DRUG ALLERGY

Timothy J. Sullivan, M.D.

Reactive metabolites Haptenation Dehaptenation

Sensitization Antigen valence Risk factors

Immunopathologic reactions AIDS

Multiple drug allergy Diagnosis Avoidance

Premedication Desensitization

Internal Medicine Grand Rounds

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OUTLINE

PAGE

Allergic reactions to drugs are among the most common, diverse, and important forms of immunopathologic processes in modern clinical medicine (1-12). Systematic studies of immune reactions to haptens and drugs have contributed substantially to our understanding of normal immune function and of the mechanisms of immunopathologic processes. Indeed our systems for classifying immunopathologic reactions are derived from immunochemically and immunopathologically defined reactions to drugs. Recognition and characterization of immune effector systems has permitted the recognition of drug-induced reactions that extend from specific antibody or lymphocyte interaction with drug derived determinants, to direct drug-induced activation of immune effector systems, to drug-induced autoimmune reactions.

Allergic reactions to drugs occur in approximately 5% of hospitalized patients and in a substantial number of outpatients with diverse acute and chronic diseases (1-12). In addition to the morbidity and mortality ensuing from these reactions, the inability to use drugs of choice can prolong illnesses and induce otherwise unnecessary morbidity and mortality. Fear of recurrent allergic reactions to drugs often leads to repeated avoidance of drugs of choice. Clearly, measures that avoid, minimize or reverse allergic reactions to drugs can have a major impact on the success, efficiency, and cost of patient care.

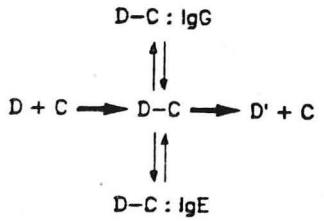
This grand rounds reviews the central concepts of drug-induced immune responses, drug-induced immunopathologic processes, factors influencing the expression of drug allergy, diagnosis of drug allergy, and management of drug allergy.

DRUGS AS ANTIGENS

Heteroantisera, chymopapain, insulin, and other macromolecules administered as therapeutic agents are complete antigens that can induce immune responses and elicit immunopathologic reactions. In order for low molecular weight drugs, such as penicillin or sulfonamides, to induce an immune response, the drug or a reactive metabolite must be bound to a macromolecular carrier (13-23).

The process of drug coupling to a carrier molecule is called haptenation [from the Greek "haptein" meaning to fasten]. Beta-lactam antibiotics are highly reactive with proteins (12-14) and can directly haptenate carriers. Haptenation by most drugs, however, arises from chemically reactive metabolites of the parent drug. Immunologically important haptenation usually is accomplished through the formation of acyl, amide or disulfide bonds (12,24-39). Molecules such as glucose and acetaldehyde can haptenate via keto groups by forming aldimine (Schiff base) adducts that are converted by Amadori rearrangenents to stable ketoamine adducts (25-32). Net

haptenation of carrier molecules is the equilibrium achieved by nonenzymatic haptenation balanced by enzymatic and nonenzymatic dehaptenation (Figure 1).



Haptenation and dehaptentation of macromolecules. Chemically reactive drugs (*D*) or drug metabolites can form covalent linkages to macromolecular carrier molecules (*C*). The drug-carrier conjugate (*D-C*) can be acted upon by dehaptenating enzymes, resulting in the release of a drug cleavage product (*D'*). The concentration of free *D-C* is influenced by the haptenation-dehaptenation equilibrium and by the concentration and affinity of any anti-*D* immunoglobulin present.

Figure 1

DEHAPTENATION

Another immunochemical factor that can influence sensitization and elicitation of hapten mediated reactions is dehaptenation (24). Both amide bound penicilloyl groups and disulfide bound determinants can be removed from carrier molecules at a very rapid rate by plasma enzymes. In order for persistent haptenation to occur, the rate of haptenation must exceed the rate of dehaptenation (Figure 1; Table 1; 24-41).

Human dehaptenating activity: The current general method uses the following incubation conditions:

Drug substituted human serum albumin in phosphate buffered saline 50 ug in 50 uL

Sample containing possible dehaptenating activity 2 to 50 uL

Phosphate buffered saline sufficient to give a total of 100 uL

Incubations are conducted at pH 7.4, at 37 C, usually for 30 minutes. The cleavage of penicillin determinants is assessed by adding 2.0 mL of 1.5% trichloroacetic acid: centrifugation at 400 x g for 10 minutes: aspiration of the supernatant: and dissolution of the pellet in 500 uL of phosphate buffered saline. Counts detected in the supernatant and pellets accounted for all of the counts added, taking experimental error into consideration. The current assay measures the radioactivity retained in the pellet and that released into the supernatant. The supernatant values confirm inferences drawn from pellet measurements and have a coefficient of variation

among replicates (5.3%) that is smaller than that for pellets (10.4%).

As summarized in Table 1, values detected in human serum and plasma were not significantly different. Cord blood values were slightly higher than adult values. The activity was retained within a dialysis membrane for 3 days of dialysis against phosphate buffered saline (pH 7.4) at 4 C without loss of activity. Approximately 43% of the activity remained after heating at 100 C for 10 minutes. A similar heat stability (48%) was noted for the rat serum dehaptenating activity.

When penicilloyl poly-L-lysine conjugates were studied, the dehaptenation rate was indistinguishable from that observed with penicilloyl-HSA in the same experiments. The radioactive product recovered from incubations with penicilloyl-poly-L-lysine and serum cochromatographed with penicilloic acid supporting the concept that the amide bond is the site of cleavage.

Abnormal dehaptenation activity in serum of penicillin allergic patients (24): Serum from 22 penicillin allergic patients contained an average of 48% (± 4 SEM) of the normal dehaptenating activity when disulfide linked determinants were studied. Only one patient had normal activity; 3 sera contained less than 7% of normal activity. Studies with amide linked determinants are incomplete, but defective dehaptenation has been detected in several subjects including a graduate student (2 years from finishing her dissertation) in our laboratory. The results of this study to date indicate that dehaptenation of amide-linked (major) and disulfide-linked (minor) penicillin determinants occurs, that dehaptenation capacity is substantial but variable, and that as a group penicillin allergic patients are slow dehaptenators. Systematic studies of the relationship to defective dehaptenation and 1.) IgE and IgG responses to major and minor determinants; and 2.) clinical expression of immediate hypersensitivity, hemolytic anemia, and serum sickness reactions to penicillin, given the presence of IgE or IgG, should prove enlightening.

Dehaptenation activity in serum from other species: Serum from all six species studied to date (human, rat, mouse, dog, cow, and rabbit) contains amide bond cleaving dehaptenating activity (Table 1). Fetal calf serum and human umbilical cord blood samples were the most active, mouse serum the least.

TABLE I

DEHAPTENATION OF PROTEINS SUBSTITUTED WITH PENICILLIN DETERMINANTS

	Dehaptenation* (nmol/min/ml)		
	Amide Linked	Disulfide Linked	(n)
Human Dehaptenating Activity:			
Normal human serum	16.8 (± 0.4)	7.8 (± 0.2)	(47)
Normal human plasma	14.9 (± 0.5)	8.2 (± 0.3)	(22)
Cord blood serum	19.3 (± 1.2)	NT	(3)
Dialyzed human serum	17.7 (± 0.6)	7.9 (± 0.4)	(3)
Human serum 100 C x 10 min.	7.2 (± 0.3)	NT	(3)
Expression in Other Species:			
Normal rat serum	10.2 (± 0.4)	NT	(15)
Rat serum 100 C x 10 min	4.9 (± 0.5)	NT	(3)
Normal dog serum	13.8 (± 0.6)	NT	(3)
Normal rabbit serum	9.5 (± 0.8)	NT	(3)
Fetal calf serum	20.6 (± 1.1)	NT	(3)
C57/B6 mouse serum	4.1 (± 0.3)	NT	(12)
C57/B6 $W^V/+$ serum	3.9 (± 0.2)	NT	(3)
C57/B6 $W^V W^V$ serum	4.2 (± 0.2)	NT	
WC/B6-F1 mouse serum	3.8 (± 0.3)	NT	(3)
WC/B6-F1 Sl/Sl serum	4.1 (± 0.3)	NT	(3)
Expression and Secretion by Mast Cells:			
Rat peritoneal MC (10^6/ml) homogenate	2.3 (± 0.2)	NT	(4)
Resting RMC supernatant	0.3 (± 0.1)	NT	(4)
Antigen stimulated RMC sup.	1.2 (± 0.2)	NT	(4)

Mast cell secretion of dehaptenating activity: Since mast cells secrete granule associated proteases and other enzymes along with histamine, the possibility of secretion of dehaptenating enzymes was explored. As summarized in Table 1 rat peritoneal mast cells express the amide bond cleaving activity. When mast cells sensitized with monoclonal IgE to DNP were stimulated with 1 ug/mL DNP_{16}-BSA, approximately 52% of the activity was released in a noncytotoxic reaction that included release of a similar proportion of histamine.

In order to assess the overall contribution of mast cells to the serum values, two kinds of mast cell deficient mice were studied (Table 1). Normal levels of serum dehaptenating activity were detected, indicating that the mast cell is not the primary source of the serum activity. Recognition of one cell source of dehaptenating activity, however, should facilitate identification of a mouse or rat cell line (eg PT 18) that can be a source of large amounts of less contaminated enzyme for purification and possible structural analysis studies.

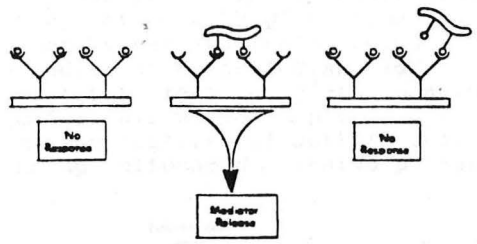
These studies strongly indicate that the dehaptenating activity in the microenvironment is dynamic, subject to alteration by local changes in vascular permeability and mast cell secretion. Immediate hypersensitivity reactions apparently can lead to increased dehaptenating enzyme being present. If countervailing forces such as protease or other enzyme inhibitors are not increased, dehaptenating activity also should increase.

Presentation of haptens to T lymphocytes at the initiation of an immune response appears to proceed most efficiently when molecules such as alpha-2- macroglobulin on the surface of antigen presenting cells become haptenated (41-42). Soluble haptenated proteins usually are much less effective or ineffective in activating T lymphocytes.

Immunopathologic reactions to haptens ensue from several mechanisms. IgM can initiate complement activation when bound to a single determinant, whereas multivalent hapten-carrier molecules or multiply substituted membranes are needed to activate IgG, IgE, or lymphocyte mediated reactions. The requirement for a multivalent hapten-carrier conjugate for activation is particularly clinically relevant for IgE mediated reactions (Figure 2). The concentrations of univalent ligands and multivalent conjugates are critically important in determining the occurrence, intensity, and rate of reactions.

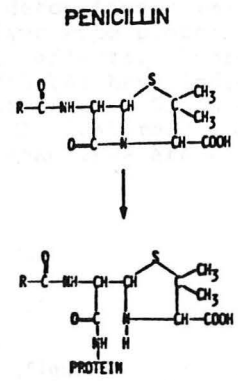
Penicillin allergy has been studied extensively as a clinically important model of direct haptenation (15-22, 43-50). The most common form of haptenation by penicillin is in the penicilloyl configuration (Figure 3). Nonenzymatic conversion of penicillin in solution to a series of derivatives (15-22) permits haptenation in several other molecular forms including penicillenate and penicillamine-protein conjugates. The penicilloyl determinant, coupled by acyl or amide bonds, is the most abundant and therefore is referred to as the major determinant. The other determinants,

coupled by disulfide bonds, are referred to as minor determinants. The terms major and minor refer to abundance, not clinical importance, since any determinant present in sufficient abundance can initiate an immunopathologic reaction.



Requirement for multivalent hapten-carrier molecules to elicit immediate hypersensitivity reactions. Binding of univalent ligands to IgE on the surface of a mast cell or basophil (*left*) does not lead to IgE crosslinking and therefore does not lead to mediator release. Carriers bearing at least two hapten determinants can cross-link IgE and can elicit immediate hypersensitivity reactions (*center*). If an excess of univalent ligands is present (*right*), cross-linking of IgE by multivalent conjugates is inhibited and mediator release is inhibited.

Figure 2



PENICILLOYL DETERMINANT ON CARRIER MOLECULE

Haptenation of macromolecules by penicillin. The formation of an amide bond between the beta-lactam ring of penicillin and an amino group on a protein results in the formation of the penicilloyl determinant. Penicillin metabolities also conjugate to carriers through acyl and disulfide linkages.

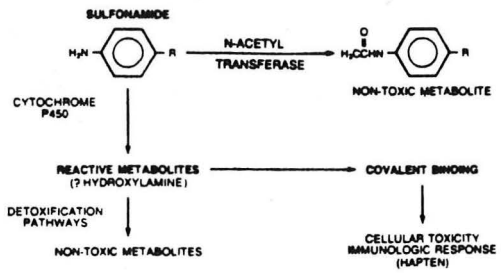
Figure 3

The other members of the beta-lactam antibiotic class (13) share the beta-lactam ring structure and therefore the marked propensity to couple to carrier molecules. Penicilloyl equivalent haptens appear to be formed from these molecules, but the immunochemistry of these agents is not thoroughly understood.

The chemical purity of penicillin preparations used for therapy and the period of time that the drug is allowed to stand in solution before administration influence in vivo immune reactions (45-50). Penicillium mold proteins heavily substituted with penicillin determinants contaminate therapeutic materials. In addition, beta-lactam drugs tend to polymerize in solution. Each of the beta-lactam drugs has varying degrees of contamination with materials of this sort. The relative importance of free drug haptenating in vivo, drug polymers, and preformed drug-protein conjugates in sensitization and elicitation of allergic reactions remains somewhat controversial (21,41,42).

Most drugs are not intrinsically reactive with proteins and must be metabolized to a reactive form for haptenation to occur (51-67).

A well-studied example of this process is illustrated in Figure 4. Sulfonamides are metabolized primarily by hepatic N-acetylation and by cytochrome P450 catalyzed N-oxidation. Genetically slow acetylators are more prone to generate hydroxylamine metabolites of sulfonamides. The hydroxylamine metabolites, detoxified primarily by conjugation with glutathione, are highly reactive with proteins, thereby haptenating proteins and exerting toxic effects. Indeed, studies of human IgE_4 and IgM to sulfonamides (59,60) have indicated that the predicted N^4-sulfonamidoyl determinant (Figure 5) is the major sulfonamide haptenic determinant (59). Clinical reactions having features of both immunologic and toxic reactions are common among sulfonamide-treated patients.



Pathway of sulfonamide metabolism and proposed role of reactive metabolites in the pathogenesis of adverse reactions.

Figure 4

Reference 56

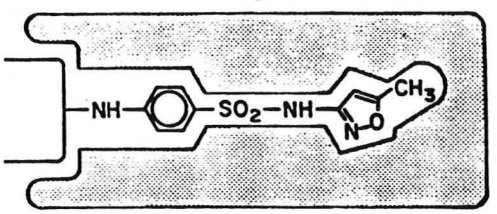


Figure 5

Haptenation of macromolecules by sulfonamides. The N^4-sulfonamidoyl determinant depicted appears to be the major determinant recognized by antibodies to sulfonamides. Antibody binding appears to be influenced by the entire determinant (depicted by the shaded area), but does not require a free p-amino phenyl substituent.

Adverse reactions to sulfonamides, dapsone, rifampin and other drugs metabolized by N-acetylation are common when these drugs are used to treat infections in patients with the acquired immunodeficiency syndrome (62-67). The approximately 50% incidence of reactions to sulfonamides is nearly 10 times the rate among patients not infected with the human immunodeficiency virus (HIV). Although no mechanism has been proved, speculation has centered upon the possibility of increased toxicity and haptenation among slow acetylators, combined with increased vulnerability to injury because of chronic cytomegalovirus infection and other infections.

Some small molecules, such as succinylcholine and other quarternary ammonium muscle relaxants, have sufficient distance between terminal determinants (approximately 6 angstroms) to permit them to act as bivalent antigens without the need for conjugation to a carrier (68,69). Aminoglycosides also satisfy this spatial requirement and may act as complete antigens with antibody binding to terminal sugars instead of acting as haptens.

DRUG-INDUCED IMMUNOPATHOLOGIC PROCESSES

Classic immediate hypersensitivity, cytotoxic reactions, serum sickness, and contact sensitivity reactions can be induced, but pharmacologic agents also can directly activate immune effector systems, induce autoimmune reactions, and exert toxic effects. Not surprisingly, the range of recognized clinical immunopathologic disorders is extraordinarily large (70-88). Drug-induced anaphylaxis can be uniphasic, biphasic, or protracted, indistinguishable from other forms of anaphylaxis (70-72). IgM-mediated hemolytic anemia can occur with low oral doses of penicillin (73,74), but this is an exteremly rare event, suggesting that net haptenation of red blood cells and other formed elements of the blood is not common until massive doses are given (15,16). Currently, serum sickness reactions are most often induced by therapy with beta-lactam drugs or other haptenating agents (75), but complement-mediated immune complex disease remains a common complication of antilymphocyte globulin and heteroantiserum therapy (76-78).

Reactions characterized by fever, lymphadenopathy, rash, and arthritis often are called serum sickness and are presumed to be immune complex-mediated reactions. The evidence that this is the mechanism is equivocal, particularly when histologic study discloses no vasculitis or immune reactants (76-78).

Pharmacologic activation of immune effector systems, or pseudoallergic reactions, are induced by a variety of substances (80-82). Radiocontrast media can induce immediate hypersensitivity-like reactions without interacting with specific IgE antibodies (81-82), but the mechanisms involved are not defined with certainty. These media can activate complement, offering anaphylatoxin generation as one attractive hypothesis (81). The hyperosmolar nature of the media has been offered as an alternative force that might activate mast cells and basophils, since hyperosmolar challenge in vitro can activate mediator release. The mechanism of aspirin-induced reactions remains obscure: no compelling evidence for specific IgE, arachidonic acid shunt to the 5-lipoxygenase pathway, acute prostaglandin E_2, PGE_2 or thromboxane A_2 deficiency, or other hypotheses have been developed.

Recent studies have presented evidence consistent with the concept that anaphylatoxin--mediated or bivalent antigen-mediated anaphylaxis may be somewhat different from multivalent antigen-induced anaphylaxis (83). Anaphylatoxins and bivalent antigens can stimulate mast cell and basophil granule release, but under normal circumstances do not lead to leukotriene or

prostaglandin D_2 (PGD_2) release. This raises the possibility that anaphylatoxin and bivalent antigen-induced anaphylaxis is primarily histamine mediated, whereas multivalent antigen may be mediated by both histamine and the mast cell and basophil lipid mediators.

Some adverse reactions to drugs appear to be immunologically-mediated on epidemiologic and clinical grounds, but have no clear immunopathogenesis (86,87). Systematic studies have begun to clarify reactions such as drug fever (84,85) and toxic epidermal necrolysis (86), but the mechanisms of these reactions remain obscure.

Drug-induced lupus like syndromes remain an important clinical problem (2,16,88). Drugs such as procainamide, isoniazid, hydralazine, practolol, quinidine, and some anticonvulsants are the most common offenders. Slow acetylator phenotype confers increased likelihood and more rapid onset of this syndrome, but the exact mechanism of induction of autoimmunity remains obscure.

RISK FACTORS FOR DRUG ALLERGY

Immune responses to drug determinants occur in only a small percentage of exposed patients and clinical expression of drug allergy occurs in only a fraction of the responding patients (1-12). Several factors have been identified that influence the expression of immune responses and clinical reactions to drugs (89-103). Sustained immune responses to drugs are more likely in adults with specific HLA phenotypes and drug metabolism propensities; more likely when the drug or drug metabolites are highly reactive with proteins; more likely with high doses and long durations of exposure; and more likely after topical rather than parenteral therapy which is in turn more sensitizing than oral therapy (89-102). The purity and chemical state of a drug can influence the likelihood of a response (45-50). Responses to different classes of drugs appear to be influenced to different degrees by these factors.

Specific HLA genes markedly increase the risk of sulfonamide-induced toxic epidermal necrolysis, levamisole-induced agranulocytosis, hydralazine induced lupus, and gold- or penicillamine-induced nephrotoxicity (92,93). Slow N-acetylation phenotype and hydroxylamine detoxification phenotype appear to dispose to reactions to drugs such as sulfonamides and procainamide (94-98).

Clinical expression of drug allergy appears to be influenced by genetic factors including atopy, concurrent medical therapy, concurrent medical illnesses, persistence of the immune response, chemical reactivity of the drug in question, the purity and chemical state of the drug, as well as the dose and route and duration of therapy (89). Anaphylaxis appears to be more severe in atopic patients and those receiving beta adrenergic blocking agents (100-102). Cardiac disease and atopy appear to increase risks of severe radiocontrast medium reactions (103).

Patients who have experienced allergic reactions to other drugs

appear to be more likely to become allergic to penicillin (99). Although there are few data bearing on the epidemiologic factors of multiple drug allergy, there is a suggestion that some patients are in some way generally prone to hapten-induced allergic reactions. To the degree that dehaptenation rates influence sensitization and elicitation of allergic reactions, and to the degree that dehaptenation capacity is genetically or otherwise variable, defective dehaptenation may contribute to a propensity to multiple drug sensitivity.

ADVERSE REACTIONS TO DRUGS IN PATIENTS WITH AIDS

Since their introduction in 1936 the sulfonamides have played an important role in the treatment of several human bacterial and parasitic infections. Sulfonamides (SM) have assumed new importance in the context of AIDS as the drugs of choice for Pneumocystis carnii pneumonia and other infections. Approximately 3% of non-HIV-infected patients treated with SM develop adverse reactions that require cessation of therapy. SM cause approximately 25% of drug-induced rashes and 75% of the most severe cutaneous reactions. Rechallenge of patients with histories of such reactions can induce severe or fatal responses. Drug fever, cutaneous reactions, blood dyscrasias, hepatitis, nephritis, and cardiac toxicity are the most common forms of adverse reactions to SM (reviewed 62-66, 94).

Severe adverse reactions occur in approximately one-half of AIDS patients treated with sulfamethoxazole (SMX), alone or in combination with trimethoprin. Cutaneous reactions are approximately 10-fold higher in AIDS patients than in uninfected patients and the incidence of hepatitis, leukopenia, and thrombocytopenia reactions is even more markedly increased in AIDS patients. These reactions introduce additional morbidity and force the use of drugs such as pentamidine or dapsone which also cause a high incidence of severe adverse reactions. Fear of another adverse reaction usually precludes use of SMX when another susceptible opportunistic infection appears.

The mechanisms of these reactions are unknown. Neither high blood levels nor prolonged therapy account for the high incidence in AIDS patients. AIDS patients do have an increased incidence of lupus anticoagulants [autoantibodies] and antiplatelet antibodies raising the possibility of antibody-mediated reactions. There is conservation of many antibody responses in HIV-infected patients. Chronic infection with Epstein-Barr virus or cytomegalovirus might increase vulnerability to drug reactions. To data no data have been presented that unambiguously clarify the mechanisms of these severe, high frequency reactions in AIDS patients.

Sulfonamides are metabolized primarily by N^4-acetylation and to a lesser extent by N^4-oxidation by cytochrome P-450 enzymes (94). The toxic N^4-oxidation product, thought to be a hydroxylamine apparently is detoxified by conjugation with glutathione. Accumulation of N^4-hydroxylamine metabolites of SM leads to covalent attachment to macromolecules resulting in toxic injury and haptenation (94). A similar process is believed to account for

procainamide haptenation and toxic injury.

Clearly, diminished N^4-acetylation of SM would favor oxidation and diminished glutathione conjugation would favor accumulation of N^4-oxidation products. This in turn would favor haptenation and toxic effects. Recently Shear and coworkers studied 6 patients who had experienced severe adverse reactions to SM (94). Each of the 6 was a slow acetylator as assessed by a caffeine metabolism assay and each displayed marked vulnerability to toxic effects of N^4-SM oxidation products in a lymphocyte toxicity assay. Thus in the 6 patients studied, who displayed clinical reactions very similar to those observed in AIDS patients, combined slow acetylation giving a propensity to form oxidation products of SM, and increased vulnerability to the toxic effects of these metabolites was observed.

TABLE II

HISTORIES OF ADVERSE DRUG REACTIONS AMONG PATIENTS AT THE PMH AIDS CLINIC

	ASYMPTOMATIC HIV INFECTED	ARC	AIDS
BACTRIM/ OTHER SULFONAMIDE	2 (2%)	9 (7%)	52 (39%)
PENICILLIN (ANY)	15 (17%)	17 (14%)	26 (19%)
TETRACYCLINE	3	4	4
CODEINE	4	13	8
TRIMETHOPRIM	0	1	6
DAPSONE	0	1	5
ASPIRIN	0	3	6
TOTAL PATIENTS	(88)	(125)	(135)

Taking the new metabolic and immunologic data together, an integrated set of testable hypotheses about the basis for SM reactions in AIDS patients emerge. Approximately half of AIDS patients would be expected to be slow acetylators (2, 17,19). The slow acetylators would be expected to be more likely to form toxic and immmunogenic metabolites. AIDS patients might have unusual vulnerability to toxic effects of SM (15). As noted below, antibody responses to N^4-sulfonamidoyl haptens derived from the same toxic

molecules may be occurring and contributing to the problems.

Alternatively, there might be a heightened susceptibility to hapten induced immunologic or toxic reactions through diminished dehaptenation capacity, or increased responsiveness of tissues to immune or toxic injury.

A September, 1987 review of the records of Parkland Memorial Hospital (PMH) patients in the AIDS clinic (Table 2) for evidence of adverse reactions to SMX or other drugs disclosed that a history of adverse reactions to SMX/TM or SMX was present in 2% of 88 asymptomatic HIV infected patients, 7% of 125 patients with ARC, and 39% of 135 patients with AIDS. These data agree with the reported high incidence of reactions to SMX and indicate that we have an excellent population to draw upon for the proposed studies.

We have just completed a pilot study of acetylator phenotypes of AIDS patients at PMH that suggests that slow acetylator phenotype is not the pivotal factor in the increased rates of reactions to sulfonamides in most patients. Using a modification of the caffeine metabolism assay of Shear (94) we found increased rather than decreased rates of acetylation in the sulfonamide reactors (Table 3).

TABLE III: Relationship of Acetylator Phenotype to Bactrim Reactions

Subjects	Number	(%)
Bactrim treated AIDS patients	24	
Adverse reactions	15	(63%)
Slow Acetylator Phenotype - Reactors	3/15	(20%)
Slow Acetylator Phenotype - Nonreactors	7/9	(78%)

We did detect a striking relationship between reactions to sulfonamides and reactions to other drugs (Table 4). All patients who had experienced allergic reactions to drugs before the diagnosis of AIDS or afterwards, reacted to Bactrim. No patient who tolerated Bactrim had a history of other drug allergy nor reacted to drugs used to treat infections occurring during AIDS. While these are major differences, much work must be done to characterize and explain this apparent insight.

TABLE IV: Relationship of Multiple Drug Hypersensitivity to Bactrim Reactions

Other Drug Reactions	Bactrim Reaction		Total
	No	Yes	
No	9	8	17
Yes	0	7	7
Total	**9**	**15**	**24**

DIAGNOSIS OF DRUG ALLERGY

In view of the diverse immunopathologic, toxic, and pharmacologic effects of the multitude of medications used in current medical practice, the tasks of identifying and characterizing allergic reactions to drugs are formidible. The average hospitalized adult patient receives 10 medications and the average outpatient receives 2 medications regularly (4), making candidates for causes of allergic reactions to drugs abundant. Fortunately, approaches to classifying reactions, identifying the causal agent, and monitoring the immunopathologic processes have been developed that are useful in the diagnosis of drug allergy.

Allergic reactions to drugs should be characterized according to the classic immunopathologic scheme of Gell and Coombs, or if not in conformity with that scheme, according to the predominant clinical manifestations (Table 5). Stratification of this kind permits rational selection of therapy, prognostication, and formulation of plans for future therapy of the underlying disease. In addition, careful characterization of a reaction is an important first step toward identification of the cause.

Identification of the cause of an allergic reaction may be straightforward, but often this is not the case. Six basic dimensions are used to analyze reactions: (1) characterization of the reaction, (2) classification of the reaction, (3) compilation of a complete list of possible causes, (4) consideration of the known propensities of the possible drugs to cause such a reaction, (5) proximity of the onset of therapy to the onset of the reaction, and (6) immunodiagnostic testing (104-114). The manifestations of the patient's allergic reaction should be determined in addition to all concurrent illnesses; the indications, dosages, onsets and durations

TABLE V: CLASSIFICATION OF ALLERGIC REACTIONS TO DRUGS ON THE BASIS OF THE PRINCIPAL CLINICAL MANIFESTATIONS

- Anaphylaxis
  - Hypotension; bronchial or laryngeal obstruction
- Destruction of Formed Elements of the Blood
  - Hemolytic Anemia
  - Thrombocytopenia
  - Granulocytopenia
- Serum Sickness
- Drug Fever
- Systemic Vasculitis
- Specific Organ Inflammation
  - Cutaneous Reactions
    - Urticaria/Angioedema
    - Vasculitis
    - Stevens-Johnson Syndrome/Erythema Multiforme/Toxic Epidermal Necrolysis
    - Exfoliative Dermatitis
    - Contact Sensitivity
    - Fixed Drug Eruption
    - Other
  - Hepatitis
  - Nephritis
  - Pneumonitis
  - Other Organs
- Drug Induced Autoimmune Disease
  - Lupus Erythematosis
  - Other Forms

of therapy for each medication; previous exposures to these or related drugs; the impact of discontinuation, rechallenge, or suppressive medications; and if available, relevant genetic factors such as acetylator phenotype. Each possible cause is considered from the perspectives of propensity to cause such a reaction and the timing of exposure. The proximity of onset of therapy is an important factor. In general, primary immune responses take several days to lead to a clinical reaction. Reactions can begin rapidly if sensitization has occurred during previous exposures and is persistent. In general, medications in use for long periods are less likely causes than recently introduced agents. Propylthiouracil is an exception, often causing reactions months after the onset of therapy.

In some instances, particularly immediate hypersensitivity reactions, immunodiagnostic tests are useful (115-150). Wheal-and-flare skin tests with insulin, chymopapain, and other protein drugs are sensitive tests for the presence of specific IgE (115-118). Similarly, immediate wheal and flare skin tests are sensitive tests for IgE to beta-lactam antibiotics (119-126). In vitro tests for specific IgE have been developed to beta-lactam, sulfonamide, trimethoprim, isoniazid, protein, and other drug determinants (127-147). Lymphocyte-transformation tests for T lymphocyte responses to drugs also have been developed (148-150). The interpretation of these tests in relation to clinical disease differs according to the reaction, the drug involved, and the sensitivity of the assay. In most instances assays for specific IgG, IgA, and IgM are not clinically useful. Many more patients express immune responses to drug determinants than express clinical disease (3,16,89). The presence of immune reactants that could mediate the form of clinical reaction being analyzed can be taken as support for a causal role for the drug tested, but cannot be equated with clinical allergy.

Recently, sensitive tests have been developed to detect some forms of ongoing immunopathologic reactions (Table 6). Blood levels of mast cell granule tryptase have been shown to be useful biochemical markers of anaphylaxis (151) and are helpful in the diagnosis of mastocytosis. Systematic study of tryptase levels in various forms and extents of immediate hypersensitivity reactions are needed to clarify the precise uses of this assay. Sensitive assays for complement anaphylatoxins (78), and other activation markers of classic and alternative pathway activation (75) have markedly improved monitoring of complement activation over the insensitive assays for remaining unactivated complement proteins. This area of clinical immunology should provide powerful new tools in analyzing the nature of and impact of interventions on allergic reactions to drugs.

Tests for IgE to drugs have been shown to be useful in identifying individuals at risk of anaphylaxis or milder immediate hypersensitivity reactions to therapeutic doses of beta-lactam drugs (119-126). The effectiveness and safety of this diagnostic testing have been unambiguously demonstrated. The procedure undoubtedly

would save many lives and avoid considerable morbidity if put into general use. Penicillin therapy of patients with histories of immediate hypersensitivity reactions to penicillin but currently negative skin tests is accompanied by a 1% to 3% chance of urticaria at some time during therapy (the same as those without a positive history). Anaphylaxis in a history-positive, skin test-negative treated patient appears to occur in less than 0.1%. Reactions among history-negative, skin test-negative patients are 10- to 100-fold less common.

TABLE VI: NEW TESTS FOR MONITORING HUMAN CLINICAL IMMUNOPATHOLOGIC REACTIONS*

Mast Cell Tryptase	Serum, lavage fluids
Prostaglandin D_2	Lavage fluids, Metabolites in urine
Anaphylatoxins C3a, C4a, C5a	Plasma, urine, cerebrospinal fluid, lavage fluids
C1:C1-Inhibitor Complexes	Plasma, potentially other fluids.
C5b-9 Complexes	Plasma, cerebrospinal fluid, tissue sections.

* Examples of promising methods likely to become generally available for clinical monitoring.

Skin testing has proved useful in the population of patients who have had allergic reactions to penicillin and who are regarded at risk for a reaction to renewed therapy. Many patients stop expressing IgE to beta-lactam drugs within months of a reaction (119-126). This is particularly likely in children and in patients treated with oral medication. Skin testing permits accurate identification of patients no longer sensitive, who can receive the drug of choice when a beta-lactam drug is indicated. A new course of therapy can resensitize, indicating skin testing again before a second course of therapy. Although occult exposure to penicillin in

foodstuffs has caused systemic reactions in rare circumstances (152-154), occult exposures to the antibiotics in milk, beef, pork, and other foodstuffs is not thought to cause primary sensitization (155-158). Occult exposures, particularly in milk, might contribute to sustained expression of IgE to penicillin seen in some patients.

The degree of cross-reactivity of determinants formed from penicillins and cephalosporins with IgE to the beta-lactam drugs has been a matter of considerable uncertainty (119, 127-135). Several groups have demonstrated frequent positive skin test reactions to first-generation cephalosporins in penicillin skin test-positive patients. Inhibition of radioallergosorbent test (RAST) binding of IgE to the penicilloyl group by first-generation cephalosporin determinants has been reported, but the concentrations required were several orders of magnitude higher than for comparable inhibition by penicillin determinants. As summarized in recent reviews (119,130), the degree of clinical cross-reactivity is much lower than the in vitro cross-reactivity. Recent RAST inhibition studies confirm that cephalosporin determinants often do not cross-react, but some sera cross-react avidly. The risks of administering a first-generation cephalosporin to a penicillin-allergic person are much lower than administering penicillin but are not negligible. Antibodies to the second- and third-generation cephalosporins usually are directed to the side chains rather than to the ring structures (119). Consideration of possible cross-reactions among the new beta-lactam drugs apparently should focus on the side chains (13) more than on the ring structures that determine the binding to penicillins (119).

MANAGEMENT OF ALLERGIC REACTIONS TO DRUGS

Acute reactions: Allergic reactions to drugs are managed according to three general principles: (1) identification of the active immunopathologic mechanisms; (2) identification of the offending agent and a decision about withdrawal or continuation; and (3) introduction of suppressive or remittive therapy (159). Assessment of patients and rational therapy demand accurate assessment of the processes involved and knowledge of the nuances of the agent involved (159-202). Reactions such as anaphylaxis, urticarial, and angioedema are treated according to conventional guidelines. Drug-induced immune cytopenias can be managed by withdrawal of the offending agent, reduction in dose (for beta-lactam antibiotics, to doses less than 6 grams a day), or in selected cases hapten inhibition (167-169). Drug-induced serum sickness can be suppressed by drug withdrawal, antihistamines, and corticosteroids. Plasmapheresis can be extremely useful in the management of patients with severe serum sickness which is sometimes encountered as a complication of the use of antivenins, antisera, and antilymphocyte globulin, or less often other drugs. Contact sensitivity reactions to drugs (most often seen in pharmacy and nursing personnel but occasionally seen in parents administering suspensions of medications to children) are managed according to conventional avoidance and symptomatic medication regimens. Reactions such as toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome, and the pseudolymphoma syndrome seen with phenytoins demand immediate drug withdrawal and supportive

care (161).

Withdrawal of the offending agent is usually but not always a central component of management. A decision to withdraw a drug that is inducing a patient's allergic reaction must weigh the nature and intensity of the reaction in progress, the probable course of treated and untreated reactions, and alternative medications available to treat the patient's disease process that led to the drug being used in the first place. For example, urticaria appearing during a course of beta-lactam antibiotic therapy often can be suppressed with antihistamines, alone or in combination with low dose corticosteroids, without further complication in patients for whom acceptable alternative antibiotics are not available (171-173). Anaphylaxis has not been reported to occur after the first hours of uninterrupted therapy with beta-lactam antibiotics and has not been observed during sustained therapy in the presence of urticaria (171-173). Anaphylactic reactions, however, can be induced by a dose administered 12 to 24 hours after discontinuation. The therapeutic and antiallergic alternatives should be considered carefully before a drug is discontinued, since reintroduction may present more difficulty than continuing the drug accompanied by suppressive therapy.

Accurate identification of the agent inducing a patient's reaction, is important. Plans to avoid future allergic reactions should be formulated as a final phase of the management of patients with an acute reaction.

Drug therapy in patients allergic to medications: Agents for therapy of drug allergic patients are selected according to three general principles: (1) selection of alternative drugs with therapeutic actions similar to the drug in question but with no immunologic cross-reactivity, (2) premedication to avoid or suppress a reaction, and (3) acute desensitization.

Alternative medications: Great care must be taken to avoid the use of an agent that can cause renewed expression of toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome, or other reactions for which no effective desensitization, premedication, or reversal procedures are available (86,111,161). Although single-dose challenges can cause fatal recurrences (86,112,161), immune reactions to drugs are dynamic and may remit. Safe reintroduction may be possible, but accurate assessment of a patient's vulnerability is not yet possible. Rarely, the failure to use a drug for fear of a reaction (e.g an anticonvulsant) poses more of a risk to the patient than does cautious reintroduction. This should be a carefully considered decision accompanied by detailed formal informed consent.

Fortunately, alternative drugs are available for most clinical situations. Many alternative antimicrobial agents are available for use in allergic patients. Several forms of insulin, antilymphocyte globulin, and other protein agents are available as alternatives for allergic subjects (159,160). Effective protocols for the evaluation and management of insulin allergic subjects are available (116,160). The general approach, discussed below, is to select an agent

immunologically distinct from the agent that caused a reaction and then introduce the drug under close supervision.

Local anesthetic agents (or preservatives in them) seldom cause allergic reactions, but a possible allergic mechanism often is suspected by patients and their dentists or physicians to explain what was in reality a pharmacologic action of a large amount of absorbed drug, vasovagal syncope, a hyperventilation syndrome, or an anxiety reaction. Patients with suspected local anesthetic allergy can be approached using standardized drug selection and drug challenge protocols (162-164). As summarized in Table 7, local anesthetics can be divided on an immunochemical basis into two groups: those that contain the para-aminophenyl substituent and those that do not. Para-aminophenyl derivatives are thought to be immunologically cross-reactive, primarily on the basis of apparent contact sensitivity cross-reactivity, whereas the other agents are thought not to cross-react with antibodies to para-aminophenyl drugs or with each other (164). An agent immunologically distinct from the agent thought to have caused a reaction is selected and then administered in an increasing dose challenge. Preservative-free local anesthetics are available for use in patients who are sensitive to parabens or other preservatives.

TABLE VII: CLASSIFICATION OF LOCAL ANESTHETICS BY THE PRESENCE OR ABSENCE OF THE p-AMINOPHENYL SUBSTITUENT*

p-Aminophenyl Group	
Present	**Absent**
Injectable Agents	
Procaine	Lidocaine
Tetracaine	Mepivacaine
	Dibucaine
	Bupivacaine
	Etidocaine
Ophthalmic agents	
Benoxinate	Proparacaine

(TABLE VII cont.)

Topical Agents

Benzocaine	Dimethisoquine
Butamben	Cyclomethicaine
	Dyclonine
	Pramoxine
	Cocaine

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* Examples of commonly used agents

Premedication: Premedication with antihistamines alone or in combination with corticosteroids has been proved effective in reducing the incidence and severity of immediate hypersensitivitylike reactions to radiocontrast media and some reactions to opiates and parenteral muscle relaxants (160,165,166). No general premedication regimens have proved effective against the life-endangering aspects of anaphylaxis induced by antigens, although hapten inhibition has been effective in selected cases (167-169). Anaphylaxis induced by anaphylatoxins or by other non-IgE mast cell stimuli may be more vulnerable to corticosteroid inhibition, and as noted above histamine may play a more dominant role in these reactions than in antigen ignited reactions. Hypotension induced by histamine is mediated by both H^1 and H^2 receptors, suggesting a role for combined H^1 and H^2 inhibition. Most premedication studies have not distinguished urticarial reactions from anaphylactic reactions (hypotension, laryngeal obstruction, bronchial obstruction, cardiac or respiratory arrest), thereby precluding an analysis of the value of the addition of H^2 blockade. PGD_2 contributes to the hypotension occuring during anaphylaxis in patients with mastocytosis, suggesting a possible role for cyclo-oxygenase inhibitors in general premedication regimens. The net effect of systemic cyclo-oxygenase inhibition on anaphylaxis is not yet known, however, and could be detrimental. Systematic studies of the value of beta-adrenergic agonists for premedication to avoid anaphylaxis have not been reported. Since patients with reactive airway disease are at increased risk of severe or fatal anaphylaxis, premedication with appropriate levels of theophylline, beta agonists, and other antiasthmatic agents should be considered in addition to other precautions. The introduction of new mast cell-suppressive drugs such as ketotifen, 5-lipoxygenase inhibitors, and inhibitors of receptors for leukotrienes and platelet-activating factor (PAF) could revolutionize approaches to premedication to avoid anaphylaxis.

Studies of patients with histories of immediate hypersensitivitylike reactions to radiocontrast materials have unambiguously shown that premedication (Table 8) can reduce the incidence of reactions from approximately 30% to 2% to 5% and the severity of the reactions that do occur is in most instances reduced (165,166). Newer, more isotonic radiocontrast agents have been

introduced that cause fewer reactions than the hyperosmolar agents (166). A combination of the newer agents and premedication should markedly reduce the risk of a recurrent reaction. Life-endangering reactions can occur despite these precautions, particularly in patients with cardiac disease (103). Since fatal and life-endangering reactions are rare, and since the increased cost of routinely using the newer agents is substantial, these precautions usually are reserved for patients who have experienced adverse reactions in the past. Routine use of these precautions in high-risk patients (103) who have not yet experienced an adverse reaction appears justified. The premedication regimen has few significant side effects and is simple to implement, this intervention should be considered for all subjects requiring radiographic contrast studies.

TABLE VIII: PROTOCOL FOR PREMEDICATION TO AVOID ANAPHYLAXIS IN PATIENTS RECEIVING INJECTIONS OF RADIOCONTRAST MEDIA

Time Before Procedure	Agent*	Dose**
13 Hours	Prednisone	50 mg
7 Hours	Prednisone	50 mg
1 Hour	Prednisone	50 mg
	Diphenhydramine	1 mg/kg

* Alternative corticosteroids or H1 antihistamines can be used by oral or parenteral routes.

** Dosages given are for adults.

Acute desensitization: Patients who express IgE antibodies to drugs may develop illnesses that cannot be treated effectively with alternative medications. Since fatal or near-fatal anaphylaxis may ensue from conventional therapy with the drugs in question, attempts have been made to develop protocols for acute desensitization. Beta-lactam antibiotics and insulin are the most frequent agents involved, but a wide range of antimicrobial agents, proteins, and other drugs have been introduced by these methods (170-202). The basic approach has been to administer gradually increasing doses of the drug over a period of hours to days, typically beginning with one ten-thousandth of a conventional dose.

Patients allergic to a beta-lactam antibiotic required for treatment pose a particularly difficult problem. Conventional doses of these highly reactive chemicals can cause acute reactions in approximately two thirds of challenged allergic patients, life-endangering anaphylaxis in 5% to 10%, and fatal anaphylaxis in

of these highly reactive chemicals can cause acute reactions in approximately two thirds of challenged allergic patients, life-endangering anaphylaxis in 5% to 10%, and fatal anaphylaxis in 0.2% to 0.5% (1-10). Acute oral desensitization of penicillin allergic patients was introduced by O'Donovan and Klorfajn in 1946, refined by Parker, and applied widely in recent studies (171-176). The rationale for oral desensitization is based upon the observations that (1) oral administration of penicillin is less likely to provoke a systemic allergic reaction than parenteral administration of the drug (170); (2) there have been just 9 reported cases of fatal anaphylaxis from oral beta-lactam drug therapy (171); (3) preformed polymers and conjugates of penicillin major and minor determinants to Penicillium proteins are not appreciably absorbed when administered orally (45-49); (4) blood levels gradually rise, favoring univalent haptenation and only gradual appearance of multivalent hapten-carrier conjugates; and (5) in 93 reported cases of oral desensitization, without masking premedication, no fatal or life-endangering reactions have occurred (171). Parenteral desensitization has been favored by some investigators, even when oral forms of the drug are available and feasible, because of the more certain control over drug administration (177-184). No properly controlled comparative trials have been reported, but published cases suggest a much higher rate of severe reactions during parenteral desensitization of skin test-positive patients (173).

Conventional full-strength penicillin skin tests can introduce as much as 150 ug or 250 units of penicillin (0.05 ml of 3.0 mg/ml). If the patient has tolerated high-dose skin testing with only a local reaction, the protocol outlined in Table 9 can be used. If skin tests are positive at lower concentrations of penicillin reagents, proportionately lower starting doses are used (171,172). Doubling doses are administered at 15-minute intervals until full therapeutic doses are achieved, typically within 4 hours.

Often a patient with clinical and immunologic evidence of IgE sensitivity to one beta-lactam drug requires therapy with a related but different beta-lactam drug (e.g., ticarcillin therapy in a patient who has had a clinical reaction to penicillin G). In view of the immunochemical data reviewed above indicating that IgE responses to beta-lactam drugs can be specific for the sensitizing drug and may not cross-react with determinants formed from other beta-lactam drugs, desensitization usually should be performed with the agent required for therapy. If the drug determinants formed interact with the IgE present, desensitization should occur. If no interaction occurs, no clinical reaction will occur.

TABLE IX: PROTOCOL FOR ORAL DESENSITIZATION OF BETA-LACTAM ANTIBIOTIC ALLERGIC PATIENTS*

Step	Beta-Lactam Drug (mg/mL)	Amount (mL)	Dose Given (mg)	Cumulative Dose (mg)
1	.5	0.1	.05	.05
2	.5	0.2	.10	.15
3	.5	0.4	.20	.35
4	.5	0.8	.40	.75
5	.5	1.6	.80	1.55
6	.5	3.2	1.60	3.15
7	.5	6.4	3.20	6.35
8	5.0	1.2	6.00	12.35
9	5.0	2.4	12.00	24.35
10	5.0	4.8	24.00	48.35
11	50.0	1.0	50.00	98.35
12	50.0	2.0	100.00	198.35
13	50.0	4.0	200.00	398.35
14	50.0	8.0	400.00	798.35
		Observe patient for 30 minutes		
		Administer 1 gm of same agent intravenously		

* Interval between doses 15 minutes

** Drug suspension diluted in 30 mL of water for ingestion

If the patient cannot tolerate oral medication, or the beta-lactam drug needed is not available in an oral form, parenteral desensitization can be conducted according to the general protocol in Table 10. Starting doses are influenced by the patient's skin test reactivity, as for oral desensitization. Even if skin tests are negative with the drug to be used for therapy, the absence of a systemic reaction to 150 ug in the skin is informative. Several methods for increasing the infused concentrations have been advocated, none of which have been subjected to systematic study. Three-fold increases in doses infused over 20 minutes approximate the antigen delivery by the oral route.

Complications of oral beta-lactam drug desensitization include mild cutaneous pruritus or pruritic rashes in one third of patients, and occasional penicillin-induced serum sickness, hemolytic anemia, and nephritis (171). A study of antibody responses following penicillin desensitization (160) indicated that desensitization may be followed by a marked penicillin-specific IgG antibody response, in keeping with the apparently increased incidence of IgG-mediatedcomplications of penicillin therapy. Severely ill and pregnant patients appear to tolerate oral desensitization with the same incidence of reactions as clinically stable and nonpregnant patients (171,172). Patients with cystic fibrosis appear to have a high incidence of drug allergy and may be particularly difficult to desensitize (175,177). Parenteral desensitization has been associated with more severe and rare fatal reactions (173), but the incidence of reactions is difficult to estimate from the small number of skin test-positive cases reported (171-184).

In virtually all reported cases full-dose parenteral therapy has been possible after acute desensitization. Comparison of the chances of increased morbidity and mortality conferred by not using a beta-lactam drug of choice for serious infections (for fear of an allergic reaction), to the chances of increased morbidity or mortality from an allergic reaction during or after proper desensitization, has shown that acute beta-lactam drug desensitization appears to be an acceptably safe and effective method for introducing optimal antibiotic therapy for severe infections (173).

Some desensitized patients have predictable future requirements for exposures to beta-lactam drugs. Selected patients with conditions such as cystic fibrosis, chronic neutropenia, or occupational exposure may benefit from sustained oral desensitization (171,175,181). Chronic twice a day oral penicillin therapy, to sustain a desensitized state between courses of high dose parenteral therapy, appears to be feasible, effective, and safe (171,175).

TABLE X: PROTOCOL FOR PARENTERAL DESENSITIZATION OF BETA-LACTAM ANTIBIOTIC ALLERGIC PATIENTS*

Step	Beta-Lactam Drug (mg/mL)	Amount** (mL)	Dose Given (mg)	Cumulative Dose (mg)
1	0.1	0.1	.01	.01
2	0.1	0.2	.02	.03
3	0.1	0.4	.04	.07
4	0.1	0.8	.08	.15
5	1.0	0.16	.16	.31
6	1.0	0.32	.32	.63
7	1.0	0.64	.64	1.27
8	10	0.12	1.20	2.47
9	10	0.24	2.40	4.87
10	10	0.48	4.80	10
11	100	0.10	10	20
12	100	0.20	20	40
13	100	0.40	40	80
14	100	0.80	80	160
15	1000	0.16	160	320
16	1000	0.32	320	640
17	1000	0.64	640	1,280
	Observe patient for 30 minutes Administer 1 gm of same agent intravenously			

*Interval between doses 15 minutes
**Doses administered subcutaneously (or intramuscularly, orintravenously)

The desensitized state achieved is dependent upon the continuous presence of the beta-lactam drug, with a return of skin test reactivity and clinical sensitivity in as little as 2 days (171). The persistence of cutaneous responsiveness to histamine and some IgE-mediated signals after desensitization clearly indicate that tachyphylaxis to mediators such as histamine or mediator depletion play no significant role in the clinical desensitization. Hapten-specific IgG might neutralize antigen before IgE binding and mast cell activation, but no systematic studies of this possibility have been reported. In many patients cutaneous wheal-and-flare responses to penicillin determinants become negative, while other antigen-IgE responses are unchanged, suggesting the acquisition of antigen-specific mast cell desensitization. According to this hypothesis, slow accumulation of univalent hapten-carrier conjugates and of multivalent conjugates allows slow IgE crosslinking with ultimate antigen specific desensitization (185). Alternatively, mast cell granules may contain enzymes that can dehaptenate penicillin substituted carriers. Gradual appearance of such enzymes in the microenvironment, as a consequence of subclinical mast cell granule release, might inhibit both penicillin skin tests and clinical reactions. The relative importance of these factors remains to be determined.

The greatest danger inherent in beta-lactam drug desensitization detected to date lies in the incomplete understanding of the nature and mechanisms of acute desensitization on the part of the patient, nurses, and physicians involved in the patient's care (171). The need for uninterrupted therapy after desensitization and the return of anaphylactic sensitivity after the drug is withdrawn must be clear to all concerned and carefully monitored.

Successful, and complicated, acute desensitization procedures for immediate hypersensitivity have been reported with numerous other drugs that appear to act as haptens including aminoglycosides (194), sulfonamides (186-193), allopurinol (195-196), and other agents (198-199).

When insulin-allergic patients have significant IgE-mediated sensitivity to all available forms of insulin, acute insulin desensitization can be considered (116,160,199). Several successful protocols have been described. The principles are similar to beta-lactam drug desensitization. Skin tests usually are used to guide the selection of starting doses, often 0.001 unit administered subcutaneously. Doses can be doubled every 20 to 30 minutes until therapeutic levels are achieved. Alternatively, desensitization can be conducted over several days. Conventional doses of insulin at conventional intervals usually can be instituted at the completion of the procedure.

Although insulin can cause anaphylaxis, fatal reactions are extremely uncommon and mild allergic complications of desensitization reported have been restricted to the skin. If generalized urticaria appears during desensitization, the drug is stopped and the urticaria

allowed to subside. Desensitization is then reinstituted with a longer interval between doses. As many as 15% of patients do not respond to desensitization. Antihistamines alone or in combination with corticosteroids may be needed to suppress the allergic reactions to insulin. Fortunately, most patients stop expressing IgE to insulin within a matter of weeks after the onset of insulin allergy. Acute desensitization is complicated by some degree of transient IgG-mediated insulin resistance in approximately one third of cases. In keeping with the IgG responses after desensitization with penicillin, insulin specific IgG levels often increase substantially after desensitization, in parallel with the observed insulin resistance. In most instances clinical insulin allergy remains suppressed without recurrences, unless the insulin therapy is interrupted or a new species of insulin is introduced (116,160).

Skin test responses to insulin usually become negative after desensitization with preservation of responses to histamine, opiates, and concurrent antigen induced wheal-and-flare responses. Although this appears to indicate antigen-specific mast cell desensitization, additional studies are needed to determine the incidence and nature of the changes induced by insulin desensitization.

In addition to methods for acute desensitization with haptens and complete antigens, methods have been developed for acute desensitization of aspirin sensitive patients (201-202). Although aspirin and other nonsteroidal anti-inflammatory drugs can induce acute asthma, rhinitis, urticaria, and even full anaphylaxis in susceptible patients, suggesting mast cell activation, data demonstrating mast cell secretion are meager. Increased levels of mast cell tryptase were detected in one patient with aspirin-induced bronchospasm and urticaria (151), but the generality of this response in the more common patients with isolated respiratory tract reactions is not yet known. Acute desensitization followed by sustained therapy can be used to permit nonsteroidal anti-inflammatory drug therapy in sensitive patients and may have a beneficial effect on upper respiratory tract inflammation (202).

In contrast to acute antigen desensitization, this procedure routinely induces a pronounced acute asthmatic reaction. The desensitized state appears after the acute reaction subsides. Gradually increasing doses of aspirin or another nonsteroidal anti-inflammatory drug are administered at 3 hour intervals until a pulmonary reaction takes place. After the reaction subsides, the dose is repeated. A state of unresponsiveness is produced that, similar to antigen-induced desensitization, continues as long as the drug is continued and resolves within days after cessation of nonsteroidal anti-inflammatory drug therapy. The nature of the acute reactions and the mechanisms of desensitization are not well understood. Nevertheless, aspirin desensitization usually is successful and permits the use of an important group of medications in sensitive patients.

SUMMARY

The high incidence, morbidity, mortality, disruption of optimal care, and cost of allergic drug reactions make this set of disorders one of the most important aspects of current clinical allergy and immunology. Studies of allergic reactions to drugs have revealed many important aspects of human immunology and immunopathologic processes. Our expanded knowledge of the molecular basis of allergic reactions to drugs, coupled with recent clinical studies, has markedly improved our ability to avoid, diagnose, or manage these reactions.

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