Drug Hypersensitivity Reactions: Classification and Relationship to T-Cell Activation

Werner J. Pichler

Division of Allergology, Department for Rheumatology and Clinical Immunology/Allergology, Inselspital, University of Bern, Bern, Switzerland

Abstract
The clinical characteristics of drug hypersensitivity reactions are very heterogeneous as drugs can actually elicit all types of immune reactions. The majority of allergic reactions involve either drug-specific IgE or T cells. Their stimulation leads to quite distinct immune responses, which are classified according to Gell and Coombs. Here, an extension of this subclassification, which considers the distinct T-cell functions and immunopathologies, is presented. These subclassifications are clinically useful, as they require different treatment and diagnostic steps.

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Introduction
Drug-induced adverse reactions are common and normally classified as type A reactions, which represent predictable side effects due a pharmacological action of the drug or type B reactions, which are not predictable and comprise idiosyncratic reactions due to some individual predisposition (e.g. an enzyme defect), and hypersensitivity reactions [1]. Drug hypersensitivity reactions account for about one sixth of all adverse drug reactions. They comprise allergic and so-called pseudoallergic reactions. The latter is characterized by having the features of an allergic reaction without detectable reactions of the adaptive immune system.

Drug hypersensitivity reactions can become manifest in a great variety of clinical symptoms and diseases, some of which are quite severe and even fatal [2, 3]. The most common allergic reactions occur in the skin and are observed in about 2–3% of hospitalized patients [4, 5]. Any drug is assumed to be able to elicit hypersensitivity reactions. Antibiotics and antiepileptics are the drugs most frequently causing them. The risk of sensitization and the severity of clinical symptoms depend on the state of immune activation of the individual, the dose and duration of treatment, female sex and the immunogenetic predisposition (in particular HLA-B alleles), while a pharmacogenetic predisposition has rarely been detected [see chapters of Hung et al., pp 105–114, and Nolan et al., pp 95–104].

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

Classification of Drug Hypersensitivity Reactions

Drug hypersensitivity reactions can cause many different diseases. To account for this heterogeneity and to better explain the various clinical pictures, Gell and Coombs [7] have classified drug hypersensitivity as well as other immune reactions in four categories termed type I–IV reactions: This classification relies on formation of IgE antibodies, which bind to high-affinity IgE receptors on mast cells and basophilic leukocytes, on complement-fixing antibodies and on T-cell reactions, which orchestrate different forms of inflammations. One has to be aware that these reactions are tightly connected, as for example the maturation of B cells to IgE- or IgG-producing plasma cells depends on the help of T cells. Moreover, this classification was developed in the 1960s, before any functional heterogeneity of T cells was known. In the meantime it has become clear that the immune system is not only specific and has a kind of memory, but is also well adapted to the type of challenge it faces, as for example the defense against intracellular pathogens requires a different approach than the defense against extracellular bacteria, etc. This discrimination seems to be regulated by different types of T cells [8]. To better take into account this heterogeneity of T-cell functions, which are important to understand different forms of diseases, the classification of Gell and Coombs has recently been revised [8] as discussed below.

This modified and extended Gell and Coombs classification has an impact on classifying disease severity, treatment, level of cross-reactivity with other, structurally-related drugs, natural course and prognosis. It requires knowledge of underlying immune mechanisms, and of how these mechanisms result in different forms of clinical disease. On the other hand, one has to be aware that a classification is a simplification of complex events occurring in vivo. The immune system often combines different approaches to defend against a real or – as is the case with allergies – putative pathogen. On the other hand, in many hypersensitivity diseases a certain type of immune reaction dominates the clinical picture, even if the immune response is rather complex.

In drug hypersensitivity, an additional level of complexity derives from the p-i concept (pharmacological interaction with immune receptors), as drugs may act more like superantigens [discussed in the chapter by Gerber and Pichler, pp 66–73]:

- The p-i concept postulates a bypassing of the development of a normal immune response, as a direct, pharmacological stimulation of memory and effector T cells is implied;
- Therefore, it does not follow the normal rules of an immune response, which may already explain some as ‘bizarre’ classified clinical features;
- It could appear at the first encounter with the drug, as no sensitization is required;
- Those T cells which happen to be stimulated by drugs are assumed to actually have a peptide specificity (to which they were primed); however, which peptides are recognized is unknown.

It is unclear (a) whether the drug-induced stimulation of peptide-specific T cells results in a different clinical picture, if the peptides, which are recognized by the drug-stimulated T cells, are present in the body; (b) whether the function of the stimulated T cells remains the same, if the T cell is stimulated by the drug or by its natural ligand, a certain MHC-associated peptide, and (c) whether the constant presence of the presumed natural ligand, the peptide, may contribute to the
persistence of drug-allergic reactions over years in spite of strict avoidance of the drug.

These questions are open and explain why the naming of type B reactions as ‘bizarre’ reactions is actually not so far fetched.

**Antibody-Mediated Drug Hypersensitivity Reactions**

The hapten-like features of a drug allow the modification of soluble and cell-bound proteins. For example, a penicillin molecule could bind covalently to a lysine within a serum protein, but also to cell-bound proteins [see figure 2 in chapter of Torres et al., pp 190–203]. The ‘normal’ reaction of the immune system to such modified proteins is the development of a humoral immune response, consisting of many distinct antibodies with hapten specificity. Consequently, if a coordinated humoral immune response develops (based on T-cell help), one may conclude that the eliciting drug has hapten-like features forming hapten-carrier complexes or is itself a protein bearing ‘foreign’ determinants [e.g. a chimeric antibody, see figure 1 in chapter of Pichler and Campi, pp 151–165]. Indeed, as shown in table 1, the majority of drugs able to elicit IgE-mediated allergies are known to be haptons, or they contain foreign antigenic structures (fig. 1) [9].

**Type I (IgE-Mediated) Allergies**

The IgE system is geared to react to small amounts of antigens. It achieves this extraordinary sensitivity by the ubiquitous presence of mast cells armed with high-affinity Fc-IgE receptors (Fc-IgE-RI), to which allergen/drug-specific IgE is bound. Very small amounts of a drug are apparently sufficient to interact and stimulate these receptor-bound IgE molecules, as occasionally even skin tests with drugs can elicit systemic reactions [see contribution of Barbaud, pp 366–379]. Upon cross-linking the Fc-IgE-RI, various mediators (histamine, tryptase, leukotrienes, prostaglan-

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**Table 1. IgE-mediated drug allergies**

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<thead>
<tr>
<th>Condition</th>
</tr>
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<tbody>
<tr>
<td>Up to 50% of patients with IgE-induced anaphylaxis to certain drugs have no history of previous drug exposure!</td>
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<td>Anaphylaxis occurs rapidly (&lt;20 min), seldom later</td>
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<td>Asphyxia is probably the main cause of lethal anaphylaxis</td>
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<td>Cardiac arrest can be the sole symptom of an anaphylaxis (in particular in perioperative anaphylaxis)</td>
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dins, TNF-α, etc.) are released, which cause the immediate symptoms and may start and facilitate late allergic reactions.

IgE-mediated reactions to drugs are usually thought to depend on the prior development of an immune response to a hapten/carrier complex: B cells need to mature into IgE-secreting plasma cells, and T cells help in this process by interacting with B cells (i.e. CD40-CD40L interaction) and by releasing IL-4/IL-13, which are switch factors for IgE synthesis. This sensitization phase is asymptomatic and may have occurred during an earlier drug treatment. Upon renewed contact with the drug, a hapten-carrier complex is formed again, which then cross-links preformed drug-specific IgE on mast cells. The drug itself is normally too small to cross-link two adjacent IgE molecules, and needs to bind to proteins to cross-link [see chapter of Torres et al., pp 190–203]. However, it is to be noted that in ca. 50% of patients with immediate reactions, no prior contact with the drug can be elucidated [see contribution of Christiansen, pp 233–241] and that 80% of the patients with lethal anaphylaxis had no prior contact with the drug [10]. This indicates that either (a) a silent sensitization to a cross-reactive compound had occurred, or (b) preformed IgE existed which happened to react with the small
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Fig. 1. Hapten and prohapten concept and the non-covalent drug presentation to T cells. 

**a** Hapten: Drugs are haptenes if they can bind covalently to molecules, be they soluble or cell bound (e.g. penicillin G). They can even bind directly to the immunogenic major histocompatibility complex (MHC)/peptide complex on antigen-presenting cells (APC), either to the embedded peptide or to the MHC molecule itself. Thus, the chemical reactivity of haptenes leads to the formation of many distinct antigenic epitopes, which can elicit both humoral and cellular immune responses. Some examples of a B- or T-cell-mediated immune response are listed on the right side.

**b** Prohapten: Other drugs are ‘prohaptenes’, requiring metabolic activation to become haptenes (= chemically reactive). The metabolism leads to the formation of a chemically reactive compound (e.g. 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 real hapten.

**c** The p-i concept (pharmacological interaction with immune receptors): Drugs are often designed to fit into certain proteins/enzymes to block their function. Some drugs may happen to bind also into some of the available T-cell receptors. Under certain conditions (see text), this drug–T-cell receptor interaction may lead to an immune response of the T cell with a ‘fitting’ T-cell receptor. For a full T-cell stimulation by such an inert drug, an interaction of the T-cell receptor with the MHC molecule is required. This type of drug stimulation results in an exclusive T-cell stimulation.

**Clinic: ‘Everything’**
1 and 2: binding to cell-bound and soluble proteins = IgE or IgG to hapten-protein: anaphylaxis, hemolytic anemia, thrombocytopenia
3: MHC class I and II modification: T-cell reaction with exanthems, hepatitis, interstitial lung disease, contact dermatitis, AGEP, TEN...

**Clinic: ‘Everything’**
Potentially immunogenic for B and T cells; Immunogenicity and clinical manifestation might be restricted to the liver (hepatitis) or kidney (interstitial nephritis), where metabolism occurs.

**Clinic: Only T cells**
An exclusive T-cell response might develop with exanthems, hepatitis, etc. Whether B cells (by drug binding to Ig) can similarly be stimulated, remains unclear.
molecular compound, or (c) that the reaction was pseudoallergic (see below).

These reactions were erroneously considered to be dose-independent, as sometimes very small amounts can already cause severe reactions. But further diminishing the dose – as is done in desensitization procedures – illustrates that also these reactions are clearly dose-dependent.

IgE-mediated reactions can cause mild to very 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 reach from simple local itch, local wheal-and-flare reaction upon parenteral drug application, to acute bronchospasm and generalized urticaria and edema, preferentially periorbital, perioral or genital. More severe and complex reactions are called anaphylaxis, whereby in most cases with anaphylaxis some circulatory events with collapse and (transient) unconsciousness are observed together with a generalized redness, itch or urticaria.

Anaphylactic shock occurs often within 15 min, and asphyxia due to laryngeal edema often between 15 and 60 min. Starting symptoms may be a palmar, plantar, genital or axillar itch, which should be seen as an alarm sign, as it often heralds a possibly severe, anaphylactic reaction, following rapidly within minutes (fig. 2): the skin becomes red (diffuse erythema), often first at the trunk, later over the whole body. In the next ~30–60 min an urticaria may appear, together with swelling of the periorbital, perioral and sometimes genital area. Asphyxia may account for 60% of anaphylaxis-related deaths [11]: laryngeal swelling may be suspected if the voice becomes hoarse, the patients have difficulty speaking and swallowing as the tongue is swollen. Patients may also complain about chest tightness and dyspnea – signs of acute bronchospasm. Some patients develop gastrointestinal symptoms (nausea, cramps, vomiting and fecal incontinence). The blood pressure may collapse – either just due to a shift of volume into the extravascular space or – and more severely – if a cardiac arrhythmia develops. The full syndrome is anaphylactic shock, which is lethal in ca. 1–2% of all anaphylaxis cases and the more dangerous the more rapid it appears! Risk factors for a severe course are high dose, preexisting (undertreated) asthma and older age, as myocardial infarction or cerebral hypoxia and brain damage can lead to death days after the acute event. In perioperative anaphylaxis, the symptoms may affect initially only one organ system (e.g. the cardiovascular system with arrhythmia), and skin symptoms appear later. Anaphylaxis is a severe event, and survivors do not rarely have some cognitive or intellectual impairment. Table 2 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, as the mild symptoms might be due to a relatively low dose, and each treatment might also boost the drug-specific IgE response.

**Pseudoallergy (Non-Immune-Mediated Hypersensitivity)**

An unsolved problem are so-called ‘pseudoallergic’ reactions (non-immune-mediated hypersensitivities), which in fact are as frequent as true IgE-mediated reactions. Detection of a specific immune mechanism is negative. The majority of these reactions imitate the clinical features of milder immediate reactions (erythema, urticaria), but some reactions cause anaphylaxis and can be lethal. For non-steroidal anti-inflammatory drug (NSAID)-induced pseudoallergic reactions, it seems that they tend to arise less rapidly (often >15 min) than true IgE-mediated allergies and they may require higher drug doses than for true IgE-mediated reactions. Elevated tryptase levels in the acute stage underline the role of mast cell degranulation, at least in some of these reactions.
‘Pseudoallergic’ reactions can be elicited by many drugs, but some drugs seem to elicit them more often (table 2). Some drugs might elicit both pseudoallergic and also presumably real allergic reactions, as positive prick skin tests can be detected in very severe reactions (contrast media, neuromuscular-blocking agents). In vitro, these drugs do not release mediators from basophils.

A certain group of people seems to show a higher susceptibility to react in this way, as they develop similar, mostly mild symptoms to a quite heterogeneous panel of drugs, with clearly distinct chemical and pharmacological features. Neither IgE nor T-cell reactions can be demonstrated, the reactions are recurrent, but provocation tests are often negative, suggesting that additional cofactors might be needed to develop clinical symptoms. A few patients may have constantly elevated tryptase levels as a sign of a mastocytosis. Such patients sometimes report about multiple anaphylactic reactions to various triggers (food, drugs, hymenoptera stings, etc.). Some milder reactions can be suppressed by pretreatment with antihistamines, but it is unclear wheth-

Fig. 2. Anaphylaxis is a complex and severe allergic reaction affecting multiple organs. It can be seen as the summary of different, severe allergic manifestations in various organs. In many, but not all cases, the cardiovascular system is involved either as result of relative hypovolemia, due to a shift of intravascular volume to extravascular space (less dangerous), or due to arrhythmia. Its most severe form is anaphylactic shock, which can result in death in 1–2% of affected persons (for details, see text).
er pretreatment with antihistamines and corticosteroids can prevent more severe reactions, e.g. to contrast media [12]. The most common form of such reactions is related to NSAIDs and is discussed in detail in the contribution by Sczecklik et al. [pp 340–349].

IgG-Mediated Reactions (Cytotoxic Mechanism, Type II)

Type II and III reactions rely on the formation of complement-fixing IgG antibodies (IgG1, IgG3). Occasionally, IgM is involved. They are similar, as both depend on the formation of immune complexes and interaction with complement and Fc-IgG receptor (Fc-IgG1, Ila & IIIa) bearing cells (on macrophages, NK cells, granulocytes, platelets), but the target structures and physiological consequences are different:

In type II reactions, the antibody can be directed to cell structures on the membrane (rarely) or immune complex activation occurs on the cell surface: both events can lead to cell destruction or sequestration. Affected target cells include erythrocytes, leukocytes, platelets and probably hematopoietic precursor cells in the bone marrow [see also chapter of Aster, pp 306–320]. The mechanism of type II reaction is not as clear as originally thought, since a clear hapten-specific immune reaction can often not be documented [13, 14]. One differentiates between:

(a) Development of complement-fixing antibodies (IgG1, IgG3, rarely IgM) to the hapten-carrier complex, mostly after longer duration of high-dose treatment. It is rather rare and best documented for high-dose penicillin and cephalosporin treatments. Some antibody reactivity may be directed to the carrier molecule itself (= autoantibodies). This autoimmune form is less abrupt, but longer lasting (weeks instead of days) after cessation of the drug.

(b) Non-specific adherence with autoantibody inductions can occur when a drug or metabolite is somehow adsorbed to the erythrocyte or thrombocyte membrane, creating a new antigenic complex in combination with the cell membrane. For example, quinine-induced immune thrombocytopenia is caused by a remarkable class of IgG and/or IgM immunoglobulins that react with selected epitopes on platelet membrane glycoproteins, usually GPIIb/IIIa (fibrinogen receptor) or GPIb/IX (von Willebrand factor receptor) only when the drug is present in its soluble form [13]. Well-documented cases are due to quinine, quinidine or sulphonamide antibiotics. The

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**Table 2. Drugs causing IgE-mediated or pseudoallergic reactions**

<table>
<thead>
<tr>
<th>Drugs involved in IgE-mediated allergies</th>
<th>Drugs causing ‘pseudoallergic’ reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreign proteins (chimeric antibodies)</td>
<td>(Radio)contrast media</td>
</tr>
<tr>
<td>Immunglobulin preparations (IgE anti-IgA)</td>
<td>Plasma expanders</td>
</tr>
<tr>
<td>β-Lactam antibiotics</td>
<td>NSAIDs: acetylsalicylic acid, diclofenac,</td>
</tr>
<tr>
<td>Penicillin</td>
<td>mefanamic acid, ibuprofen, …</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td></td>
</tr>
<tr>
<td>Pyrazolones</td>
<td>Pyrazolones</td>
</tr>
<tr>
<td>Quinolones</td>
<td>Quinolones</td>
</tr>
<tr>
<td>Neuromuscular-blocking agents</td>
<td>Neuromuscular-blocking agents</td>
</tr>
</tbody>
</table>

1 Not complete; only main groups mentioned.
2 The main causes of perioperative anaphylaxis are neuromuscular-blocking agents, followed by antibiotics (mainly i.v. cephalosporins) and latex. Skin tests may be positive even if the drug was given the first time.
antibodies are clearly not hapten-specific, and it remains enigmatic how a soluble drug can promote binding of an otherwise innocuous antibody to a membrane glycoprotein to cause platelet destruction.

The antibody-coated cells will be sequestrated to the reticuloendothelial system in 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 anti-inflammatory drugs. Today, cephalosporins are the main cause. The clinical symptoms of hemolytic anemia are insidious and may be restricted to symptoms of anemia (fatigue, paleness, shortness of breath, tachycardia) and jaundice with dark urine. The laboratory investigation may reveal reduced erythrocyte and hemoglobin levels, increased reticulocytes, a positive direct and – if the drug is present during the test – indirect Coombs test. Indirect bilirubin levels are elevated, haptoglobin decreased. In urine, hemoglobin and hemosiderin are increased.

Thrombocytopenia is a relatively common side effect of drug treatment: Acute, sometimes severe and life-threatening thrombocytopenia is a recognized complication of treatment with quinine, quinidine, sulfonamide antibiotics and many other medications. It is a not so rare complication of treatment with biologicals. Drug-induced immune thrombocytopenia usually develops after 5–8 days of exposure to the sensitizing medication, or after a single exposure in a patient exposed previously 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, but examples have been reported. After discontinuation of the provocative medication, platelet counts usually return to normal within 3–5 days.

A special, intermediate form between type II and III reactions is heparin-induced thrombocytopenia: Platelets contain low-affinity (Fc-IgG-RIIa) Fc receptors that are capable of binding immune complexes, leading to platelet activation [15]. Heparin is a high molecular weight, sulfated, linear polysaccharide that inhibits blood coagulation by activating regulatory proteins such as antithrombin III. About 50% of patients anticoagulated with heparin for at least 7 days produce antibodies that recognize complexes consisting of heparin and platelet factor 4, a CXC chemokine normally stored in platelet α-granules. When a patient with such an antibody is given heparin, heparin/PF4 complexes are formed that react with antibodies to form immune complexes, which bind to the platelet Fc-IgG-RIIa receptors, leading to platelet activation, additional PF4 release and eventually, platelet destruction. Thrombocytopenia occurs in about 5% of patients given heparin and is rarely severe enough to cause bleeding. However, about 10% of the affected patients experience paradoxical thrombosis which can be life-threatening.

These thrombocytic reactions due to heparin have to be differentiated from other heparin- or heparinoid-induced immune reactions. They may be due to a T-cell-mediated allergy with exanthematous or eczematous skin reactions, and very rarely anaphylaxis due to heparin-specific IgE has been described [16]. In delayed reactions due to subcutaneous applications, intravenous administration of heparin or subcutaneous applications of structurally different anticoagulants like for example fondaparinux of hirudin may be tolerated.

IgG-Mediated Reactions (Immune Complex Deposition, Type III)

Formation of immune complexes is a common event in the frame of a normal immune response and does not normally cause symptoms. Immune complexes may also be formed during drug treatment: either if the drug forms a hapten-carrier
Vasculitis may be localized mainly to the skin as ‘palpable purpura’ – purplish, red spots, usually found on the legs [see figure 5 on hypersensitivity vasculitis in chapter of Bircher, pp 352–365]. In children, it is often referred to as Henoch-Schönlein purpura, sometimes appearing together with an arthritis. Lesions may coalesce to form plaques and may ulcerate in some instances. The internal organs most commonly affected are the gastrointestinal tract, kidneys and joints. The prognosis is good when no internal involvement is present. The disorder may be acute or chronic. Histology can reveal IgA-containing immune complexes, and the histology of kidney lesions is in fact identical to IgA nephropathy, a main cause of chronic renal failure.

**T-Cell-Mediated, Delayed Drug Hypersensitivity Reactions**

**Subclassification of Type IV Reactions**

The old Gell and Coombs classification was established before a detailed analysis of T-cell subsets and functions was available. In the meantime, immunological research has revealed that the three antibody-dependent types of reactions require an involvement of helper T cells. Moreover, T cells can orchestrate different forms of inflammations. Therefore, T-cell-mediated type IV reactions were further subclassified in IVa-IVd reactions as proposed in figure 3 [8]. This subclassification considers the distinct cytokine production by T cells and thus incorporates the well-accepted Th1/Th2 distinction of T cells; it includes the cytotoxic activity of both CD4 and CD8 T cells (IVc), and it emphasizes the participation of different effector cells like monocytes (IVa), eosinophils (IVb), or neutrophils (IVd), which are the cells causing the inflammation and tissue damage (fig. 4):

*Type IVa* reactions correspond to Th1-type immune reactions: Th1-type T cells activate macrophages by secreting large amounts of interfer-
on (IFN-γ), drive the production of complement-fixing antibody isotypes involved in type II and III reactions (IgG1, IgG3), and are co-stimulatory for pro-inflammatory responses (TNF, IL-12) and CD8+ T-cell responses. The T cells promote these reactions by IFN-γ secretion and possibly other cytokines (TNF-α, IL-18, etc.). An in vivo correlate would on the one hand be a monocyte activation, for example in skin tests to tuberculin or even granuloma formation as seen in sarcoidosis. On the other hand, these Th1 cells are known to help in the activation of CD8 cells, which might explain the common combination of IVa and IVc reactions (e.g. 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 [8]. 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).

**Type IVc:** T cells can also act as effector cells themselves: they emigrate to the tissue and can kill tissue cells like hepatocytes or keratinocytes in a perforin/granzyme B- and FasL-dependent manner (fig. 5) [19, 20]. Such reactions occur in most drug-induced delayed hypersensitivity reactions, mostly 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 as well as in neutrophilic inflammations (acute generalized exanthematous pustulosis – AGEP), and in contact dermatitis. Type IVc reactions appear to be dominant in bullous skin reactions, where activated CD8+ T cells kill keratinocytes [8, 19, 20], but may also be the dominant cell type in hepatitis or nephritis.

**Type IVd:** Rather neglected was the possibility that T cells could coordinate (sterile) neutrophilic inflammations as well. Typical examples would be sterile neutrophilic inflammations of the skin, in particular AGEP. In this disease, CXCL8- and GM-CSF-producing T cells recruit neutrophilic leukocytes via CXCL8 release and prevent their apoptosis via GM-CSF release [21]. Besides AGEP, such T-cell reactions are also found in Behçet’s disease and pustular psoriasis [22].

**Tolerance mechanism:** Most patients can take drugs without developing immune-mediated side effects. One could argue that they lack precursor cells able to interact with the drug, but the great heterogeneity of the immune response to drugs [8], a high precursor frequency in sensitized patients [23] and the finding that 2–4% of the normal population, but that 30 to >50% of HIV-infected patients may react with sulfamethoxazole, suggests that not a lack of precursor cells but other factors like the underlying immune status (preactivation of memory T cells) and ‘regulatory’ mechanisms may be important.

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**Fig. 3.** Urticaria with itching wheals (pseudoallergic reaction).
Fig. 4. Revised Gell and Coombs classification of drug reactions. Drugs can elicit all types of immune reactions. In fact, all reactions are T-cell regulated, but the effector function rely mainly on antibody-mediated effector functions (type I–III) or more T-cell/cytokine-dependent functions (type IVa–IVd) [8]. Type I reactions are IgE-mediated. Cross-linking IgE molecules on high-affinity IgE receptors (Fc-IgE-RI) on mast cells and basophilic leukocytes lead to degranulation and release of mediators, which cause a variety of symptoms (vasodilatation, increased permeability, bronchoconstriction, itch, etc.). 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 corresponds to Th1 reactions with high IFN-γ/TNF-α secretion and involves monocyte/macrophage activation. Often, one can also see a CD8 cell recruitment (type IVc reaction). 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: the cytotoxic reactions (both by CD4 and CD8 cells) rely on cytotoxic T cells themselves as effector cells (type IVc). They seem to occur in all drug-related delayed hypersensitivity reactions. Type IVd correspond to a T-cell-dependent, sterile neutrophilic inflammatory reaction. It is clearly distinct from the rapid influx of PMN in bacterial infections. It seems to be related to high CXCL8/GM-CSF production by T cells (and tissue cells).