the protein if the epitopes are localized far enough away to allow binding of separate IgEs. If the protein contains only 1 epitope, or if the epitope is too close and thus prevents binding of a second IgE, no cross-linking can ensue (A, B). The potent allergenicity of haptens may be related to their ability to generate new hapten epitopes on a protein: with hapten modification, not 1, but several identical epitopes appear on the protein (C). Not only different IgEs, specific for distinct protein epitopes (B), but even IgEs with identical (hapten) specificity can be cross-linked (C). This may accelerate mast cell degranulation. For details, see the text.
anaphylaxis was found to be sixfold more frequent in Norway than in Sweden. Phol-codein was licensed in Norway, but not in Sweden. Phol-codein use stimulated the production of phol-codein- and morphin-specific IgE molecules, which also reacted with tertiary and quaternary ammonium groups contained in NMBA. Thus, in Norway many people were silently sensitized to a cross-reactive compound contained in an antitussive. Their reactions were clearly IgE mediated and phol-codein/NMBA/quaternary ammonium specific, but not elicited by NMBA.

3. Anaphylactic reactions were often considered to be dose independent, as sometimes very small amounts can cause severe reactions. However, all drug-induced reactions are dose dependent. However, the reaction due to IgE is often caused by minute amounts. Further diminishing the dose, as is done in desensitization procedures, shows that even these reactions are dose dependent.

Clinical features of IgE-mediated reactions
IgE-mediated reactions can cause mild to severe, even lethal, diseases: in sensitized individuals, the reaction can start within seconds after contact with the parentally applied drug, and minutes after oral drug uptake. Symptoms may start with palmar, plantar, genital, and axillar itch, and facial and thoracal redness. These symptoms should be considered an alarm sign, as they often herald a severe, anaphylactic reaction, developing rapidly within minutes (Fig. 3). The symptoms rapidly generalize and, within approximately 10 to 20 minutes, a generalized urticaria may develop. The patient becomes restless and anxious. Laryngeal swelling may be suspected if he/she has difficulty speaking or swallowing, because the tongue is swollen. He or she may also complain about chest tightness and dyspnea; signs of acute bronchospasm. Periorbital and perioral swellings often occur later. More severe and complex reactions are called anaphylaxis, and, in most cases with anaphylaxis, some circulatory events with decrease of blood pressure and (transient) unconsciousness are observed, together with a generalized redness, itch, or urticaria.

Anaphylactic shock occurs often within 10 to 15 minutes, and asphyxia due to laryngeal edema often occurs between 15 and 60 minutes. Asphyxia may account for 60% of anaphylaxis-related deaths. Some patients develop gastrointestinal symptoms (nausea, cramps, vomiting, and fecal incontinence). The reduction in blood pressure may be due to a shift of intravascular volume into the extravascular space or to the development of a cardiac arrhythmia, which is more serious. The full syndrome is anaphylactic shock, which is lethal in approximately 1% to 2% of all anaphylaxis cases. The more rapidly it appears, the more serious it is likely to be. Risk factors for a severe course are high-dose, preexisting (undertreated) asthma, and older age, because myocardial infarction, cerebral hypoxia, and brain damage can lead to death days after the acute event. Patients with recurrent anaphylactic reactions to various triggers (eg, food, drugs, hymenoptera stings) may have mastocytosis.

Although most patients show the involvement of different organs, in perioperative anaphylaxis the symptoms may initially affect only 1 organ system (eg, the cardiovascular system with arrhythmia); skin symptoms may not be visible but can appear later. Anaphylaxis is a severe event, and survivors often have some cognitive or intellectual impairment. Table 1 summarizes the main drugs causing anaphylaxis.

Most IgE-mediated reactions to drugs are less severe, and often only an urticaria, angioedema, or a local wheal may develop. However, any IgE-mediated drug allergy can be potentially life threatening, because the mild symptoms might be due to a low dose, and each treatment might boost the drug-specific IgE response.
PSEUDOALLERGY (NON–IMMUNE-MEDIATED HYPERSENSITIVITY)

So-called pseudoallergic reactions (non–immune-mediated hypersensitivities) to drugs, which are as frequent as true IgE-mediated reactions, are a pathogenetically poorly defined problem.

Most of these reactions resemble the clinical features of milder forms of immediate, IgE-mediated reactions (erythema, urticaria), but some reactions cause anaphylaxis and can be lethal. Detection of specific immune mechanism is negative. NSAID-induced pseudoallergic reactions seem to arise less rapidly (often >15 minutes after intake) than true IgE-mediated allergies, and they may require higher drug doses than true IgE-mediated reactions. Increased tryptase levels in the acute stage underline the role of mast cell degranulation in some of these reactions (see Table 1).

Pseudoallergic reactions can be elicited by many drugs, but some drugs seem to elicit them more often (see Table 1). Some drugs might elicit either pseudoallergic, or presumably true allergic reactions, because positive prick skin tests can be...

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**Fig. 3.** Anaphylaxis. Anaphylaxis is a complex and severe allergic reaction affecting multiple organs. It can be seen as the sum of different, severe allergic manifestations in various organs. Symptoms resemble mild to moderate allergic reactions (urticaria, angioedema, bronchospasm). In many, but not all, cases, the cardiovascular system is involved, as a result of relative hypovolemia, due to a shift of intravascular volume to extravascular space (less dangerous), or due to arrhythmia. The most severe form is anaphylactic shock, which can result in death in 1% to 2% of affected persons (see text). (From Pichler WJ. Drug hypersensitivity: classification and relationship to T-cell activation. In: Pichler WJ, editor. Drug hypersensitivity. Basel (Switzerland): Karger; 2007. p. 168–89; with permission.)
detected (contrast media, NMBAs). In vitro, these drugs do not spontaneously release mediators from basophils.

Some people seem to show a higher tendency to react in this way (urticaria), because they develop similar, mostly mild symptoms to a heterogeneous panel of drugs, with clearly distinct chemical and pharmacologic features. Neither IgE nor T-cell reactions are evident, the reactions are recurrent, but provocation tests often remain negative, which makes this disease hard to diagnose and to understand. Additional cofactors are probably needed for patients to develop clinical symptoms after receiving a drug. A few patients may have slightly increased tryptase levels, but further diagnostic workup does not reveal mastocytosis. Some milder reactions can be suppressed by pretreatment with antihistamines, but it is doubtful whether pretreatment with antihistamines and corticosteroids can prevent more severe reactions, such as to contrast media. The most common form of such reactions is related to NSAIDs (see the article by Mario Sánchez-Borges elsewhere in this issue for further exploration of this topic).

### IGG-MEDIATED REACTIONS (CYTOTOXIC MECHANISM AND IMMUNE COMPLEX DEPOSITION, TYPES II AND III)

Type II and type III reactions rely on the formation of complement-fixing IgG antibodies (IgG1, IgG3). IgM is occasionally involved. They are similar, in that both depend on the formation of immune complexes and interaction with complement and Fc-IgG receptor (Fc-IgG1, IIa, and IIIa)–bearing cells (on macrophages, natural killer [NK] cells, granulocytes, and platelets), but the target structures and physiologic consequences are different.

In type II reactions, the drug-specific antibodies formed lead to cell destruction or sequestration. Affected target cells include erythrocytes, leukocytes, platelets, and probably hematopoietic precursor cells in the bone marrow. The antibody-coated cells will be sequestered to the reticuloendothelial system in the liver and spleen by Fc- or complement-receptor binding. More rarely, intravascular destruction may occur by complement-mediated lysis.
Hemolytic anemia has been attributed to penicillin and its derivatives, cephalosporins, levodopa, methyldopa, quinidine, and some antiinflammatory drugs. Cephalosporins are currently the main cause. The clinical symptoms of hemolytic anemia are insidious and may be restricted to symptoms of anemia and jaundice with dark urine. Occasionally a positive direct and (if the drug is present during the test) indirect Coombs test can be found.

Thrombocytopenia is a common side effect of drug treatment, in particular following quinine, quinidine, and sulfonamide antibiotics. It is a common complication of treatments with certain biologicals (mainly monoclonal antibodies). Drug-induced immune thrombocytopenia usually develops after 5 to 8 days of exposure to the sensitizing medication, or after a single exposure in patients previously exposed to the same drug. Patients with this condition often present with widespread petechial hemorrhages in the skin and buccal mucosa, sometimes accompanied by urinary tract or gastrointestinal bleeding. Intracranial hemorrhage is rare. After discontinuation of the provoking medication, platelet counts usually return to normal within 3 to 5 days. (See the article by Trautmann and Seitz elsewhere in this issue for further exploration of this topic).

Formation of immune complexes is a common event in a normal immune response and does normally not cause symptoms. It is not clear why, under certain circumstances, an immune complex disease develops: Very high immune complex levels; a relative deficiency of some complement components, and thus lower capacity to eliminate immune complexes; or an aberrant Fc-IgG-R function might be considered.40 Thus, reduced removal of immune complexes may lead to inappropriate deposition of immune complexes and recruitment of inflammatory cells, in particular polymorphonuclear cells (PMNs), because of immune complex binding to Fc-IgG-R on PMNs. In addition, anaphylatoxins C3a and C5a, generated as a result of local complement activation, may attract PMNs.

A type III reaction may result in a small vessel as vasculitis or serum sickness: In serum sickness, antibodies are generated within 4 to 10 days. Complement (C1q)-containing immune complexes are deposited in the postcapillary venules and attract neutrophilic leukocytes by interacting with their Fc-IgG-RIII,41 which thereby release proteolytic enzymes that can mediate tissue damage.

Nonprotein and protein drugs (biologicals) are responsible for serum sickness. Hypersensitivity vasculitis reportedly has an incidence of 10 to 30 cases per million people per year. Most reports concern cefaclor, followed by trimethoprim-SMX, cephalexin, amoxicillin, NSAID, and diuretics. Biologicals such as rituximab, infliximab, and natalizumab have increasingly been associated with serum sickness42 (see the article by Hausmann and colleagues elsewhere in this issue for further exploration of this topic). Vasculitis may be localized, mainly to the skin, as palpable purpura; purplish red spots, usually found on the legs. In children, it is often referred to as Henoch-Schönlein purpura, sometimes appearing in combination with an arthritis. The prognosis is good when no internal involvement is present. Histology can reveal IgA-containing immune complexes, and the histology of kidney lesions is identical to IgA nephropathy, a main cause of chronic renal failure (Fig. 4).

**T-CELL–MEDIATED, DELAYED DRUG HYPERSENSITIVITY REACTIONS**

**Subclassification of Type IV Reactions**

The detailed analysis of T-cell subsets and functions in the last 30 years has revealed that T cells play a major role in most immune reactions: as helper T cells, which regulate B-cell maturation to antibody-producing cells; as drug-specific T cells, which
orchestrate different forms of inflammation; or as effector T cells mediating cytotoxicity. Based on these findings, as well as studies of immune reactions to drugs in vitro and in vivo, a refined subclassification of T-cell–mediated type IV reactions was developed. It considers the distinct cytokine production by T cells, and thus

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**Fig. 4.** Revised Gell and Coombs classification of drug reactions. Drugs can elicit many different immune reactions. All reactions are T-cell–regulated, but the effect or function relies mainly on antibody-mediated effector functions (types I–III) or more T-cell/cytokine-dependent functions (types IVa–IVd).7 Type I are IgE-mediated reactions. Cross-linking IgE molecules on high-affinity IgE receptors (Fc-IgE R1) on mast cells and basophilic leukocytes leads to degranulation and release of mediators, which cause a variety of symptoms (vasodilatation, increased permeability, bronchoconstriction, itch, and so forth.). Type II reactions are IgG mediated, and cause cell destruction due to complement activation or interaction with Fc-IgG receptor–bearing killer cells. Type III reactions are also IgG mediated: complement deposition and activation in small vessels and recruitment of neutrophilic granulocytes via Fc-IgG receptor interaction leads to a local vascular inflammation. Type IVa reactions correspond to Th1 reactions with high IFNγ/TNFα secretion, and involve monocyte/macrophage activation. CD8 cell recruitment (type IVc reaction) often occurs. Type IVb reactions correspond to eosinophilic inflammation and to a Th2 response with high IL-4/IL-5/IL-13 secretion; they are often associated with an IgE-mediated type I reaction. Type IVc reactions: the cytotoxic reactions (by CD4 and CD8 cells) rely on cytotoxic T cells as effector cells (type IVc). They seem to occur in all drug-related delayed hypersensitivity reactions. Type IVd reactions correspond to a T-cell–dependent, sterile neutrophilic inflammatory reaction. It is distinct from the rapid influx of polymorphonuclear cells (PMN) in bacterial infections. It seems to be related to high CXCL-8/GM-CSF production by T cells (and tissue cells). (From Pichler WJ. Drug hypersensitivity: classification and relationship to T-cell activation. In: Pichler WJ, editor. Drug hypersensitivity. Basel (Switzerland): Karger; 2007. p. 168–89; with permission.)
incorporates the well-accepted Th1/Th2 distinction of T cells; it includes the cytotoxic activity of CD4 and CD8 T cells (IVc); and it emphasizes the participation of different effector cells such as monocytes (IVa), eosinophils (IVb), or neutrophils (IVd), which are the cells causing inflammation and tissue damage.7

Type IVa reactions correspond to Th1-type immune reactions: Th1-type T cells activate macrophages by secreting large amounts of interferon-γ, drive the production of complement-fixing antibody isotypes involved in type II and III reactions (IgG1, IgG3), and are costimulatory for proinflammatory responses (tumor necrosis factor, IL-12) and CD8+ T-cell responses. The T cells promote these reactions by IFNγ secretion and possibly other cytokines (eg, TNFα, IL-18). An in vivo correlate would be a monocyte activation (eg, in skin tests to tuberculin or even granuloma formation, as seen in sarcoidosis), but Th1 cells are also known to help in the activation of CD8 cells, which might explain the common combination of IVa and IVc reactions (eg, in contact dermatitis).

Type IVb corresponds to the Th2-type immune response. Th2 T cells secrete the cytokines IL-4, IL-13 and IL-5, which promote B-cell production of IgE and IgG4, macrophage deactivation, and mast cell and eosinophil responses: The high production of the Th2 cytokine IL-5 leads to an eosinophilic inflammation, which is the characteristic inflammatory cell type in many drug hypersensitivity reactions.7 In addition, there is a link to type I reactions, as Th2 cells boost IgE production by IL-4/IL-13 secretion. An in vivo correlate might be an eosinophil-rich maculopapular exanthem but also infestations with nematodes, or an allergic inflammation of the bronchi or nasal mucosa (asthma and rhinitis).

In type IVc reactions, T cells can themselves act as effector cells. They emigrate to the tissue and can kill tissue cells such as hepatocytes or keratinocytes in a perforin/granzymeB-, granulysin-, and FasL-dependent manner (Fig. 5).27,43,44 Such reactions occur in most drug-induced delayed hypersensitivity reactions, usually together with other type IV reactions (monocyte, eosinophil, or PMN recruitment and activation). Cytotoxic T cells thus play a role in maculopapular or bullous skin diseases (with high granulysin production) as well as in neutrophilic inflammations (eg, acute generalized exanthematous pustulosis [AGEP]), and in contact dermatitis. Type IVc reactions seem to be dominant in bullous skin reactions, in which activated CD8+ T cells kill keratinocytes,7,43,44 but they may also be the dominant cell type in hepatitis or nephritis.27

Type IVd reactions involve the new concept that T cells can also coordinate (sterile) neutrophilic inflammations.45 Typical examples would be sterile neutrophilic inflammations of the skin, in particular AGEP. In this disease, CXCL8 and granulocyte-macrophage colony-stimulating factor (GM-CSF)–producing T cells recruit neutrophilic leukocytes via CXCL8 release, and prevent their apoptosis via GM-CSF release.46 In addition to AGEP, such T-cell reactions are also found in Behcet disease and pustular psoriasis.47 To what extent the cytokine IL-17, associated with neutrophilic inflammations, is involved in these reactions is not yet clear.

Tolerance Mechanism

Most patients can take drugs without developing immune-mediated side effects. It could be argued that these patients lack precursor cells able to interact with the drug. However, the great heterogeneity of the immune response to drugs,7 a high precursor frequency in sensitized patients,48 and the finding that 2% to 4% of the normal population, but 30% to more than 50% of human immunodeficiency virus–infected patients may react with SMX suggest that, rather than a lack of precursor cells, other factors such as the underlying immune status (preactivation of memory
T cells) and regulatory mechanisms may be important. Thereby regulation may occur on different levels. At present, these regulatory mechanisms in immune responses to small molecules are not yet well understood: in DRESS and SJS/TEN, Treg cells were investigated: they were expanded during acute DRESS, but contracted after resolution, leading to an enhanced response to more drugs, as well as to

Fig. 5. True multiple drug hypersensitivities, flare-up reactions, and cross-reactivities. Immune-mediated multiple drug hypersensitivities can be attributed to different mechanisms: (A) 2 structurally distinct drugs elicit a separate immune response and sometimes also different clinical symptoms. The sensitization may occur separately or during the same time span and simultaneous treatments. This response corresponds to a true multiple drug hypersensitivity. (B) so-called flare-up reactions are due to massive immune stimulation during a drug allergy: the preexisting drug allergy is a risk factor for a second reaction: if, because of the prior drug hypersensitivity, the drug is changed, the second drug may cause a transient aggravation of preexisting symptoms. This reaction is often interpreted as second drug allergy, but the second drug is usually (but not always) tolerated again later. (C) Structurally related drugs can cause reappearance of symptoms due to cross-reactivity. The second reactions occur more rapidly. (From Pichler WJ. Drug hypersensitivity: classification and relationship to T-cell activation. In: Pichler WJ, editor. Drug hypersensitivity. Basel (Switzerland): Karger; 2007. p. 168–89; with permission.)
autoimmunity. In contrast, the functional defects of Tregs in TEN were restored on recovery. Further work is needed, but the frequently observed multiple-drug hypersensitivity syndrome after DRESS may be explained by this Treg defect. Tolerance mechanisms to drugs are

1. Ignorance: even if drugs bind to immune receptors, the interaction (affinity, surface contact) is too weak to elicit a significant reaction

2. Lack of danger signals and preactivation: the hapten-carrier complexes do not sufficiently stimulate the innate immunity, which is necessary to develop a primary immune response. Or, in the case of the p-i concept, TCR stimulation by the drug is not sufficient to induce cytokine production and proliferation, because the T cells are not sufficiently preactivated to react to this signal

3. Regulatory T cells may be insufficiently activated in some patients, making them prone to react to small chemical compounds. These patients may have multiple drug allergies and may also suffer from autoimmunity

4. The liver as a tolerogenic organ: the generation of reactive metabolites in the liver may induce tolerance, which might prevent the development of an immune reaction to the drug in the periphery.

Clinical Symptoms of T-cell–mediated Reactions

The most frequent manifestations of drug allergies are delayed cutaneous reactions; so-called rashes. Rashes comprise a broad spectrum of clinical and distinct histopathological features that usually appear between 6 hours and 10 days after drug intake. The skin is most often affected during drug hypersensitivity, but liver involvement is common if moderate elevations of liver enzymes are considered (they are often attributed to a toxic effect of the drug, but may be immune mediated). Other organs such as kidney, lung, and pancreas may also be involved. (For details of the clinical symptoms see the articles by Harr and colleagues and Scherrer and colleagues elsewhere in this issue for further exploration of this topic).

Multiple drug hypersensitivity syndrome and flare-up reactions

The term multiple drug hypersensitivity is widely used for different side effects to various drugs: it is used to characterize patients with multiple drug intolerance (pseudallergy to various, structurally distinct NSAID, and so forth); others reserve this term for well-documented repeated immune-mediated reactions to structurally unrelated drugs. Cross-reactivity due to structural similarity is not included.

In our experience, about 10% of patients with well-documented drug hypersensitivity (positive skin or lymphocyte transformation test) have multiple drug allergies: they may have reacted to an injected lidocain with a massive angioedema; years later the same patient develops an allergy to corticosteroids. Both drugs are positive in skin and lymphocyte transformation tests. Alternatively, a patient reacts to amoxicillin, phenytoin, and SMX within a few months, but with different symptoms (maculopapular exanthema [MPE], drug-induced hypersensitivity syndrome [DiHS]/DRESS, erythrodermia). Most patients with multiple drug hypersensitivity have had severe reactions to at least 1 drug. An IgE-mediated reaction might be followed by a T-cell–mediated reaction. The pathomechanism of this syndrome is unknown, but it

is tempting to speculate that the tolerance mechanism to small molecular compounds fail in these patients (see Fig. 5).

An immune reaction to a drug, via a hapten or p-i mechanism, can be seen as a failure of tolerance, and the same patient might not only develop other drug allergies but also autoimmunity. Preliminary data suggest that a previous drug allergy might be a risk factor for the development of a delayed hypersensitivity reaction to contrast media.

Multiple drug hypersensitivity should be differentiated from flare-up reactions and true cross-reactivity (see Fig. 5). Flare-up reactions are clinically important and frequent: patients with systemic drug allergies show a massive activation of their immune system, similar to acute viral infections. This immune activation may make existing drug allergies risk factors for future drug allergies (see earlier discussion). Flare-up reactions occur when, as a result of an existing drug allergy, drug therapy is changed to a new drug: the second drug may then exacerbate the existing drug allergy (more symptoms of exanthema, increased alanine aminotransferase [ALAT], and fever after 1 or 2 days), and it is often confused with a new drug allergy. Such flare-up reactions are common in severe reactions such as DiHS/DRESS (see earlier discussion). With some exceptions, they are normally not dangerous. The mechanism is unclear, but possibly related to the p-i concept explained earlier: the second drug may not have caused its own, specific immune reaction, but the drug may still bind to the immune receptors of preactivated T cells, and thus briefly augment the symptoms. However, later, in remission, the second drug may again be tolerated, as the costimulatory conditions no longer exist. However, there are also accounts of sensitizations to the second drug, which occurred during the DRESS/DiHS disease.

SUMMARY

Small chemical compounds can interact with the immune system in 2 ways: by forming hapten-carrier complexes, which can stimulate innate and adaptive immunity (T and B cells) and cause localized or systemic reactions due to an immune response against the hapten-carrier complex; alternatively, chemicals that are unable to form covalent bonds can directly interact with proteins by van der Waals and other forces. Some of these labile interactions occur with immune receptors (pharmacologic interaction with immune receptors, p-i concept). Because the immune system offers more than $10^{12}$ different TCR and a few hundred MHC molecules, some of these drug-protein interactions are affine enough to elicit signaling in the receptor-bearing T cell. The type of immune response may differ as a function of the primary interaction of the drug with a particular MHC class I molecule or with the TCR. Full activation of the reactive T cell always requires TCR interaction with the MHC molecule. The consequence of the hapten and p-i mechanisms are drug-allergic diseases, which can appear within minutes to hours. They are mainly caused by mast cell degranulation due to drug-specific IgE or by a direct effect of the drug on mast cells. Delayed reactions start after 6 hours; some even after many days. Delayed reactions become manifest as different types of exanthems, with or without internal involvement, in which the function of drug-specific T cells and their cytokines regulate the type of allergic reaction. This process leads to the further subclassification of type IV reactions as types IVa, IVb, IVc, and IVd, corresponding to T-cell reactions with monocyte/DC (IVa), eosinophil (IVb), cytotoxic T cell (IVc), and neutrophil (IVd) activations.
REFERENCES


