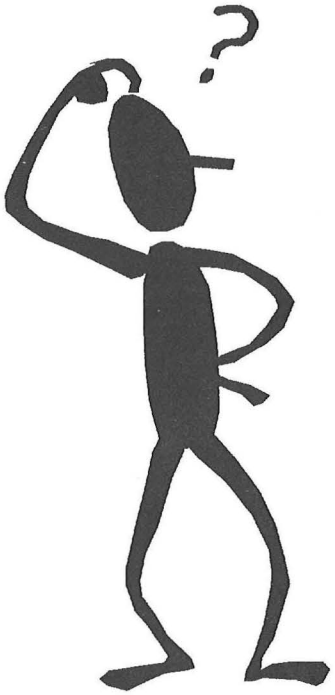
UNDERSTANDING DRUG ALLERGIES: An Oxymoron?



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INTRODUCTION

Allergists oftentimes are called upon to evaluate patients with "multiple drug allergies". By the time the patient is referred to the allergist, the referring physician usually is very frustrated and, therefore, requests that the allergist perform "tests" to determine if their patient, who states that they have multiple drug sensitivities, is indeed allergic. Thus, a great deal of pressure is placed on the allergist since a "black and white" answer is desired by both the referring physician and the patient.

Unfortunately, drug reactions are quite complex and it is not often that black and white answers can be given. Despite this complexity, logical approaches can be devised for the management of these patients. Recent exciting data is allowing us to better elucidate the various mechanisms underlying drug-induced reactions and, because of this information, we are beginning to be able to develop more optimal treatment plans for our patients.

ADVERSE DRUG REACTIONS - SCOPE OF THE PROBLEM

Adverse drug-induced reactions (ADRs) have been defined by the World Health Organization as any noxious, unintended, and undesired effect of a drug that occurs at doses used in humans for prevention, diagnosis, or treatment [1]. Unfortunately, due to inadequate reporting methods, it has been and it continues to be difficult to determine the actual incidence of ADRs. Several groups have evaluated the extent of under-reporting and, in doing so, have found that in hospitals, including university hospitals, a maximum of 6-12% of ADRs only are reported [2, 3].

Despite extensive under-reporting, ADR estimates have been made. In a recent meta-analysis of 39 prospective United States studies from 1966 to 1996, the percentage of serious ADRs in hospitalized patients was found to be 6.7% and, when both serious and nonserious reactions were considered together, this percentage rose to 15.1% [4]. Not only are these reactions associated with significant morbidity and mortality, but also substantial costs. Bates et al. [5] recently estimated that a 700-bed teaching hospital spends $5.6 million on ADRs in a single year alone!

Not surprising, most ADRs involve the skin. While most of these reactions are not associated with serious morbidity, they are important because they are the most frequently encountered ADR and they are the major reason that drug therapy is discontinued. The Boston Collaborative Drug Surveillance Program, one of the most extensive studies that has evaluated the problem, evaluated data from over 37,000 patients to determine the frequency of cutaneous drug reactions to drugs commonly used in the hospital [6, 7]. The data was evaluated in two series and the number of reactions per exposed patient was found to be approximately 2% for both series. Reaction rates were highest for amoxicillin (51 per 1000 exposed patients), trimethoprim-sulfamethoxazole (TMP-SMX) (34 per 1000 exposed patients) and ampicillin (33 per 1000 exposed patients) and the most frequent reactions encountered were: pruritus, morbilliform rashes and urticaria.

ADRs that are thought to be immunologically mediated have been designated "hypersensitivity" or "allergic" drug-induced reactions. While they comprise only 6-10% of the ADRs seen in hospitalized patients [8], these reactions oftentimes are serious and potentially life-threatening. In France, the Centers of Pharmacovigilance recorded 226 deaths due to ADRs in 1998 and at least 5 of these were considered to be allergic in nature [9]. In the meta-analysis of Lazarou et al. [4], it was estimated that allergic reactions accounted for 23.8% of the ADRs demonstrated and many of these were serious.

CLASSIFICATION OF ADVERSE DRUG REACTIONS

Describing and characterizing drug-associated reactions can be a difficult task. While labels, such as "toxic reaction", "allergic reaction" or "idiosyncratic reaction", often are attached to reflect reaction types, in many instances these labels confuse as oppose to clarify the situation. The confusion stems from the fact that limited knowledge exists regarding the mechanisms responsible for many drug-induced reactions especially those that are not related to its pharmacologic properties. In addition, another factor that adds to the confusion is the fact that pharmacologists, toxicologists, and immunologists oftentimes use different terminology. Thus, while classification systems exist, their limitations must be realized and, they constantly must be critiqued and modified as new mechanistic data accumulates.

Rawlins and Thompson [10] devised a classification scheme in 1991 and it continues to be the most frequently used. In their scheme, shown in Table 1, ADRs are divided into two categories: those reactions that are common, predictable and that may occur in any individual (Type A reactions) and those reactions that are uncommon, not predictable and that occur only in susceptible individuals (Type B reactions). Approximately 80% of all ADRs fall into the Type A category [11] and, since Type A reactions are predictable and common, as well as dose-dependent and typically result from an augmentation of the pharmacologic actions of the drug, they often are easily recognized by the physician. Drug-induced overdosage or toxicity, side effects, secondary effects and drug interactions are examples of Type A reactions and, for each prescription medication, these reactions are usually well-described in the Physicians' Desk Reference [12].

In contrast to Type A reactions, Type B reactions are not dose-dependent and, except for one reaction type, they usually are not related to the pharmacologic actions of the drug. In addition, since they are uncommon and not predictable, they often are not discovered until after the drug has been marketed. Both environmental and genetic factors are thought to be important to the development of reactions of this type [13]. Included in this category are: a) drug intolerance, an undesirable effect that is produced by the pharmacologic actions of the drug at therapeutic or subtherapeutic dosages; b) idiosyncratic reactions, uncharacteristic reactions that are not explicable in terms of the known pharmacologic actions of the drug; and c) allergic or hypersensitivity reactions, aberrant reactions that result from the involvement of one or more

immunologic mechanism.

Table 1. Classification of adverse drug reactions

Type A reactions (predictable, common and related to the pharmacologic actions of the drug)

- Toxicity or overdose - hepatic failure with high dose acetaminophen
- Side effect - sedation with antihistamines
- Secondary effect - development of diarrhea with antibiotic therapy due to altered gastrointestinal bacterial flora
- Drug interaction - theophylline toxicity in the presence of erythromycin therapy

Type B reactions (unpredictable, uncommon and usually not related to the pharmacologic actions of the drug)

- Intolerance - tinnitus with aspirin use
- Idiosyncratic reaction - development of anemia with the use of antioxidant drugs in the presence of glucose-6-phosphate dehydrogenase deficiency
- Hypersensitivity (immunologic) reaction - anaphylaxis with penicillin administration
- Pseudoallergic (nonimmunologic) reaction - radiocontrast dye reaction

FEATURES OF ALLERGIC DRUG REACTIONS

Evaluating whether or not a drug reaction involves an immune mechanism is not always easy to determine. However, there are several features of allergic drug reactions that are common to immunologic reactions in general. Typically, the initial course of therapy is uneventful since there must be a period of sensitization. Thus, if a first-dose reaction does occur, either the reaction is not allergic in nature or there was previous exposure to the drug or a cross-reacting agent. Reactions are restricted to a limited number of syndromes that are known or are thought to have an

immunopathologic basis. Examples of typical drug-induced hypersensitivity reactions include: urticaria, angioedema, anaphylaxis, hemolytic anemia and allergic contact dermatitis among many others. Unfortunately, while many reactions are thought to have an immunologic etiology, we have yet to identify the actual mechanism involved. Drug hypersensitivity reactions occur in a small proportion of the population only. The reason that reactions of this type do not occur in a higher proportion of the population is due to the fact that multiple factors interact with each other to determine whether or not an allergic reaction will be elicited. These factors include the molecular characteristics of the drug, its route of administration, the genetic and metabolic predisposition of the individual, and environmental factors such as concomitant infection.

Table 2. Features of allergic drug reactions [14]

- Immunologic drug reactions are preceded by a period of sensitization
- First dose reactions imply that the patient either was previously sensitized to the drug or a crossreacting agent, or that the reaction was not allergic in nature
- Allergic drug reactions are restricted to a limited number of syndromes that have a known or a presumed immunopathologic basis
- Immediate drug reactions may be triggered by a drug amount that is far below the therapeutic range
- Allergic drug reactions are temporally related to drug exposure and usually subside with drug discontinuation

PROBLEMS WITH CURRENT CLASSIFICATION SYSTEMS

In 1975, Gell and Coombs [15] developed a classification system for hypersensitivity reactions that we still use today. In their scheme, hypersensitivity reactions are classified into one of four categories based upon the immune mechanism involved or thought to be involved. Immediate type hypersensitivity reactions are mediated by drug-specific IgE antibodies and include: urticaria, angioedema, and anaphylaxis. Drug-induced cytotoxicity reactions are mediated by drug-specific IgG and/or IgM antibodies and include drug-induced hemolytic anemia, drug-induced thrombocytopenia, and drug-induced leukopenia. Drug-induced immune complex reactions are mediated by drug-specific IgG antibodies and include: drug-induced vasculitis and glomerulonephritis. Drug-induced T cell mediated reactions are mediated by drug-specific T lymphocytes and include: allergic contact dermatitis and possibly drug-induced maculopapular eruptions, bullous eruptions, fixed drug eruptions and Stevens-Johnson syndrome. Details regarding this classification system are provided in an excellent review by DeSwarte [16] on drug allergy.

Unfortunately, most drug-induced allergic reactions can not be classified easily into one of the Gell and Coombs classification categories. A major reason for this difficulty is that, for most reactions, the mechanisms responsible are not known. While many drug-induced cutaneous and other organ-specific reactions have features consistent with a hypersensitivity mechanism, the actual mechanism itself has not been identified making classification difficult. Very importantly, we need to begin thinking "out of the box". Not only do many drug-induced hypersensitivity reactions not fit nicely into the Gell and Coombs classification scheme, but also, adding to the complexity, is the fact that some reactions most likely involve both immune and non-immune mechanisms. Once the underlying mechanisms are better elucidated, a more comprehensive and more accurate classification scheme can be developed for allergic drug reactions. In addition, this knowledge will allow us to design more efficient methods to predict and prevent these reactions as well as to manage them once they occur. Unfortunately, however, elucidating these mechanisms will not be easy since drug-induced hypersensitivity reactions are uncommon, unpredictable and not reproducible in animal models.

MOLECULAR CHARACTERISTICS OF ALLERGENIC AGENTS, DRUG METABOLISM AND ANTIGEN PROCESSING

Some drugs, due to their macromolecular structure, are immunogenic in their native form. Drugs in this category include proteins and peptide hormones. Most drugs however are of low molecular weight, less than 1000 daltons, and they are incapable of inducing an immune response unless they are modified in some way. Since these drugs can and do elicit immune responses, it has been demonstrated that their ability to do so is related to their propensity to combine covalently with large molecular weight compounds [17] coupled with successful processing and presentation of the formed immunogenic drug complex by antigen-presenting cells [18].

Our understanding of how drug hypersensitivity reactions occur is largely based upon the hapten hypothesis [19, 20]: since most drugs are not chemically reactive, they must be metabolized or "bioactivated" to chemically reactive products. In most instances, drug metabolism is a good thing, a type of detoxification process whereby drugs are converted from lipid-soluble, nonpolar compounds to more polar, hydrophilic compounds that are cleared by renal or biliary excretion [21]. Typically, two sequential biochemical reactions, termed phase I and phase II reactions are involved. Phase I reactions involve intramolecular rearrangements, and these are mediated oftentimes by hepatic enzymes of the cytochrome P450 mono-oxygenase system through oxidation, reduction or hydrolysis. The products formed may be biologically reactive and more toxic than the parent drug. However, typically, once these reactive intermediates are formed, they are promptly detoxified in phase II reactions through conjugation with glucuronyl, sulfate, or acetyl groups. Thus, in order to protect the organism, bioactivation is followed by bioinactivation (Figure 1) [13]. In some individuals, however, genetic or environmental factors may cause a perturbation of the normal balance between these two processes leading to increased formation of, or decreased

elimination of, reactive drug metabolites. If not eliminated, these metabolites may do one of several things. In some cases, they bind to macromolecules such as lipids, proteins or nucleic acids and cause direct cellular damage. A well-known example of this type of direct cellular toxicity is acetaminophen-induced hepatotoxicity [22]. Acetaminophen is metabolized to nontoxic metabolites by sulfation or glucuronidation. However, a very small amount (5-10%) is oxidized by a number of cytochrome P450 enzymes to N-acetylbenzoquinoneimine. While this reactive metabolite typically is detoxified by conjugation with glutathione, in an overdose situation, the conjugation pathways are saturated, inadequate detoxification results, and hepatic necrosis ensues [13, 23].

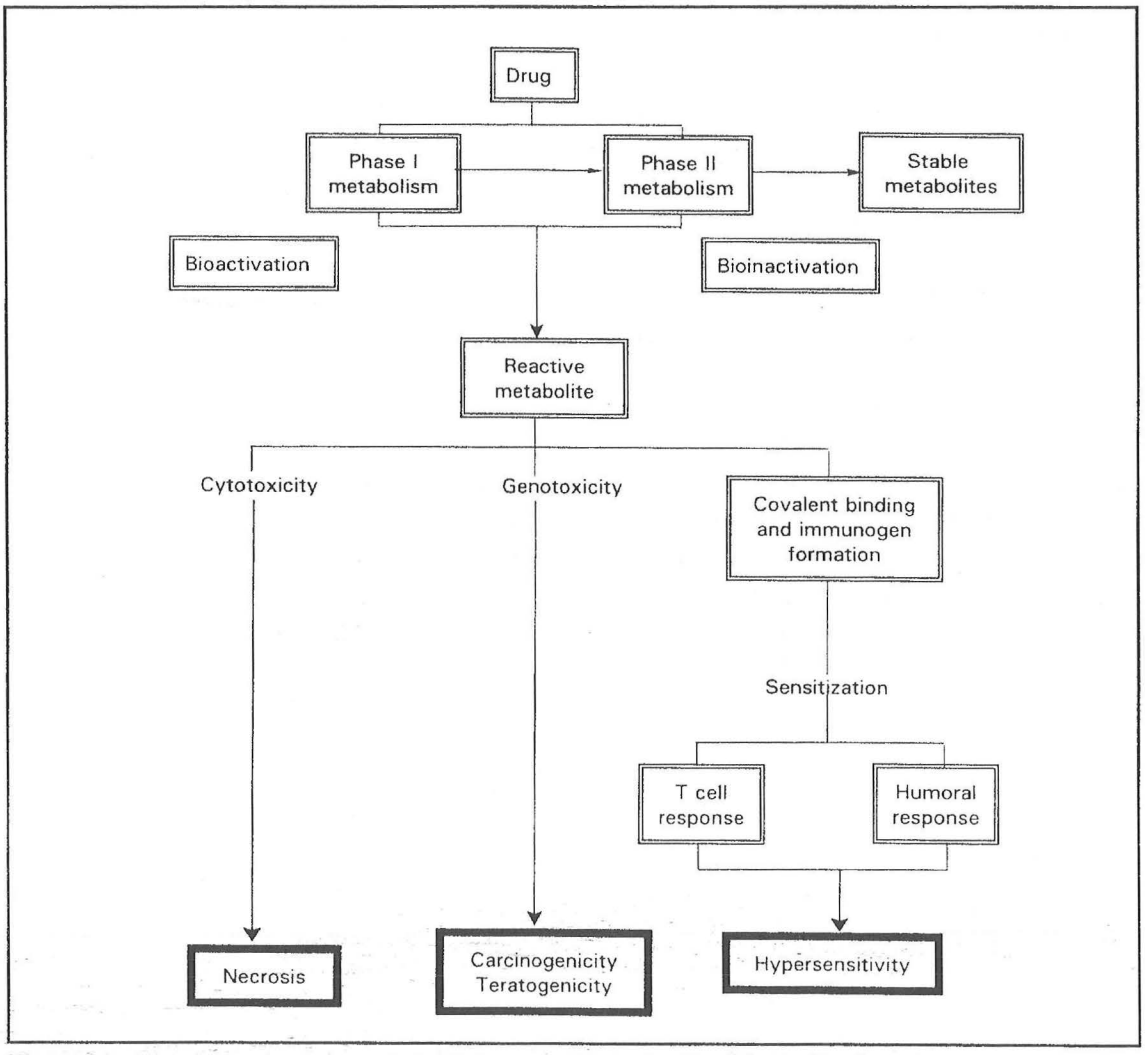

Figure 1. The role of drug metabolizing enzymes in the bioactivation and bioinactivation of drugs [13].

In addition to being directly cytotoxic, some reactive drug metabolites may covalently bind to, or haptenate, macromolecules leading to the formation of immunogenic complexes that may then initiate a hypersensitivity reaction. The type of

immune response that is elicited towards the hapten is dependent upon the pathway by which the hapten is processed and presented to T cells and, it appears that the particular pathway involved is dictated by the chemical properties of the hapten. Small lipid-soluble molecules (e.g., urushiol) can enter the cytoplasm and can be presented on major histocompatibility complex (MHC) class I molecules for recognition by CD8+ cells via the "endogenous" pathway (Figure 2). In contrast, polar haptens such as nickel or cobalt are more likely to be presented on MHC class II molecules for recognition by CD4+ cells ("exogenous" pathway- Figure 3). Some haptens such as dinitroflurobenzene may be processed by both the endogenous and exogenous pathways for presentation to both CD8+ and CD4+ T cells [18].

Until recently, there has been little known about the antigen-processing pathways involved in drug-induced hypersensitivity reactions. However, due to our increased understanding of drug metabolism and drug-induced diseases, we are starting to "get a better handle on" the possible immunologic mechanisms involved in these reactions. Not only are we beginning to be able to identify specific reactive drug metabolites that are formed, we also, through the histological examination of the particular drug-induced disease, are able to determine the processing pathways by which these drug-antigens are presented to the immune system.

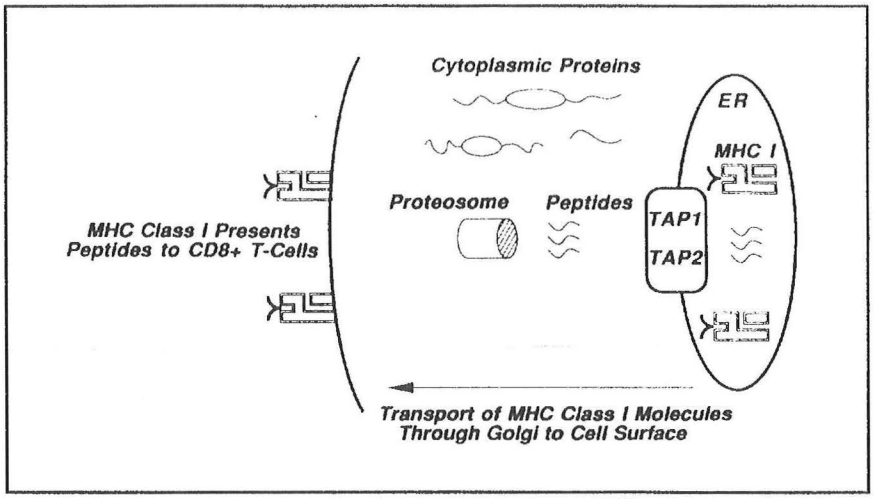

Figure 2. Processing of endogenous antigens [18]

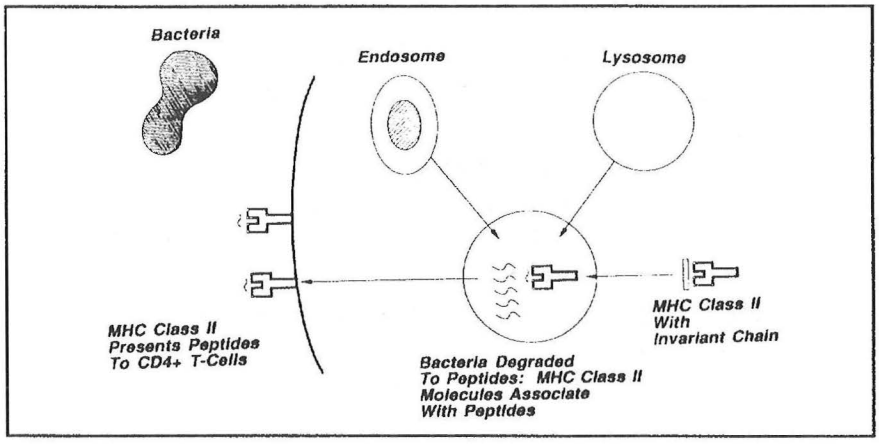

Figure 3. Processing of exogenous antigens [18]

Individuals with morbilliform eruptions to sulfonamides have been found to have sulfonamide-reactive T cells in their peripheral blood [24]. Moreover, sulfonamide-reactive CD8+ T lymphocytes have been isolated from sulfonamide-induced bullous eruptions [25]. These data lend support

to the hypothesis that, at least for some drugs, antigen presentation occurs through MHC class I presentation to CD8+ T lymphocytes. That this mechanism of antigen presentation may be operative in certain types of drug-induced hypersensitivity should not be surprising in light of the fact that we know that many haptenic drugs undergo intracellular metabolic activation. If not detoxified, these reactive drug metabolites theoretically could conjugate with cytoplasmic proteins. Subsequently these endogenous proteins would be degraded into drug-peptide complexes, transported into the endoplasmic reticulum, associated with MHC class I molecules and delivered to the cell surface where they would be presented to CD8+ T cells. While this proposed mechanism explains how drug metabolites may be presented to the immune system and how T cells may be involved in drug-induced hypersensitivity reactions, the critical question is whether or not this mechanism plays an important role in drug-induced allergic diseases. Later in this presentation, emerging new data will be presented that hopefully will convince the reader that T cells may be central to the pathogenesis of many drug-induced hypersensitivity responses.

PATHOPHYSIOLOGY OF ALLERGIC DRUG REACTIONS - EMERGING CONCEPTS

Sites of drug metabolism

The liver is the main drug-metabolizing organ. Interestingly, despite the fact that highly reactive drug metabolites constantly are being generated within this organ, adverse drug-induced hepatic reactions are relatively rare due to the liver's incredible detoxifying capacity. Nevertheless, reactions do occur. It has been shown that long-term treatment with the diuretic drug tienilic acid may lead to autoimmune hepatitis in some individuals and that the reaction is associated with the production of autoantibodies directed against the cytochrome P450 2C9 isoenzyme. Interestingly, this very enzyme is the one responsible for the metabolism of the drug to its reactive form [26, 27]. Thus, probably due to their highly reactive nature, the metabolites, immediately after they are generated, covalently bind to the enzyme responsible for their formation. A similar mechanism has been shown to be operative for both halothane-induced hepatitis [28-30] and dihydralazine-induced hepatitis [31]. In both of these cases, autoantibodies again are directed towards the neoantigen formed by the drug metabolite in conjunction with the cytochrome isozyme responsible for its formation.

Since most drug-induced reactions involve the skin, the question arises whether or not extra-hepatic drug metabolism is occurring. While it is possible that after drug metabolites are formed in the liver, they subsequently travel to distant sites where the reaction is manifested, it is more likely that these are being formed at the reaction site itself. It is known that the skin, which is the largest organ in the body, is very metabolically active containing cells that have both phase I and phase II drug-metabolizing enzymes [32, 33]. Neutrophils, monocytes, macrophages, keratinocytes and Langerhans all have drug-metabolizing enzymes that potentially could lead to the generation of reactive products [34]. The skin also is a very active immunologic organ containing numerous cell types that play a strategic role in antigen presentation, and

this function along with its metabolic properties, make it a likely target for drug-induced diseases [35].

T cell immune responses to haptens - Lessons from the mouse

It is well known that T cells recognize peptides in the context of MHC class I or class II antigens. Initially, it was thought that T cells recognized peptides only and not haptens and, that in the hapten-carrier model, T cells recognize the peptide carrier while antibodies are specific for the hapten [36]. However, more recent studies of T cell responses to TNP protein derivatives have revealed that T cells themselves do recognize and react to haptenated peptides [37-41]. While the early hapten recognition studies were performed in animal models, more recent studies have evaluated T cell responses to haptenic drugs such as penicillin and sulfamethoxazole in humans and, for that reason, we are gaining a better understanding of hapten-induced human immune disorders. However, before addressing T cell immune responses to haptenic drugs given therapeutically, it is important to grasp important new concepts that have emerged from the early murine studies.

In 1992, Martin et al. [42] generated class I-restricted, TNP-specific T cell clones and then assessed their ability to recognize a variety of haptenated peptides. A very interesting result was obtained. The hapten-specific, MHC- restricted T cells that were generated could recognize TNP-conjugated proteins irrespective of the exact amino acid sequence of the presenting peptide. In other words, instead of recognizing any portion of the carrier protein, these T cells recognized the TNP hapten only. The fact that the carrier was irrelevant was a very surprising finding. Another, equally interesting finding was that the majority of the clones reacted to a major type of class I-associated octapeptide that carried TNP lysine in the central position 4. These results together suggest that in hapten recognition by T cells, the peptide serves only to anchor the hapten to a defined position on the MHC surface and that it contributes little, if any, to the specificity of the antigenic epitope (figure 4a) [43, 44].

In subsequent experiments, using synthetic TNP-peptides to further analyze CTL responses *in vitro*, this group once again found that T cells were most easily triggered by position-4 TNP-modified peptides. However, in addition, they also were able to induce T cells specific for hapten-peptides that carried TNP-lysine in the peripheral position 7 of the octapeptide. Interestingly, these CTL, while they too demonstrated class I-restricted reactivity to TNP, unlike the ones previously characterized, they recognized portions of the carrier peptide. In fact, this peptide reactivity was so strong that target cells that had been pulsed with homologous, peptides that were not TNP-modified were lysed! Two subepitopes for these CTL were identified, one being the TNP hapten itself and the other a determinant formed by the side chains of amino acids 3 and 4 in the carrier peptide (figure 4b) [38, 43, 44] Thus, just by positioning the TNP more peripherally on the octapeptide, a dual TNP and carrier peptide response was generated. In light of this data, it was hypothesized that hapten modification of self proteins may lead to the triggering of T cells which, once activated, may also react with

unmodified self structures, inducing an autoimmune response.

Subsequent studies demonstrated that TNP-peptides also can be presented by class II molecules and that the CD4+ T cells generated, similar to the CD8+ CTL previously described, recognize TNP in the form of MHC-associated, haptenated peptides and the immunodominant TNP-epitopes are predominantly independent of the amino acid sequence of the carrier peptide [39]. Thus, these experiments together suggest that hapten-induced T cell responses can be elicited via either class I or class II antigen presentation and that the type of T cell response generated would be dependent upon the type of antigen processing that occurred. In the case of skin-sensitizing haptens, one of four mechanisms potentially could be involved: a) the reactive hapten may modify soluble proteins that are then endocytosed by Langerhans cells, processed and presented by MHC class II antigens; b) the reactive hapten may modify soluble proteins that are then endocytosed by Langerhans cells, processed and presented by MHC-like molecules; c) the reactive metabolite may bind directly to peptides already associated with MHC class I or class II antigens (no processing involved); or d) the reactive hapten may penetrate the plasma membrane and modify cytoplasmic proteins that would then be processed and presented by MHC class I molecules [44].

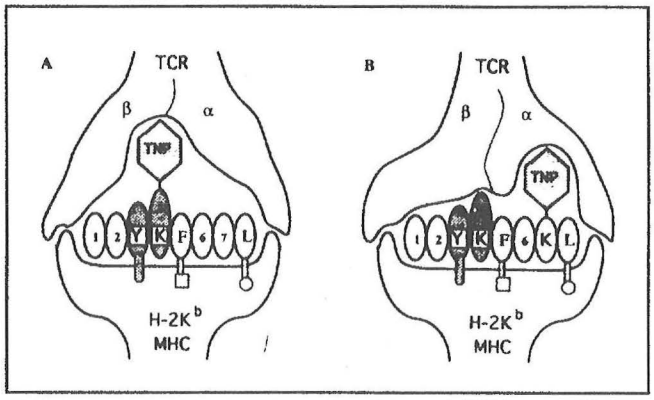

Figure 4. Two types of H-2K^b-restricted TNP determinants [44]. The immuno-dominant TNP-determinant on H-2K^b contains the hapten bound to lysine in the central position 4 of K^b-associated octapeptides (A). Many receptors recognizing this determinant predominantly contact the hapten itself in addition to haplotype-specific MHC-structures, but barely interact with side chains of the carrier peptide. In contrast, T cells specific for the peripherally (position 7) modified TNP-peptides (B), contact the hapten-peptide via two independent sub-epitopes: one represented by TNP, the other by amino acids in carrier positions 3 and 4.

Until recently, the involvement of T cells in allergic reactions to haptenic drugs in humans was unclear. However, their participation could be inferred by the fact that T-cell derived cytokines are necessary for the generation, differentiation and maturation of B cells that secrete drug-specific antibodies. Moreover, T cells themselves are directly involved in some drug-induced diseases (contact dermatitis) and more recently, drug-specific T cells have been isolated from drug-induced skin lesions [45-47]. In addition, *in vitro* T cell reactivity towards several drugs known to cause hypersensitivity reactions has been demonstrated in patients in whom reactions have occurred. Specifically-reactive human T cells have been found in patients who have developed reactions to penicillin (PCN) [48-51], sulfonamides, nonsteroidal anti-inflammatory drugs, and aromatic anticonvulsants [49].

Human T cell responses to penicillin and penicillin-induced allergic reactions

Like TNP, deWeck et al. [52] demonstrated in the early 1970's that penicillin can cause drug-specific T cell activation after it is rendered a "complete" antigen. They found that peripheral blood lymphocytes from patients who had demonstrated clinical penicillin-induced reactions demonstrated increased incorporation of ^{3}H thymidine in the lymphocyte transformation test while cells from individuals who were not allergic did not. More critical evaluation of PCN-induced T cell responses was possible when cloning technology became available. Upon examining antigen-specific T cell clones derived from the peripheral blood of β-lactam-allergic patients with maculopapular exanthems, Hertl et al. [45] found that each of these clones were CD3+, CD4-, CD8+, HLA-DR+ and each produced IL-2 and IFN-γ upon stimulation. Proliferation was dependent upon both the presence of antigen and autologous antigen-presenting cells and, the fact that the clones were CD8+, suggested that antigen recognition occurred in association with class I MHC molecules. Most importantly, this was one of the first studies to demonstrate that the penicillin molecule itself acts as a true haptenic determinant in humans and that it appears to form a critical part of the epitope that is recognized by the T cell receptor.

Subsequently, Hertl et al. [46] evaluated the actual skin-infiltrating lymphocytes in β-lactam antibiotic-induced vesiculo-bullous exanthems. Immunohistochemical studies revealed that CD8+ T lymphocytes were the predominant T cell subset in these lesions. CD8+ epidermal T cell clones that were derived from the cutaneous lesions were found to proliferate in response to penicillin-pulsed autologous antigen presenting cells but not allogeneic antigen presenting cells indicating that the clones were not only antigen-specific but also MHC restricted. In addition, these clones were cytotoxic against epidermal cells, a finding that indicated that T cells may play a role in the keratinocyte necrosis that is associated with drug-induced blister formation.

In order to determine if PCN-specific T cells from allergic patients could recognize other antibiotic agents, Mauri-Hellweg and Padovan and colleagues [50, 53] evaluated the cross-reactivity of T cell lines and clones against various β-lactam antibiotics. Interestingly, they found two types of β-lactam-specific T cell reactivity. One group of patients demonstrated a rather restricted recognition profile, in that the PCN-elicited T cell lines generated from these individuals proliferated only to the stimulating penicillin, but not to other β-lactam antibiotics, including cephalosporins, even if the side chain was identical. Thus, for these individuals, the structure recognized by T cells appeared to be composed of both the penicilloyl determinant together with a portion of the side chain. In contrast to the first group, the second group of patients had more broadly reactive PCN-specific T cells. Their cells not only were stimulated by PCN G but also by related penicillins. They were not, however, stimulated by cephalosporins. For this group, the penicillin nuclear structure (β-lactam and thiazolidine rings), common to all penicillins, appeared to be important for T cell recognition (Figure 5).

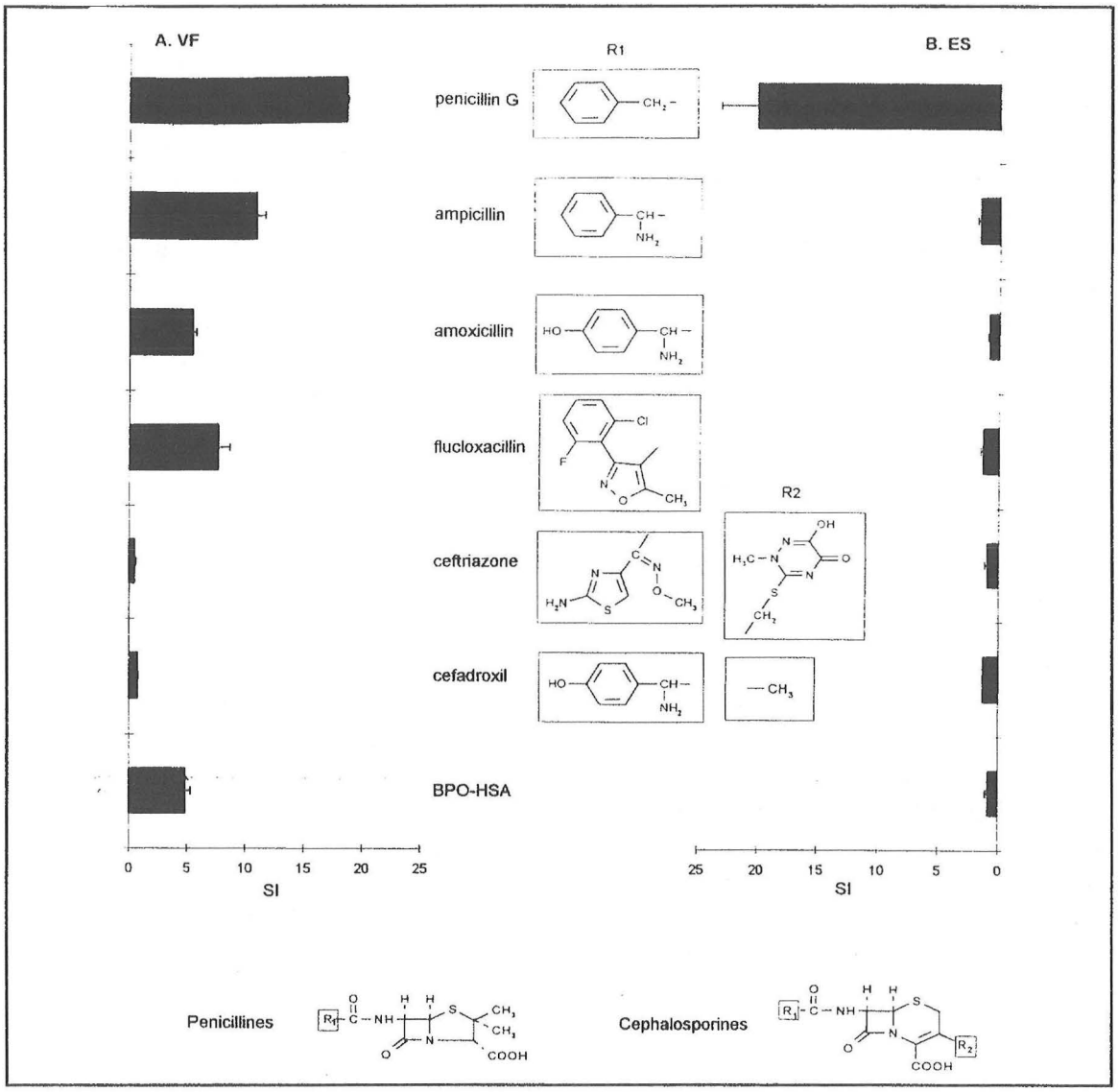

Figure 5. Proliferation of penG-generated T cell lines from donor VF (A) and donor ES (B) in response to various β-lactams [53].

Brander and Padovan and colleagues [48, 54] too found that the immune response to PCN G was heterogeneous. Upon generating T cell clones specific for PCN-G or benzyl penicilloyl-human serum albumin (BPO-HSA) from peripheral blood mononuclear cells of PCN-allergic patients, Brander et al. [48] found that even in a single individual alone, many different PCN G and BPO-HSA reactive clones were identified. The clones that were stimulated *in vitro* by PCN G were either CD4+ or CD8+ , class II or class I restricted, and they did not require antigen processing as fixed APC were capable of efficient antigen presentation. In contrast, T cell clones that were stimulated by BPO-HSA were CD4+ predominantly and antigen processing was required for T cell activation. Both PCN-G- and BPO-HSA-specific T cell clones produced a heterogenous cytokine pattern with most producing high levels of IL-2 and IFN-γ and variable levels of

IL-4 and IL-5. These data confirm the fact that the PCN hapten undergoes multiple modes of antigen presentation. In doing so, different T cell subsets may be activated leading to the extensive clinical heterogeneity that is seen in penicillin-induced human immune responses.

While T cell cloning studies have provided great insight into our understanding of how human T cells recognize the PCN hapten, the clinical implications of these studies are not clear. We know that some penicillin-allergic patients produce broadly cross-reactive antibodies that are directed to the common penicillin nuclear structure while others produce antibodies that are more selective and that are directed towards the β-lactam side chain [55-59]. These findings of antibody heterogeneity are not surprising in light of the heterogeneity of the hapten-specific T cell response that has been demonstrated in PCN-allergic patients. Currently, we try to avoid administering penicillins to individuals who have had β-lactam-induced drug hypersensitivity reactions. This therapeutic principal is based upon the belief that PCN-specific antibodies from PCN-allergic patients may be extensively cross-reactive due to the fact that they are directed towards the β-lactam ring that is common to all penicillins. In light of the fact that cephalosporins too contain this common group, they also are avoided in PCN-allergic patients. However, in reality, we do not know the extent to which the penicillins clinically cross-react either with each other or with cephalosporins. Thus, it is difficult to answer the age-old question, "Can PCN-allergic patients safely receive cephalosporins". It appears that for those reactions that are mediated by PCN-specific IgE antibodies, the antibodies are exquisitely specific, in most cases, since the incidence of cephalosporin reactions in PCN-allergic patients appears to be low [60, 61]. However, in light of the fact that these reactions can and do occur, and that some of these reactions are severe, it can not be assumed that cephalosporins will be well-tolerated in all PCN-allergic patients [62].

Stevens Johnson Syndrome/Toxic Epidermal Necrolysis

Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are serious drug-induced reactions thought by some to be similar disorders of different severity within the spectrum of erythema multiforme. Based on this concept, Bastuji-Garin and colleagues [63] developed a classification scheme of these disorders that is commonly used in the clinical setting. Both diseases have bullous lesions, mucosal involvement and skin detachment, but they differ from each other by the amount of skin detachment - less than 10% in SJS and greater than 30% in TEN. Approximately 50% of cases of SJS are drug-induced with the other half being related to an infectious process. In the case of TEN, approximately 80% of the cases are drug-related. Over 100 drugs have been implicated in these diseases with the most common ones being sulfonamides, aromatic anticonvulsants, β-lactam antibiotics, allopurinol and non-steroidal anti-inflammatory drugs (NSAIDS) [64, 65].

While the mechanisms responsible for SJS/TEN are not yet known, it is thought that, in affected individuals, there is an alteration in the ability to detoxify reactive drug

metabolites [64, 66, 67]. These may be directly cytotoxic, as previously discussed. However, in light of the fact that SJS/TEN have features consistent with immunologically-mediated hypersensitivity reactions (timing, linkage to certain HLA genotypes) [68-70], metabolites also are thought to elicit an immune response after covalent protein binding.

In light of the evidence that suggests that SJS/TEN may be immunologically-mediated reactions, efforts were initiated to detect circulating cytotoxic antibodies, circulating immune complexes, and/or complement deposition. However, these have been unsuccessful for the most part [71]. In contrast to these disappointing endeavors, recent data have been generated that suggests that T cells may play a critical role in disease pathogenesis [47, 72-76]. Merot et al.[72] in 1986 initially described the presence of T cells in skin biopsy specimens from an individual who died from drug-induced TEN. Miyauchi and colleagues [73] confirmed these initial findings and also demonstrated that the predominant cell type in the dermis were CD4+ T cells while in the epidermis, CD8+ cells predominated. Villada et al. [74] also found that the dermal infiltrate in a patient with TEN was composed of activated T lymphocytes. In addition, they found an aberrant expression of HLA-DR by keratinocytes which, prior to this study, had been previously demonstrated only in inflammatory skin disorders [77, 78]. Subsequently, skin blister fluid from TEN patients was examined by Correia and colleagues [75] and, similar to previous skin biopsy studies, they found high lymphocyte cellularity in the blister fluid. Interestingly, like Merot et al. [72] had seen, this local increase of lymphocytes in the skin was associated with a peripheral blood lymphopenia, a finding that suggests that a redistribution of lymphocytes from the blood to the skin was occurring. However, further lymphocyte analysis revealed these cells to be CD8+, CD29+ antigen-primed memory T cells (CD45RA-). The fact that these cells were found to express CD29, the common β chain of the VLA adhesion molecule, suggests that these T cell-associated adhesion molecules may be responsible for mediating T cell interactions with skin endothelium [79] and with extracellular matrix proteins [80].

While Correia et al. [75] demonstrated that blister fluid cells were memory and not naive T cells, they did not actually demonstrate that these cells were drug-specific. Thus, it is possible that the cellular infiltrate was a secondary phenomenon and not causally related to the reaction. However, evidence to support a role for drug-specific T lymphocytes was provided subsequently. In 1993, Hertl and colleagues[46] were able to generate PCN-specific CD8+ T cell clones from cutaneous lesions of two patients with PCN-induced SJS [46] and later they generated CD8+ T cell clones from the lesional skin of a patient with TMP/SMX-induced TEN [47]. These observations, taken together, suggest that drug-specific CD8+ T cells, indeed, may be directly involved in the pathogenesis of these reactions. Thus, one hypothesis, that may explain the cell necrosis seen in SJS/TEN, is that T cell recognition of MHC-associated drug antigens leads to cytotoxic T cell-mediated keratinocyte death [66]. However, while this is an intriguing hypothesis, the situation is probably not this simple. Since the extent of cell death is marked relative to the number of T cells that are present, other factors, such as cytokines, tumor necrosis factor (TNF) in particular, [81] and other cell types [76, 81, 82] are,

most likely, contributing to the pathogenic process.

Recently, the final pathway responsible for epidermal cell death in SJS/TEN has become an intensive area of research [83-85]. Since reactive drug metabolites have been implicated in these diseases, death may occur via direct cellular necrosis. However, in light of the data to suggest that an immune mechanism may be involved, and the fact that cytotoxic T lymphoctyes and tumor necrosis factor are known to induce an apoptotic signal in target cells [86], apoptosis may be the more likely mechanism responsible. A characteristic pattern of DNA cleavage is the biochemical hallmark of apoptosis. Therefore, to determine if an apoptotic mechanism was involved, two groups evaluated the extent of keratinocyte DNA fragmentation in patients with TEN [83, 84]. Both found extensive keratinocyte DNA fragmentation indicating that, indeed, cell death was occurring via an apoptotic mechanism. Moreover, Inachi et al. [84] found that apoptosis was mediated by perforin, a cytoplasmic peptide that is believed to be a major "cytotoxic weapon" of cytotoxic T cells. Thus, these results together, suggest that epidermal cell death occurs by cytotoxic T cell-mediated apoptosis.

More recently, very exciting data has implicated a role for Fas-FasL interactions in the epidermal necrolysis seen in TEN. Viard and colleagues [85] found that keratinocytes from patients with TEN, in addition to expressing Fas, which is not atypical, also expressed lytically active Fas-ligand, a very surprising finding. Moreover, they found that keratinocytes from TEN patients were capable of inducing Fas-mediated cell death in Fas-sensitive target cells. This group then went on to show that IVIG inhibited Fas-mediated cell death by blocking the Fas receptor and that IVIG treatment led to marked clinical improvement in TEN patients. Thus, as the authors suggested, it appears that up-regulation of keratinocyte FasL expression is the critical trigger for keratinocyte destruction seen in TEN. If indeed, IVIG proves to be an effective therapeutic modality for this disorder, it may also be effective in other disorders that are known to involve Fas-mediated tissue destruction.

EVALUATION OF THE DRUG-ALLERGIC PATIENT

The single most important item in the evaluation of the drug-allergic patient is the patient's history. Historical information that should be obtained includes previous exposure history, current drug usage and drug dosages, temporal relationship between initiation of therapy and onset of symptoms, and types of symptoms demonstrated [62]. It is also important to determine if the patient has any underlying renal or hepatic disease that may cause an alteration in drug excretion or drug metabolism, respectively.

In many instances, it is easy to identify the drug responsible for the adverse reaction demonstrated; however, if the patient is receiving multiple drugs, it is sometimes difficult to determine the agent responsible for the reaction. In these cases, it is important to determine the propensity that each drug has for causing a particular drug reaction. A very helpful source of information that describes and catalogues the adverse reactions associated with more than 370 commonly prescribed and over-the-

counter American drugs is the Drug Eruption Reference Manual [87]. This manual lists for each drug all the known, adverse reactions that may develop from the use of that agent. Although it primarily focuses on the dermatologic manifestations, other adverse reactions are addressed as well. In addition, appropriate references for each adverse reaction for every drug are listed, allowing the physician to gather more information regarding a particular type reaction that is associated with a particular agent. It must be emphasized that all types of adverse reactions are listed and that only some of these have an immunologic basis.

Table 3. Important historical and physical exam information in the evaluation of the drug-allergic patient [14]

- Identify all medication usage by the patient (list both prescription and nonprescription drugs and the dosages
- Determine when a medication was initiated and establish a temporal relationship between initiation of therapy and the onset of symptoms
- Determine if there was a prior history of drug exposure
- Characterize the reaction type to determine if an immunologic mechanism may be responsible (consider other potential mechanisms such as toxicity, secondary effects, drug interactions, idiosyncratic reactions and pseudoallergic reactions)
- Determine if the patient has renal or hepatic disease, as abnormal drug excretion and metabolism may result
- Determine the propensity a drug has for causing a particular type of reaction
- Remember that immunopathologic drug reactions may involve any organ system, therefore, a complete physical exam is imperative
- Distinguish between maculopapular skin eruptions and urticaria, as it is probable that only the latter is IgE-mediated
- Determine if there is any mucous membrane involvement, as the presence of this finding suggests the possibility of potentially life-threatening reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis

Often the patient evaluation occurs after the drug reaction has subsided. Although signs and symptoms no longer may be present, the physician still can gather useful information. If the reaction is dermatologic in nature, it is important to determine the type of cutaneous eruption that was manifested. It is probable that nonpruritic, maculopapular skin eruptions are not IgE mediated, whereas specific IgE antibodies are responsible for most drug-induced urticarial reactions. Patients who have had documented maculopapular, nonpruritic eruptions to drugs are not at a greater risk of subsequent anaphylaxis upon drug re-exposure; however, it is very important to realize that if the reaction history is not clear, this assumption may not be made. If there are

any questions on the part of the practitioner, an allergist should be consulted.

If the evaluation occurs while the patient is in the midst of a drug reaction, the physician may gather much information from the physical examination. Because cutaneous reactions are the most common drug allergy manifestation, a careful skin exam should be performed. Urticarial reactions and angioedema are consistent with an IgE-mediated mechanism, while purpura and petechia suggest a Type III, immune complex process. Mucous membrane involvement should be taken very seriously, as it is an important physical finding that portends potentially life-threatening reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis. Finally, it is important to remember that any organ system may be involved in allergic drug reactions and, for that reason, a complete physical examination also should be performed.

CLINICAL APPROACH TO THE PATIENT WITH DRUG-INDUCED DISEASE

Probably the simplest approach to patients who present with a history of previous ADRs is the "better-safe-than-sorry" approach [88]. This strategy involves assuming that the patient had an ADR to a particular drug, and telling the patient that, in light of this drug "sensitivity", he/she should avoid the drug in the future. While probably the safest approach, it is not the most practical and, in addition, it may deprive patients needlessly of important drugs. In addition, this philosophy is leading to a major clinical problem, the development of antibiotic resistant organisms. In a recent survey performed by Solensky et al. [89] it was found that physicians tend to choose alternative broad spectrum antibiotics as opposed to evaluating whether or not their patients who are labeled "penicillin-allergic" are truly allergic. This practice approach may be contributing significantly to the emergence, in hospitals throughout the country, of both vancomycin-resistant enteroccoccal and staphylococcal organisms. Thus, for many reasons, the "better-safe-than-sorry" strategy can not be considered an optimal management approach.

DIAGNOSTIC TESTS FOR DRUG-INDUCED DISEASE

As stated previously, the majority of ADRs are Type A, predictable reactions. These reactions are related to an agent's pharmacologic properties and they are well-described in the adverse reaction profile of a drug when it is marketed. In contrast, Type B reactions are not predictable nor are they common. For these reasons, it is desirable to have diagnostic reagents that would allow one to predict whether or not an individual is at risk for developing a subsequent, similar reaction if the same drug was readministered. Both idiosyncratic reactions and reactions due to drug intolerance will occur again if the responsible drug is readministered. Therefore, of the Type B reactions, diagnostic tools are useful only for hypersensitivity reactions or those that are or are presumed to be immunologically mediated.

General laboratory tests may be helpful for some types of drug-induced disease processes especially when there is organ-specific involvement. Depending upon the

organ system involved, one or more of the following tests may be helpful in the diagnostic evaluation: liver function tests, BUN/creatinine, complete blood count, urinalysis and chest x-ray if there is pulmonary involvement. Also helpful, as Adkinson pointed out in a recent review [90], are biochemical and immunological markers that confirm the activation of certain immunopathologic pathways. Thus, depending upon the reaction type, the following may be useful: a) total hemolytic complement levels (drug-induced immune-complex reactions that result in complement activation); b) anti-nuclear antibodies (drug-induced lupus) and c) 24-hour urine histamine metabolite determination (drug-induced anaphylaxis).

A recently developed biochemical marker that has proven useful for those disorders that involve systemic mast cell activation is the tryptase determination. Tryptase is a neutral protease that is stored in mast cell granules and it exists in two forms, an α form and a β form [91]. Alpha tryptase is a measure of mast cell number and its elevation in blood indicates that there is increased mast cell numbers, a finding that is seen in systemic mastocytosis. In contrast, the β form is a measure of mast cell activation and it is elevated in mast-cell dependent anaphylactic or anaphylactoid reactions. Therefore, the β tryptase level is elevated for both those reactions caused by drugs that cause mast cell mediator release via an immunologic mechanism (heterologous antisera, insulin, penicillin) and those drugs that cause mast cell mediator release via nonimmunologic mechanisms (opiates, muscle relaxants, volume expanders). The half-life of tryptase in plasma is approximately two hours and it is not prone to rapid degradation. For these reasons, tryptase determinations are favored over serum histamine determinations. Matsson and colleagues [92] reported two cases of intraoperative anaphylaxis to anesthetic drugs in which tryptase levels were elevated and others too [93] have reported elevated tryptase levels after drug-induced perioperative anaphylaxis. Schwartz and colleagues [94] recommend that tryptase levels be obtained one to two hours after the onset of the anaphylactic episode. Normal serum levels for β tryptase are less than 1 ng/ml. Levels greater than 1 ng/ml indicate mast cell activation and levels greater than 5 ng/ml are typically seen in mast cell dependent systemic anaphylaxis. However, despite the usefulness of this test in evaluating anaphylactic/anaphylactoid reactions, it is important to note that β tryptase levels may be normal if the reaction is without hemodynamic changes [94].

While some specific diagnostic tools exist for the evaluation of drug-induced hypersensitivity diseases, they are limited in number for two reasons. First, for many drug-induced reactions, drug metabolites or degradation products and not the "native" drug are responsible for the reaction. Unfortunately, at this time the immunochemistry of most drugs, especially those that are low molecular weight haptens are not known. Therefore, without knowledge of the clinically relevant drug determinants, diagnostic materials can not be devised. Second, in many instances, the actual mechanisms responsible for the reactions have not been elucidated. Therefore, it is not known what tests should be performed. While drug-specific antibodies may be present in a patient with drug-induced hepatitis, their presence does not ensure that they are responsible for the disease process. In some cases, these antibodies indeed may be

pathogenic and the cause of the clinical manifestations demonstrated. In other instances, their appearance may represent an epiphenomenon only.

For immediate hypersensitivity reactions, skin testing can be performed to determine if drug-specific IgE antibodies exist. Their presence indicates that the patient is at risk of developing an IgE mediated reaction, including anaphylaxis, if that agent were to be administered again. Skin testing is especially useful for polypeptides that are multivalent and of large molecular weight such as antilymphocyte globulin, toxoids, insulin and streptokinase. It is less useful for small molecular weight agents like antibiotics because, except for penicillin, the relevant immunogenic determinants for most antibiotics have not been identified. Despite this lack of knowledge, beneficial information may be obtained if skin tests are performed with nonirritative antibiotic concentrations. A positive result suggests the presence of drug-specific IgE antibodies. In contrast, a negative result could be interpreted to mean one of two things: a) drug-specific IgE antibodies are absent, or b) drug-specific IgE antibodies are present but they are not detectable because an inappropriate immunogen was used as the testing reagent.

While *in vitro* tests to detect drug-specific IgE antibodies to antibiotics exist, they have the same limitations as *in vivo* skin tests and, in addition, they are less sensitive. Thus, clinicians must be cautioned about using these assays in the diagnostic evaluation of an antibiotic-allergic individual. Currently, there are commercial laboratories specializing in allergy and immunology that offer *in vitro* diagnostic tests for drug-specific IgE antibodies to select antibiotics. However, the usefulness of these tests is unclear. The same problems that plague skin testing plague the *in vitro assays* as well. Lack of knowledge of the clinically relevant antigenic determinants makes it difficult to interpret a negative finding. The inability to detect drug-specific IgE antibodies does not mean that they are absent. It is just as likely that the antibodies are present, just not detectable, because the antigen coupled to the test disc is not the clinically relevant one. Until more information regarding the correct immunogenic determinants of the various antimicrobial agents is generated, *in vitro* assays for IgE antibodies to these agents have limited, if any, use in the diagnostic evaluation of the drug-allergic patient.

The tools that are available for the evaluation of non-IgE mediated drug-induced hypersensitivity reactions too are limited as pointed out in a recent review by Weiss and Adkinson [95]. In addition to limited knowledge of relevant antigenic determinants and pathogenic mechanisms, clinical relevance of the tests that are available must be determined. While the presence of drug-specific IgG or IgM antibody responses may play a role in some cases of drug-induced thrombocytopenia, hemolytic anemia and neutropenia, oftentimes there is no correlation between the presence of these antibodies and disease pathogenesis. A similar lack of correlation may be seen with lymphocyte transformation testing. A marked proliferative response that is induced in a drug-allergic patient's lymphocytes when they are cultured in the presence of the suspected drug indicates specific T-cell sensitization, but whether or not this finding is

clinically relevant is not clear.

In the past, patch testing has been thought to be useful only for the evaluation of drug-induced contact dermatitis. However, more recently, in light of the fact that evidence is accumulating that supports an immunopathogenic role for specific T lymphocytes in some drug-induced reactions including morbilliform eruptions, fixed drug eruptions and bullous eruptions, patch testing may have more broad applicability in the evaluation of drug-induced cutaneous hypersensitivity. Romano and colleagues [96] found that 33 of 60 patients who had maculopapular eruptions to ampicillin, amoxicillin or penicillin demonstrated positive delayed intradermal skin test responses, as well as positive patch test responses, when tested with the clinically relevant drug. Osawa and colleagues [97] also found that patients who had non-immediate-type drug-induced eruptions oftentimes had positive patch test responses. While it was noted that individuals who had eczematous eruptions were more likely to have positive patch test responses than individuals who had maculopapular eruptions, it was found that a large number of individuals who had experienced other drug-induced systemic eruptions (erythema multiforme, erythroderma, fixed drug eruption) were patch test positive as well. These exciting findings suggest that specific T cells may play a pathogenic role in several important drug-induced cutaneous hypersensitivity diseases and that patch testing may prove to be useful in their diagnostic evaluation.

Most importantly, physicians and patients, too, must realize that, in most instances, no single diagnostic test will provide the answer to the commonly-asked question, "Is the patient allergic?". While the elicitation of a wheal and flare skin test response to streptokinase in a patient previously exposed to this agent indicates that the patient has drug-specific IgE antibodies and is at risk for anaphylaxis if streptokinase is readministered, many, if not most, drug-induced hypersensitivity responses are not this easy to evaluate. For many reactions, neither the immunopathogenic mechanisms nor the clinically relevant drug metabolites are known that are responsible for inducing the reaction. However, despite the limited number of diagnostic tools that are available for the evaluation of patients who present with drug-induced disease, reasonable management strategies can still be devised.

MANAGEMENT STRATEGIES FOR DRUG-INDUCED DISEASE

If a drug-disease connection has been established, and there is a need to administer the implicated drug again, several options may be considered as outlined in a management algorithm from the recently-published Disease Management of Drug Hypersensitivity: A Practice Parameter (Figure 6) [62]. In the case of previous type A reactions, depending upon the reaction type, only minor modifications may be required before drug readministration. Reactions related to toxicity may be avoided by making dosage adjustments. Certain side effects may be minimized with dosage changes as well. Reactions related to drug interactions can be avoided by simply ensuring that co-administered drugs do not potentiate the effects of the drug that caused the previous reaction.

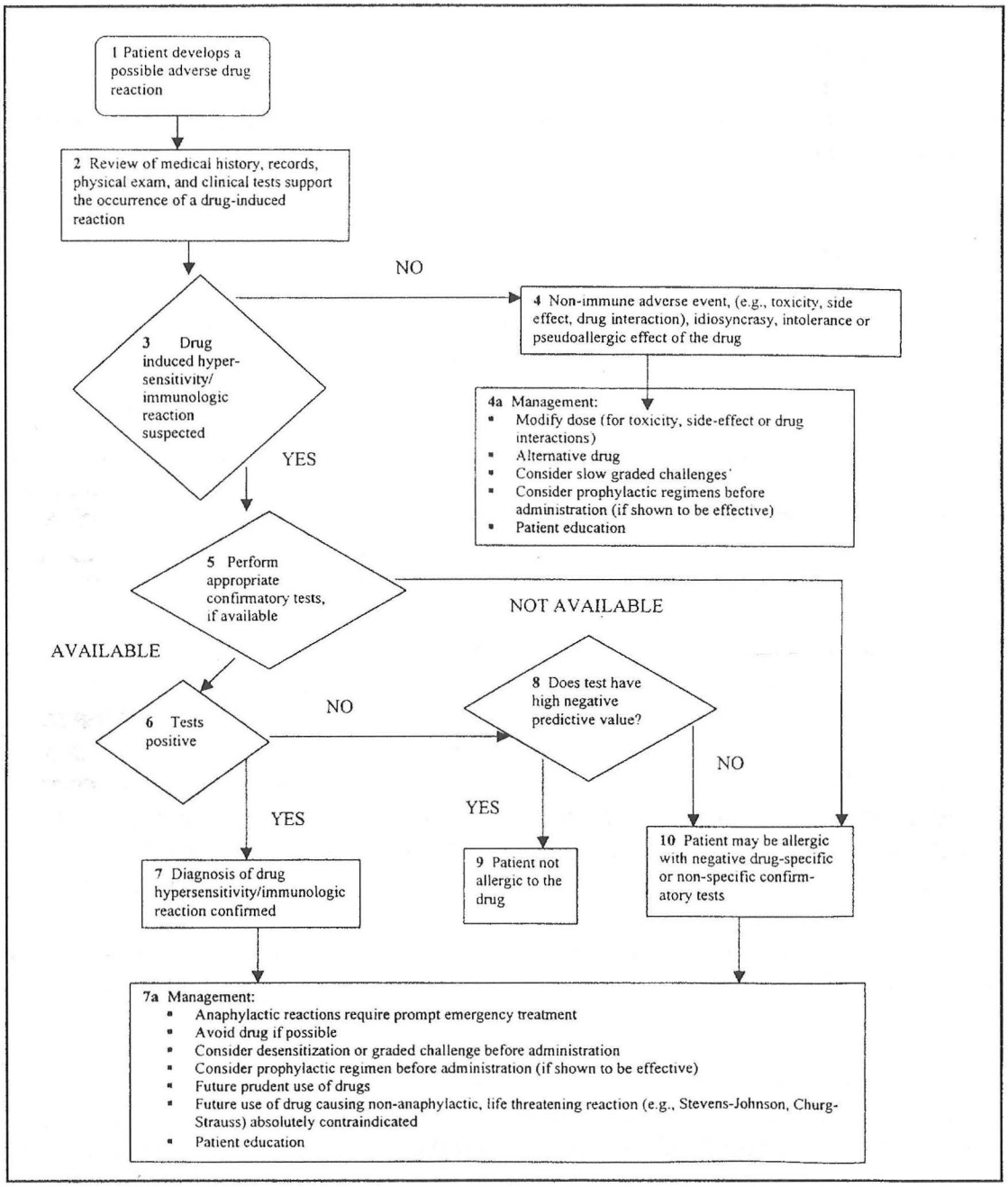

Figure 6. Algorithm for disease management of drug hypersensitivity [62]

For Type B reactions, especially drug intolerances, the implicated drug may be administered again if the previous reaction had been mild (development of tinnitus with aspirin use). Again, only a dosage change may be required. However, for idiosyncratic reactions, more caution is advised. Adkinson [90] suggests that for these reactions, the severity of the reaction must first be considered. If the previous reaction

was severe (coumadin-induced skin necrosis in the presence of protein C deficiency) the drug should be withheld and not readministered. For previous reactions that were mild to moderate, an unblinded provocational challenge may be conducted by a specialist familiar with procedures of this type. If no adverse reaction occurs upon rechallenge, the drug may be continued if it is clinically indicated. If an adverse reaction does occur, both the severity of the reaction and the need for the drug should be assessed before a decision is made about its continuation or discontinuation. Another option, in this circumstance, is to perform a placebo-controlled blinded challenge to ensure that the clinical symptoms demonstrated during the challenge were indeed drug-induced.

If the previous reaction was thought to be hypersensitive in nature, meaning it had immunologic features, confirmatory tests should be performed if they are available (i.e. skin tests for evaluation of drug-specific IgE antibodies or patch tests for evaluation of drug-specific T lymphocytes). If a test is available and it is negative, and if the negative predictive value of the test is known and is high, the patient will not redevelop the hypersensitivity reaction if the drug is readministered. If, however, the negative predictive value of the test is not known, which is often the case, a negative test can not be interpreted to mean that the patient is not allergic and, thus, the previous reaction may or may not redevelop if the drug is reintroduced.

If a confirmatory test is not available or if it is available but its negative predictive value is not known, there are several options. The simplest approach would be to avoid the drug, if an alternative drug is available and it is as clinically effective. However, if no alternative exists, a graded challenge with the implicated drug can be considered if the previous reaction was presumed not to be IgE mediated and, it was not life-threatening. Graded challenges are not indicated in cases where the previous reaction was severe such as Stevens-Johnson syndrome or toxic epidermal necrolysis. For these type reactions, reintroduction of the drug is absolutely contraindicated.

If the previous reaction was presumed to be IgE-mediated, an alternative approach to graded challenge must be taken if the drug is to be readministered. If a skin test reagent exists, the patient should be skin tested. A positive wheal and flare response would indicate the presence of drug-specific IgE antibodies (if the proper controls had been performed) while a negative skin test would indicate, for those tests with high negative predictive value (antilymphocyte globulin, streptokinase, penicillin), the absence of these antibodies. Since, in most instances the negative predictive value is not known, it cannot be assumed that the patient lacks drug-specific IgE antibodies if the skin test is negative. For these individuals and for those with positive skin tests, desensitization, a process by which a drug-allergic individual is converted from a highly sensitive state to a state in which the drug is tolerated, should be performed by an experienced allergist, if it is necessary that the drug be readministered.

ADMINISTRATION OF CEPHALOSPORINS TO PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY

The degree of clinical cross-reactivity between penicillins and cephalosporins is unclear. It is quoted in the literature that as many as 10% to 20% of patients with a history of penicillin allergy and who are skin test positive to penicillin will develop an allergic reaction if given a cephalosporin. However, these high reaction rates have not been demonstrated recently. In fact, since 1980, cephalosporin reaction rates in penicillin history-positive, skin test -positive patients have decreased to 2%[98]. While this figure is low and it could be interpreted to mean that skin testing is not necessary since a 2% reaction rate may occur even without a prior history of allergy, **IT SHOULD BE EMPHASIZED THAT MOST OF THE 2% REACTORS WERE CASES OF ANAPHYLAXIS, SOME OF WHICH WERE FATAL**[99]. An algorithm for administering cephalosporins to patients with histories of penicillin allergy is shown in Figure 7.

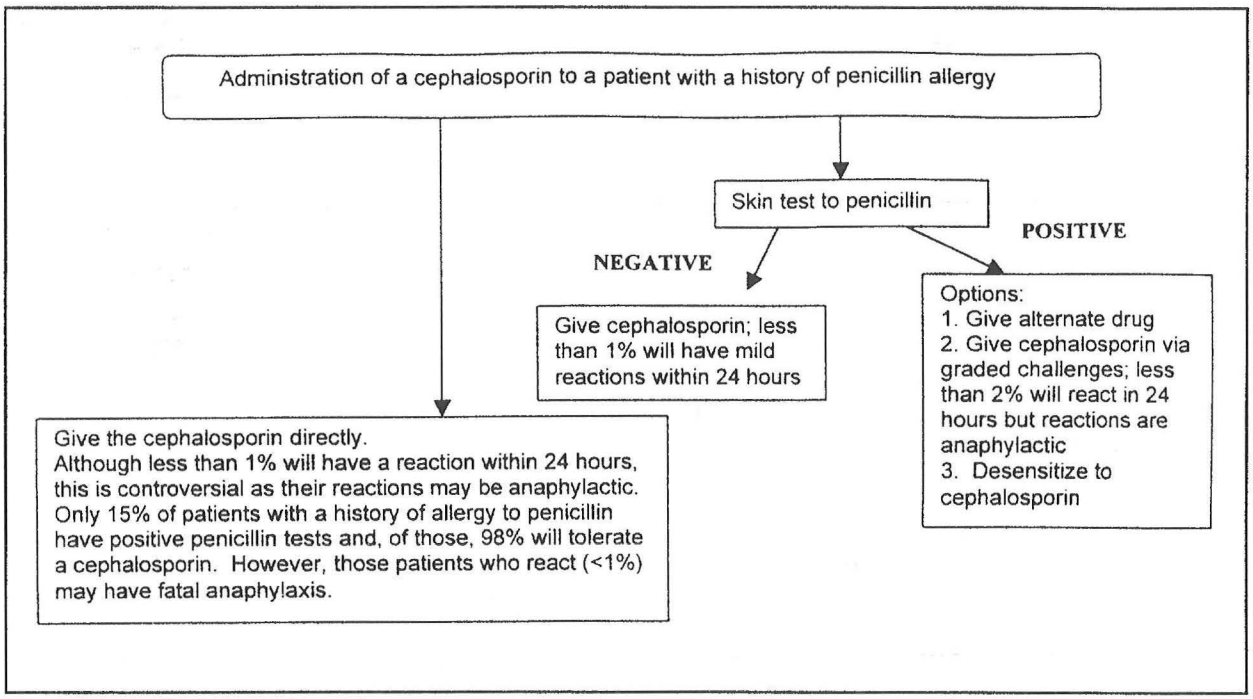

Figure 7. Administration of a cephalosporin to a patient with a history of penicillin allergy[62].

CONCLUSIONS

The management of patients who present with drug-induced reactions can be frustrating for both the patient and the physician. The patients who are most frightened are those who have had multiple ADRs. They feel that they are "allergic to everything" and that, if a life-threatening reaction were to develop, they would be doomed. In these instances, it is important that the physician seek the help of a specialist who is familiar with managing "drug-allergic" patients. Most importantly, both the physician and

the patient must be educated. In many cases, alternative agents that are non-crossreacting exist and can be used. In those cases where alternative agents are not available, drug challenge or drug desensitization may be considered.

As Adkinson [90] recently pointed out, all physicians should follow some simple "common sense" recommendations when prescribing therapeutic agents to their patients. For those patients who have multiple antibiotic "sensitivities" and who seem to need antibiotics "all the time", objective evidence of the infection should be obtained before antibiotic treatment is initiated. If recurrent infections are documented, then they should be aggressively treated in order to ensure they do not recur. In addition, underlying immunodeficiency as well as any structural abnormalities that may predispose to the development of infections should be evaluated.

In closing, it should be remembered that drugs should be given only when they are absolutely indicated. Each drug has an adverse reaction profile and some of these reactions are life threatening. Therefore, while adverse drug reactions and drug-induced diseases will continue to exist, the associated morbidity can be reduced if physicians educate themselves about the drugs they prescribe and judicial prescribing practices are adopted.

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