INTERNAL MEDICINE GRAND ROUNDS

March 7, 1991

DRUG ALLERGY - 1991

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1901 - An inexplicable, unpredictable reaction to a drug.

1936 - An immunologically-mediated reaction to a drug.

1991 - A disease resulting from a genetic or acquired propensity to make immune responses to antigenic drugs.

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In 1895, one year after the introduction of serotherapy for bacterial infections, a two year old asthmatic boy was given an equine antiserum for prophylaxis against diphtheria. Anaphylaxis occurred and the child was dead within ten minutes (1).

I. INTRODUCTION

Immunopathologic reactions to drugs constitute a very important and specific category of allergic disease (2). Six to 26% of adults in this country have a history of an allergic reaction to a drug, usually an antimicrobial drug. One to 13% of hospitalized patients experience an allergic reaction to a drug, adding substantial morbidity and rare mortality to individuals already sufficiently ill to require hospitalization. The majority of these allergic reactions are in response to therapy with antimicrobial drugs. The economic impact of the increased care, prolonged hospitalizations, and fatal reactions has been estimated to exceed $1.5 billion annually in this country alone. While considerable progress has been made in knowledge of the immunochemistry of drug allergy, diagnosis, and acute desensitization, hypersensitivity reactions to drugs remain common, difficult to predict, and often difficult to manage (reviewed in reference 2).

Two complementary schemes of classification of allergic reactions to drugs are widely used (2). The immunopathologic classification according to Gell and Coombs:

Type I	Immediate Hypersensitivity - IgE Anaphylaxis, urticaria, angioedema
Type II	Antibody mediated cytotoxicity - IgM, IgG Immune cytopenias, tissue inflammation
Type III	Immune complex disease - IgG, IgM Serum sickness, vasculitis
Type IV	Lymphocyte mediated inflammation Organ and tissue inflammation

A descriptive clinical classification also is required for reactions attributable to unknown or multiple immune effector systems.

Systemic reactions

- Anaphylaxis
- Drug fever
- Drug induced vasculitis
- Drug induced lupus erythematosus
- Serum sickness
- Pseudolymphoma reactions

Specific tissue inflammation or destruction

- Immune cytopenias
- Cutaneous reactions
- Urticaria and angioedema
- Toxic epidermal necrolysis, Stevens-Johnson, erythema multiforme
- Contact sensitivity
- Fixed drug eruption
- Hepatitis
- Nephritis
- Pneumonitis
- Other

Historical Perspective. The case noted at the beginning of this protocol was one of many instances of anaphylaxis that had been observed in humans and in experimental animals before 1902 (1,3). Even though this was the child of Professor Paul Langerhans, the mechanism of his death was not understood and, despite intense consideration, his death did not generate any new studies or insight into the nature of anaphylaxis.

The development of a model of experimental anaphylaxis and the recognition of the existence of immunopathology by Paul Portier and Charles Richet in 1902 (3), however, led to a rapid expansion in knowledge of anaphylaxis and hypersensitivity (Table 1). A Nobel Prize was awarded to Richet in 1913 for these studies.

By 1907 the ability of serum from a sensitized animal to passively transfer specific anaphylactic sensitivity to a naive animal had been discovered (4,5). Prausnitz and Kustner demonstrated local passive transfer of human IgE mediated sensitivity by injecting serum from a sensitized donor into the skin of an unsensitized recipient in

1921 (6). Using the P-K method for assessment of specific reactivity after physicochemical treatments of serum containing IgE to ragweed antigens, the Ishizakas isolated and characterized human IgE in 1967 (7). This accomplishment, coupled with the discovery of IgE myelomas (8), led to many new insights including the development of assays for specific IgE, the isolation and characterization of the IgE Fc receptors expressed on mast cells and other cell types, and identification and study of the heavy chain epsilon gene.

TABLE 1

Critical Events in Leading to Our Current Understanding of Anaphylaxis

IgE and Anaphylaxis	
1902	Discovery of experimental anaphylaxis (3)
1907	Passive transfer of experimental anaphylaxis (4,5)
1921	Passive transfer of specific human IgE to human skin (6)
1967	Isolation and characterization of human IgE (7)
Antigens and Anaphylaxis	
1902	Discovery of protein antigen-induced anaphylaxis (3)
1924	Hapten-induced anaphylaxis (9)
1936	Experimental anaphylaxis induced and elicited by a free drug (arsphenamine) (11)
1960	Demonstration of requirement for two or more IgE binding sites on a single molecule to initiate human IgE mediated inflammation (13)
Mast Cells and Anaphylaxis	
1902	Discovery of in vivo anaphylaxis (3)
1910	Discovery of in vitro tissue responses to antigen (15)
1913	Recognition of similarity of in vitro anaphylaxis to effects of histamine (16)
1953	Recognition of association of tissue histamine with mast cells (17)
1959	Development of isolated mast cell experimental systems (18)
1987	Demonstration of elevated mast cell tryptase levels during human anaphylaxis (19)

The discovery of protein antigen-induced anaphylaxis (3) also led to detailed studies of the basis for the specificity of the reactions. Landsteiner introduced the concept of haptenation, covalent attachment of a low molecular weight molecule to a larger carrier molecule, and studied precipitin and anaphylactic reactions induced by haptens (9-12). Systematic studies beginning in 1924 demonstrated that anaphylaxis could be mediated by hapten specific antibodies: haptens could be presented on any carrier (9). Indeed, anaphylaxis could be elicited without a carrier protein, if the hapten was presented in a multivalent form (10). Landsteiner showed that univalent hapten did not cause anaphylaxis (9). Univalent hapten could prevent anaphylaxis to multivalent hapten carrier conjugates, providing more evidence in support of the concept that antibody binding to more than one site on an antigen was an essential aspect of the induction of anaphylaxis (9). Landsteiner was the first to develop an in vivo experimental model of anaphylaxis induced and elicited by the administration of a low molecular weight drug, arsphenamine (11). Eisen and coworkers demonstrated the ability of carriers substituted with two or more hapten groups to activate human mast cells through IgE, and the ability of univalent haptens to inhibit (13). These principles led to a clearer understanding of how IgE activates mast cells, and the development of skin tests to detect IgE to penicillin (14) and several other drug derived haptens.

Evidence that mast cells play a critical role in anaphylaxis also can be traced directly from the same initial experiments of Portier and Richet (3). In 1910 Schultz recognized the ability of antigen to cause responses in vitro in smooth muscle preparations from anaphylactically sensitized animals (15). Dale recognized the close similarity of these responses to antigen to responses by the same tissues to the addition of histamine (16). These observations and hypotheses were presented in 1913. Riley and West demonstrated that tissue histamine is located predominantly in mast cells in 1953 and generated the hypothesis that mast cells were of central importance in anaphylaxis (17). Studies of the role of mast cells and their mediators in anaphylaxis began in earnest when experimental systems using isolated mast cells were introduced in 1958 by Uvnas and coworkers (18). These studies led to confirmation of the presence of histamine in mast cells, and the release of histamine from sensitized cells by antigen. The first unambiguous biochemical data linking mast cells to human anaphylaxis, however, arose in 1987 when Schwartz and coworkers detected increased levels of mast cell tryptase in the serum of patients experiencing anaphylaxis (19).

Studies of mediators released from antigen stimulated tissues and from mast cells have strengthened the evidence that mediators of anaphylaxis are released from mast cells (20). Mediators released from mast cells that are capable of causing tissue responses seen in anaphylaxis include histamine, sulfidopeptide leukotrienes, prostaglandin D_2, and platelet activating factor. Activation of mast cells also can lead to the release of preformed tumor necrosis factor (TNF) and the activation and expression of genes for TNF and IL-6 (21). TNF also can mediate many of the vascular and cardiac disorders seen in anaphylaxis, with IL-6 in some manner playing a

permissive role in the TNF actions (22-24). In addition to antigen-IgE mechanisms, mast cells can be activated by complement anaphylatoxins, diverse chemicals and drugs, and mast cell activating cytokines (2,20).

Taking these classical lines of evidence as a whole, there is considerable support for the concept that the release of mediators from mast cells is the central event in anaphylaxis. In experimental IgE-mediated anaphylaxis a multisystem reaction results from a sudden, massive release of mast cell mediators. In clinical anaphylaxis, the acute, life-endangering reaction is associated with mast cell mediator release.

How well does this mast cell theory account for the clinical phenomena of anaphylaxis and the responses to therapy?

II. DRUG-INDUCED ANAPHYLAXIS.

Anaphylaxis is an acute, severe, systemic reaction to antigens or other stimuli that is widely thought to be mediated by the sudden release of overwhelming amounts of mast cell mediators (2). The drugs known to cause anaphylaxis can be stratified according to the scheme outlined in Table 2 (2). In addition to antigen-IgE activation, anaphylaxis can be elicited by agents that directly activate mast cells such as opiates, vancomycin, and polymyxin B. Anaphylatoxins can cause anaphylaxis after generation by immunologic reactions to blood products or direct activation by aggregated antibodies in heterologous antiserum preparations. A syndrome resembling anaphylaxis also can occur in rare individuals during treatment with some recombinant immunoregulatory molecules such as tumor necrosis factor (TNF). Clearly clinical anaphylaxis can be initiated by several mechanisms independent of IgE.

The symptoms and signs of anaphylaxis (Table 3) are typical of IgE-mediated allergic reactions (2). None is pathognemonic of anaphylaxis. A metallic taste in the mouth is noted when the plasma histamine exceeds 4 ng/ml and is highly suggestive of anaphylaxis if characteristic acute respiratory or cardiovascular manifestations also are present.

Biphasic or protracted anaphylaxis occurs in approximately half of patients with life-endangering reactions (25). Initial response to therapy can be followed by asymptomatic intervals of up to 8 hours, with recurrence of anaphylaxis in the same organ systems involved in the early response. In some severe reactions conventional therapy is unable to fully reverse the respiratory or cardiovascular dysfunction for a period of hours to days, rarely for more than a week. In some instances anaphylaxis is rapidly fatal, and in others progression to a fatal outcome is more gradual over hours to days.

Table 2

CLASSIFICATION OF CAUSES OF DRUG-INDUCED ANAPHYLAXIS

IgE-Mediated Anaphylaxis
Haptens - Low molecular weight drugs
Complete antigens - Proteins, polysaccharides

Direct Activation of Mast Cells
Opiates
Vancomycin

Anaphylaxis Mediated by Anaphylatoxins
Transfusion reactions
Reactions to IgA

Anaphylaxis of Unknown Mechanisms

IgE and Anaphylaxis. The relationship between the presence of IgE to penicillin and risk of anaphylaxis has been determined in prospective trials (2). A patient with no IgE to penicillin has virtually no risk of anaphylaxis to penicillin. The presence of IgE indicates a risk of an acute reaction in 43%-67% of patient exposed to the antigen. The IgE is not sufficient, however, to assure a clinical reaction to an antigen. These and related data strongly indicate that IgE can mediate anaphylaxis in humans (20,26,27).

Mast Cells and Anaphylaxis. The clinical manifestations of anaphylaxis include reactions in diverse organs with manifestations typical of IgE-mediated allergic diseases that are closely linked to mast cell activation. H_1 antihistamines is associated with relief from some of the manifestations of anaphylaxis, providing additional evidence consistent with the notion that mast cells are contributing to or mediating the reactions.

The strongest evidence of a role for mast cells in anaphylaxis comes from assessments of serum tryptase during anaphylaxis (19,28). Anaphylaxis stimulated by penicillin, insect venom, exercise, food, heteroantiserum, and nonsteroidal anti-inflammatory drugs has been associated with marked increases in serum tryptase. This molecule is expressed in mast cells, and at very low levels in basophils. Serum levels reflect mast cell tryptase release since the amount that could arise from basophils is so low it would not be detected in this assay. Serum levels peak 1 to 2 hours after the onset of anaphylaxis and then decline with a half-clearance value of approximately 2 hours (28).

TABLE 3 Clinical Manifestations of Anaphylaxis

System	Manifestation
Skin	Generalized, perineal, or vaginal pruritus; angioedema; urticaria and other pruritic rashes
Eye	Pruritus, conjunctival suffusion, lacrimation
Nose	Pruritus, congestion, sneezing, rhinorrhea
Mouth	Metallic taste
Upper airway	Sensation of narrowing airway, hoarseness, stridor, oropharyngeal or laryngeal edema, complete obstruction
Lower airway	Dyspnea, tachypnea, wheezing, use of accessory muscles of respiration, cyanosis, respiratory arrest
Cardiovascular	Tachycardia, hypotension, ventricular and supraventricular rhythm disturbances, cardiac arrest
Gastrointestinal	Nausea, vomiting, cramping abdominal pain, diarrhea, bloody diarrhea
Neurologic	Fear of impending death, weakness, dizziness, syncope, seizure

There are, however, instances of apparent antigen induced or idiopathic anaphylaxis that may involve cells other than the mast cell. Mast cell deficient mice do not display evidence of anaphylaxis when stimulated through IgE (29). But these animals do express a reaction resembling anaphylaxis when sensitized animals are challenged with antigen. While much remains to be done to characterize the nature of

these reactions, the data raise the possibility that antigen can cause acute reactions in the virtual absence of mast cells.

The phenomena of delayed onset, biphasic and protracted anaphylaxis raise important new considerations. Antigen-induced mast cell secretion of histamine containing granules and of lipid mediators ceases within less than an hour in all experimental systems studied to date. The nature of the delayed onset, recurrent and sustained reactions is not known, but deserves careful study. The release of TNF, IL-6, or other cytokines after activation of mast cells genes by antigen-IgE signals (21) could account for these reactions (22-24) in a manner distinctly different from conventional granule and lipid mediator release. The roles of these mediators in the vascular and other responses in anaphylaxis have not been studied, leaving the roles of cytokines hypothetical.

The antigen-induced "anaphylaxis" in mast cell deficient mice, delayed onset, biphasic and protracted anaphylaxis present challenges to the concept that anaphylaxis is entirely the result of the release of mediators from mast cells. Since no other cell type has been shown to account for these apparent discrepancies, and no evidence for or against the other possibilities noted has been presented, these issues are currently unresolved.

Roles of Specific Mediators in Anaphylaxis. The pathophysiologic changes that result in clinical anaphylaxis are primarily the result of the effects of mediators on blood vessels, cardiac muscle, and airway smooth muscle. Vascular caliber is increased by histamine acting on both H_1 and H_2 receptors, PGD_2, PAF, and leukotrienes (20,30). Histamine, and to a lesser degree the other mediators also increase the permeability of postcapillary venules. These same mediators also are thought to cause the pulmonary responses seen in anaphylaxis (20).

Table 4

CARDIAC ANAPHYLAXIS

Tachycardia	Histamine H_2, TNF
Bradycardia	Histamine H_1
V. rhythm disorders	Histamine
Negative inotropism	H_1, LT, PAF, TNF
Positive inotropism	H_2, PGD_2
Coronary constriction	PGD_2, TXA_2, PAF

The multiple acute actions of mediators of anaphylaxis on the heart (20,30-37) are summarized in Table 4. The usual alterations in cardiac function are decreased force of contraction, decreased coronary artery caliber, sinus tachycardia, and an increased susceptibility to ventricular rhythm disturbances. These responses are the result of the combined actions of several mediators.

Since the generation of these mediators in models studied to date is limited to a short time after antigen stimulation, the basis for recurrent or prolonged cardiovascular alterations is not clear. As noted above, several explanations are possible, but none is proven.

Of particular interest in this regard is the potential contribution of TNF to the sustained cardiovascular aspects of anaphylaxis (22,23,38,39). TNF can cause tachycardia, hypotension, and negative inotropic effects in humans. The ability of mast cells to synthesize and release TNF after antigen activation (21) increases interest in this hypothesis. The precise mechanisms of action of TNF are not clear, but the cardiovascular actions of TNF appear to require secondary actions by PAF (38), prostacyclin (39), IL-6 (24), and nitric oxide (40,41).

Diagnosis of Anaphylaxis. Currently the diagnosis of anaphylaxis is primarily a clinical diagnosis. Hypotension, upper airway obstruction, or lower airway dysfunction must be present (2). The presence of the distinctive symptoms and signs of anaphylaxis (Table 3) facilitates discrimination of anaphylaxis from other causes of these vital organ failures. Recent exposure to stimuli known to cause anaphylaxis, particularly if antigen specific IgE is demonstrated to be present, assist diagnosis. Serum tryptase is a valuable biochemical marker of mast cell mediator release and can confirm the diagnosis of anaphylaxis (19,28, Figure 1).

Principles of Therapy Based on the Mast Cell Theory. The management of anaphylaxis currently is directed toward the reversal of the effects of mast cell mediators and the arrest of ongoing mediator release (2). Indeed, the nearly complete absence of controlled data bearing on pharmacologic management of anaphylaxis in humans mandates reliance on this theoretical view coupled with observational data. As summarized in Table 5, and presented in detail elsewhere (2,20), management can be separated into immediate management, monitoring for biphasic reactions, and then avoidance of new episodes of anaphylaxis.

Epinephrine is the initial drug of choice. This agent can reverse many of the actions of the diverse mediators of anaphylaxis and can prevent mediator release from mast cells (20). In many instances epinephrine is sufficient to induce complete remission of anaphylaxis.

PLASMA TRYPTASE AND HISTAMINE DURING ANAPHYLAXIS

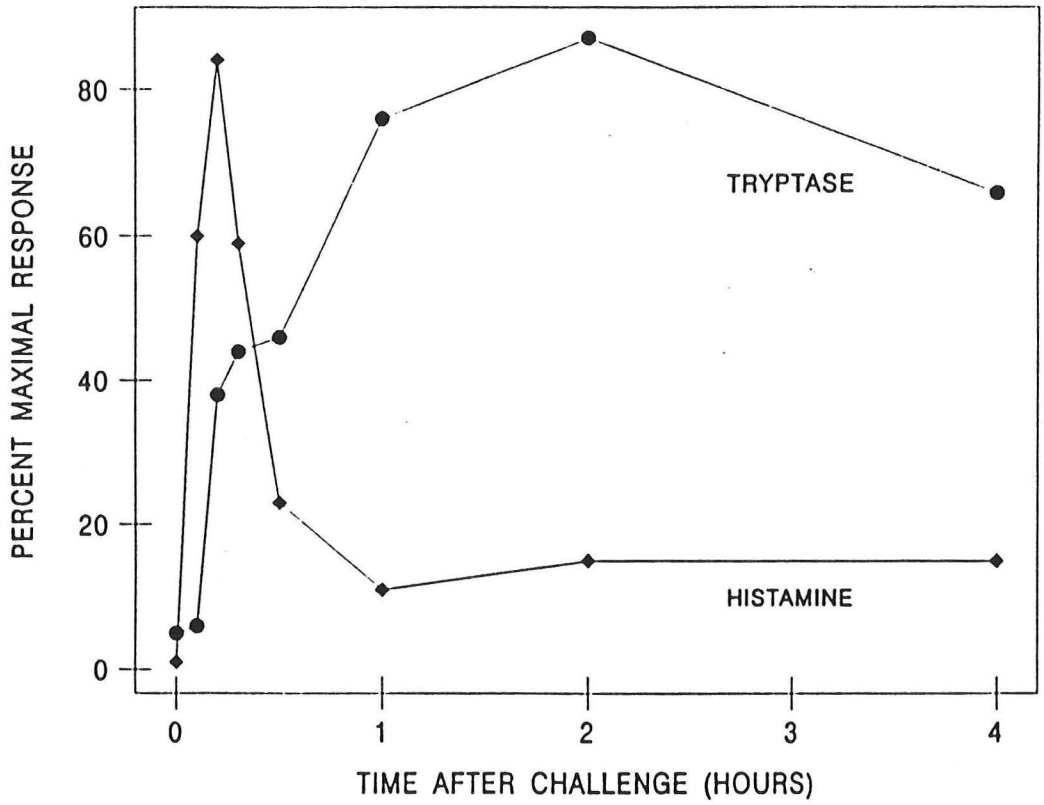


Figure 1. Prepared from data in reference 28.

The relatively high incidence of protracted or refractory anaphylaxis, however, and our inability to predict accurately which patients will not respond to initial therapy suggest that therapy and planning should be very aggressive from the time of diagnosis. Of particular concern is the organization of intraaortic balloon pump assistance or the use of military antishock trousers (MAST pants) in severely hypotensive patients, since institution of these measures may take a substantial period of time to accomplish for logistical reasons.

The relatively high incidence of protracted or refractory anaphylaxis, and occasional death, also indicate that more effective pharmacologic therapy for severe anaphylaxis is required. As noted above, TNF, IL-6, prostacyclin, PAF, TXA_2, and nitric

TABLE 5: MANAGEMENT OF ANAPHYLAXIS

- General therapeutic measures
  - Clinical assessment
  - Epinephrine (subcutaneously or by infusion)

- Specific interventions
  - Hypotension
    - Peripheral vascular defects
      - Trendelenburg position
      - Intravenous administration of isotonic sodium chloride
      - Norepinephrine or other vasopressor infusion
      - H_1 and H_2 blocking drugs
    - Cardiac dysfunction
      - Conventional therapy of dysrhythmias
      - Isoproterenol infusion
      - H_1 and H_2 blocking drugs
      - Intra-aortic balloon pump
  - Airway obstruction
    - Upper airway obstruction
      - Supplemental inspired oxygen
      - Extension of neck
      - Oropharyngeal airway
      - Endotracheal intubation
      - Cricothyrotomy
    - Lower airway obstruction
      - Supplemental inspired oxygen
      - Intravenous administration of theophylline
      - Aerosol bronchodilator therapy
      - Endotracheal intubation
      - Conventional treatment for status asthmaticus
      - Assisted ventilation

  - Biphasic anaphylaxis
    - Monitor for at least 12 hours after onset of anaphylaxis
    - Systemic corticosteroid therapy after acute reaction has been treated and again 6 hours later
    - H_1 and H_2 blocking drugs initially and again 6 hours later
    - Treated according to guidelines for acute anaphylaxis

  - Plan avoidance of recurrence of anaphylaxis

oxide may play critical roles in anaphylaxis that have not yet been fully characterized. The array of emerging agents that neutralize, compete for receptors, or prevent synthesis of these secondary mediators (24,40,41) could have very powerful beneficial effects on anaphylaxis, just as they do for septic shock (22,23,38,39).

Prevention of Anaphylaxis. Avoidance of anaphylaxis or prevention of recurrences is dependent upon the same set of concepts of causes and mechanisms that guide therapy (2,20). Identification of the stimulus for anaphylaxis (Table II) permits rational avoidance measures.

Premedication regimens are not effective for antigen induced anaphylaxis. Agents that more powerfully inhibit mast cell mediator release would be very useful. Agents that block the roles of TNF, IL-6, prostacyclin, PAF, TXA_2, and nitric oxide also may be very useful additions (22-24,38-41).

Acute antigen specific desensitization of patients expressing IgE to an antigen, first reported in 1908 (42), has been used effectively for a wide range of haptens and complete antigens (26). Hapten inhibition of IgE and other antibody mediated reactions has been proven effective in humans (13,43), but this method is not in general use. The recognition of the major N4-sulfonamidoyl determinant of sulfonamides (26) may permit the development of effective hapten inhibitors for severe reactions to sulfonamides.

Summary. Several lines of evidence indicate that mast cells play a central role in human anaphylaxis. Mast cells can be activated immunologically, directly, or indirectly by the diverse stimuli recognized to cause anaphylaxis. Mediators released from activated mast cells can cause tissue reactions that reproduce most aspects of clinical anaphylaxis. Pharmacologic suppression or desensitization of mast cells, and pharmacologic inhibition of mediator formation or actions diminish or suppress anaphylaxis. These observations form the basis for the theory that anaphylaxis is a mast cell mediated disorder, a theory that guides current approaches to the diagnosis, management, and avoidance of anaphylaxis.

Important apparent conflicts between the mast cell theory and specific clinical and experimental observations remain to be clarified. The roles of mast cells in delayed onset, biphasic, and protracted anaphylaxis must be investigated. The roles of TNF, IL-6, prostacyclin, PAF, TXA_2, and nitric oxide in anaphylaxis must be defined.

New areas of investigation also should provide much clearer definition of the mechanisms of anaphylaxis. Mast cell release of preformed TNF and the numerous cytokine genes that are expressed in activated mast cells raise critical questions about the roles of cytokines in anaphylaxis. The specific relevant targets for the mediators of anaphylaxis are incompletely understood and little is known about the secondary

mediators released from the primary target cells.

Systematic studies of anaphylaxis, the first form of immunopathology recognized, led to the discoveries of IgE and IgE receptors, hapten induced reactions, the immunologic relevance of mast cells, the mediators of immediate hypersensitivity, and cytokine production by mast cells. Anaphylaxis continues to act as a catalyst for studies of inflammatory cells and mediators. The mast cell theory of anaphylaxis provides a rational framework for understanding the diverse forces set in motion during anaphylaxis. The theory appears to be a valid basis for diagnosis, therapy, and avoidance of most forms of anaphylaxis as well as a valid basis for designing new studies.

Anaphylaxis is an increasingly well understood example of an immunopathologic reaction to drugs. This clinical phenomenon occurs only in a small fraction of patients, raising obvious questions about what differences in drug metabolism, propensity to make a specific immune response, and propensity to express a clinical reaction account for the patients who do react.

III. IMMUNOLOGY OF DRUG ALLERGY

Drugs as Antigens. Protein drugs such as insulin or heteroantisera can be recognized as conventional antigens. Low molecular weight agents such as antimicrobial drugs (AMD) usually are not immunologically detectable or relevant until they have become covalently attached to a macromolecule. This process of "haptenation" creates a new epitope on normal structures which can elicit lymphocyte and antibody responses. Some agents such as the betalactam antibiotics are intrinsically reactive with proteins and directly haptenate carrier molecules. Most non-betalactam antimicrobial drugs, however, are not chemically reactive. Haptens are formed from these agents as a consequence of metabolism, by the cytochrome P450 system or some other enzyme system, to reactive intermediates (2).

Studies of beta-lactam drugs indicate that as many as 5% of the administered molecules become covalently attached to human proteins and cells within an hour of administration. Proteins bearing cytochrome P450 derived haptens routinely appear in the peripheral blood of patients treated with inert precursor drugs. Interestingly, immune responses and immunopathologic reactions to these drugs does not seem to depend upon unusual propensity to form haptenated carriers. Haptens appear to be presented to all treated patients. While the drug, dose, route, and duration of therapy do influence outcome (2), other important factors appear to dominate the propensity to express an immunopathologic reaction.

Antimicrobial Drugs and the Immunologic Context During Infections. Several very important factors that influence immune responses to antimicrobial drugs must be considered (Table 6). Antimicrobial drugs usually are administered to patients who harbor bacteria that have produced marked tissue damage and vigorous, ongoing host responses. By the time therapy is introduced, bacterial endotoxins usually have cause a variety of pronounced changes in the immune system and related host defense systems (reviewed in 44,45). Newly formed IL-1, TNF, and IL-6 organize acute phase reactions and help regulate immunologically relevant cells and regulatory circuits. Diverse cytokines are being released from macrophages, lymphocytes, and other cells in significant amounts. Effector systems are nonspecifically enhanced. The specific immune system is actively detecting microbial antigens, expanding reactive clones of T and B lymphocytes, and expressing immune responses.

Table 6

Immunoregulatory Effects of Microbial Products

Endotoxin induced IL-1, TNF, and IL-6 (44,45)
Lysis reactions (44)
Superantigens (46)
Supercarriers (49)
Immunoregulatory proteins
C4 binding protein (47)
IL-10 activity (48)

Soon after the administration of antimicrobial drugs, a lysis reaction may occur (reviewed in 44). The sudden release of endotoxins from dying bacteria causes an additional surge of cytokine release. This can result in a marked increase in inflammation and new changes in the immunoregulatory environment (44). Striking increases in TNF and IL-1 can occur with subsequent exacerbation of inflammatory cell influx and activation.

Additional immunologically relevant changes in the regulatory environment may be occurring. Some organisms release toxins, or superantigens, that can nonspecifically stimulate the proliferation of lymphocytes of many specificities (46). Recent evidence indicates that microorganisms with human tropism may secrete molecules with immunorgeulatory properties. A C4 binding protein that suppresses

classical complement pathway effector function is made by vaccinia virus (47). Epstein-Barr virus encodes a protein with IL-10 activities (48). In addition, some microbial antigens are supercarriers for haptens (49), greatly enhancing immune system detection of the hapten. Clearly, microbial products can induce powerful positive and negative effects on the ability of the immune system to recognize and respond to drug determinants.

Haptenating antimicrobial drugs must be introduced into this raging immunologic context.

Systemic Counter-Regulation of Local Immunologic Activation Signals. Considering the activated state of the immune system and the proclivity of antimicrobial drugs to haptenate proteins, immune responses to antimicrobial drugs are not surprising. Indeed, what is surprising at first approximation, and a critical consideration, is that despite presentation of antimicrobial drug haptens in this context, most patients do not express immunopathological responses.

The forces that favor an immune response to an antigen irrelevant to the assault on the bacterial pathogen appear to be successfully opposed by systemic counter-regulatory forces in most patients (44,50-52). Presumably these same forces suppress irrelevant reactions to self, foods, and other antigens during infections. Clearly the immune system usually is capable of intense activation, specific responses, and vigorous effector function without indiscriminant responses to irrelevant, concurrently present antigens. Defects in these poorly understood systems to control systemic effects of signals generated at sites of infection (52) could present major problems for a patient, and could play important roles in the expression of drug allergy.

Immunochemistry of Haptenation. The low molecular weight antimicrobial drugs usually are not immunologically detectable or relevant until they have become covalently attached to a macromolecule. This process of "haptenation" creates a new epitope on normal structures which can elicit lymphocyte and antibody responses. Some agents such as the beta-lactam antibiotics are intrinsically reactive with proteins and directly haptenate carrier molecules. Most non-betalactam antimicrobial drugs, however, are not chemically reactive. Haptens are formed from these agents as a consequence of metabolism, by the cytochrome P450 system or some other enzyme system, to reactive intermediates.

Soluble univalent substituted materials can contribute to the expression of an immune response, but can not elicit an effector or clinical allergic reaction. In fact univalent materials inhibit mast cell activation, immune complex formation, and other effector responses (43).

Recent studies of the haptenation of proteins and cells by have provided evidence that differences in haptenation are unlikely to account for differences in expression of immune responses. Studies of penicillin G and of cefaclor indicate that serum proteins and cell surfaces become heavily haptenated. At the concentrations of beta-lactam antibiotics achieved in blood during oral therapy, mast cell and presumably other cell surfaces become densely haptenated. Extensive haptenation of serum proteins also occurs, although predominantly in a univalent manner. Differences among patients were noted, but all haptenated at high rates. Since this process involves many cells and soluble proteins with substantial amounts of substitution, the likelihood that differences in haptenation account for qualitative differences in making an immune response to beta-lactam antibiotics is very low.

Differences in the metabolism of sulfonamides and other drugs that must be metabolized to reactive forms to haptenate are well known (53). These genetic polymorphisms may influence the expression of allergic reactions in several ways, but the relative importance of these differences remains to be defined.

Studies of betalactam drugs indicate that as many as 5% of the administered molecules become covalently attached to human proteins and cells within an hour of administration. Proteins bearing cytochrome P450 derived haptens routinely appear in the peripheral blood of patients treated with inert precursor drugs. Interestingly, immune responses and immunopathologic reactions to these drugs does not seem to depend upon unusual propensity to form haptenated carriers. Haptens appear to be presented to all treated patients. While the drug, dose, route, and duration of therapy do influence outcome (2), other important factors appear to dominate the propensity to express an immunopathologic reaction.

IV. DETECTION OF ANTIBODIES TO ANTIMICROBIAL DRUGS.

Improved understanding of the mechanisms of haptenation have permitted accurate predictions of relevant haptens and the development of new diagnostic assays (reviewed in reference 2). Skin tests for IgE to penicillins, cephalosporins, aminoglycosides, and sulfonamides (see below) appear feasible and are in varying stages of development. In vitro assays for IgE to penicillins, cephalosporins, sulfonamides, trimethoprim, aminoglycosides, and other antimicrobial drugs also are in varying stages of development, but appear feasible.

Of particular importance is increasing evidence that in vitro assays for IgE to drug determinants are considerably less sensitive than skin tests. These assays are valuable for demonstrating and studying antibodies to drug haptens, but current in vitro assays do not appear to have the sensitivity necessary to reliably predict the absence of drug specific IgE.

Sulfonamides. Advances in the understanding of the metabolism of sulfonamides led to the prediction that these drugs would haptenate proteins via the nitrogen in the free amino group (2,54). Evidence has been presented that this N4 sulfonamidoyl determinant is indeed the major or sole determinant.

Recent studies in our laboratory have revealed that sulfamethoxazole is highly immunogenic, even more antigenic than the betalactam drugs. In keeping with the frequent pleomorphism of the clinical reactions to sulfamethoxazole, all isotypes of immunoglobulin may be expressed. Interestingly, HIV infected patients have a very high prevalence of antibodies to sulfamethoxazole. Antibodies are present in patients who have had no recent exposure to therapeutic doses of sulfamethoxazole. These data strongly suggest that the high incidence of adverse reactions to sulfamethoxazole in AIDS patients is the consequence of immune responses to sulfamethoxazole, and that the antibodies often are present before therapy.

Increasing evidence that the N4 sulfonamidoyl determinant is the major determinant formed from sulfamethoxazole has led to the assessment of a multivalent form for use in skin tests for IgE to sulfamethoxazole. Recent studies in our laboratory indicate that polytyrosine substituted with sulfamethoxazole appears capable of provoking antigen specific wheal and flare responses in patients with IgE to sulfamethoxazole as assessed by RAST. Normal subjects do not react to similar concentrations of the reagent. This skin test reactivity can be inhibited by inclusion of a slight excess of sulfamethoxazoyl-tyrosine monomer. Thus, a promising bedside method for the detection of IgE to sulfamethoxazole is in hand. The serologic data indicate, however, that clinical reactions to sulfamethoxazole often may involve more than IgE. The ability of this form of skin testing, read early and late, to predict clinical reactions is being investigated.

Univalent haptens have been developed that inhibit sulfamethoxazole RAST and ELISA assays, as well as in vivo inhibition of the skin test, suggesting that systemic hapten inhibition of clinical reactions to sulfamethoxazole may be possible. Systemic administration of sulfa-tyrosine or another univalent hapten should block clinical reactions, similar to the hapten inhibition of immunopathologic reactions to penicilloyl determinants reported by de Weck (43).

The development of specific assays for an increasing range of antimicrobial drugs is providing markedly improved opportunities for systematic studies of immune responses to drug haptens and the development of new rational strategies for management.

V. MULTIPLE DRUG ALLERGY SYNDROME.

Patients who express hypersensitivity reactions to more than one class of antimicrobial drug present difficult clinical management problems, and opportunities to assess the factors that contribute to the propensity to make immunopathologic reactions to drugs.

In a recent study we investigated multiple drug allergy in 437 penicillin allergic patients at PMH. Of the 312 penicillin allergic patients (anaphylaxis, urticaria, or angioedema associated with prior therapy) who had been treated with a non-betalactam antimicrobial drug, approximately 21% had reacted to a second antimicrobial drug. One third of these 64 patients had reacted to two or more additional classes of antimicrobial drug. Reactions occurred in over 50% of patients treated with sulfamethoxazole and in 20-25% of the patients treated with tetracyclines, erythromycin, and cephalosporins. The clinical manifestations of reactions to non-betalactam drugs included anaphylaxis in 8 of the 312, drug fever in 7, TEN/Stevens-Johnson/erythema multiforme in 5, and serum sickness in 4.

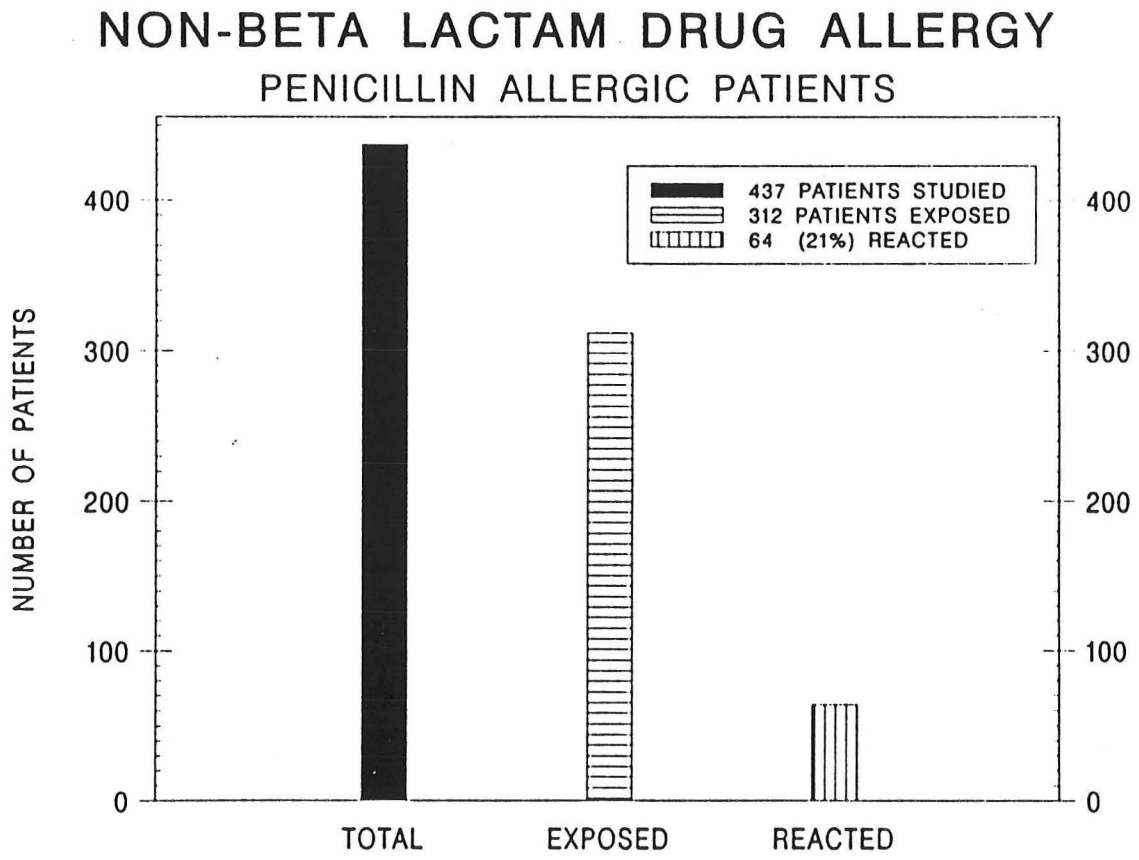
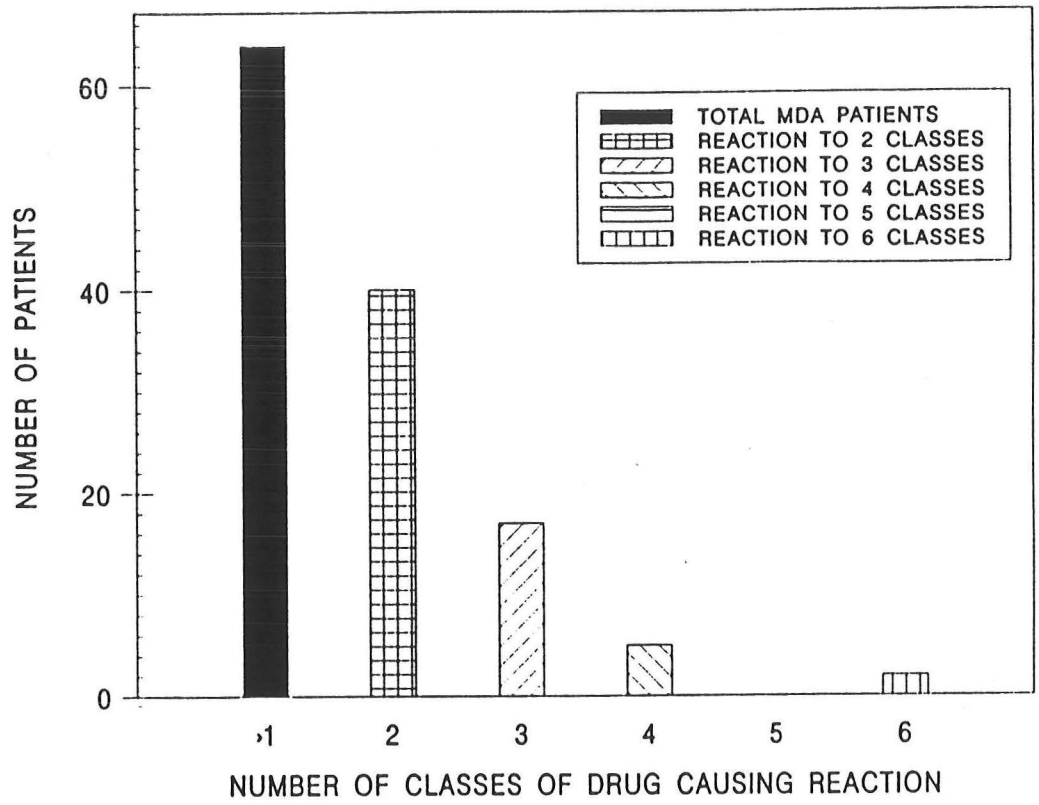


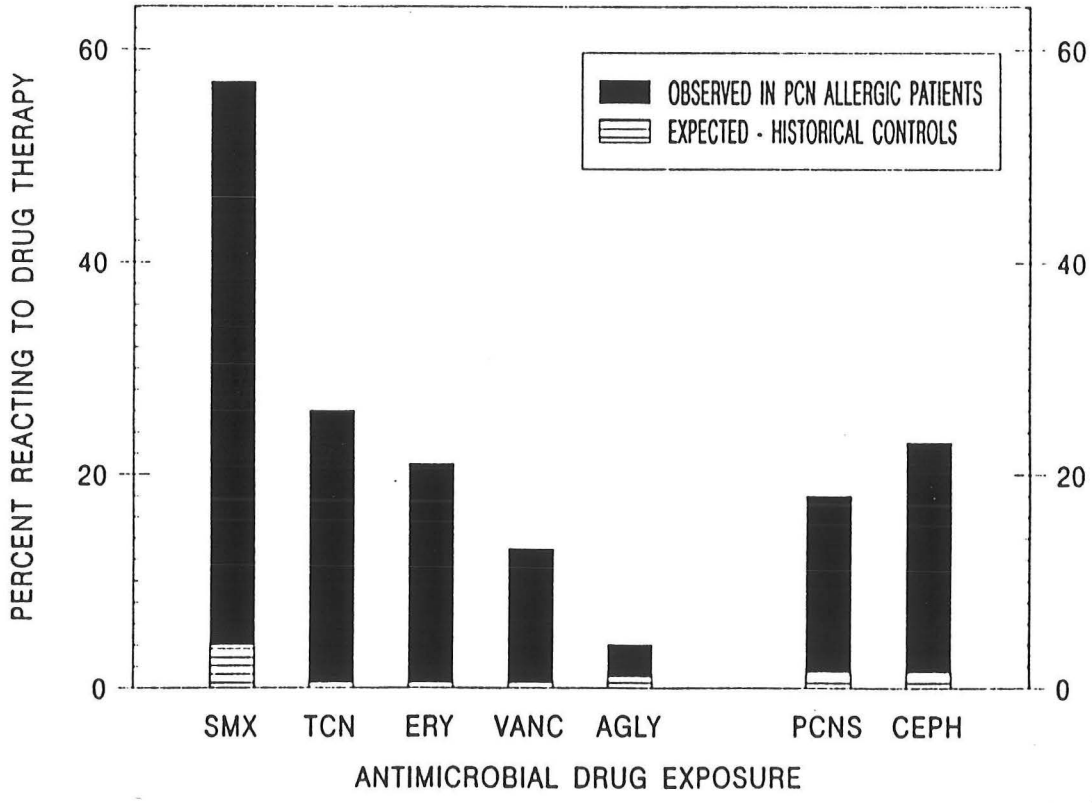
Figure 2

MULTIPLE DRUG ALLERGY IN PENICILLIN ALLERGIC PATIENTS



CLASS SPECIFIC REACTION RATES

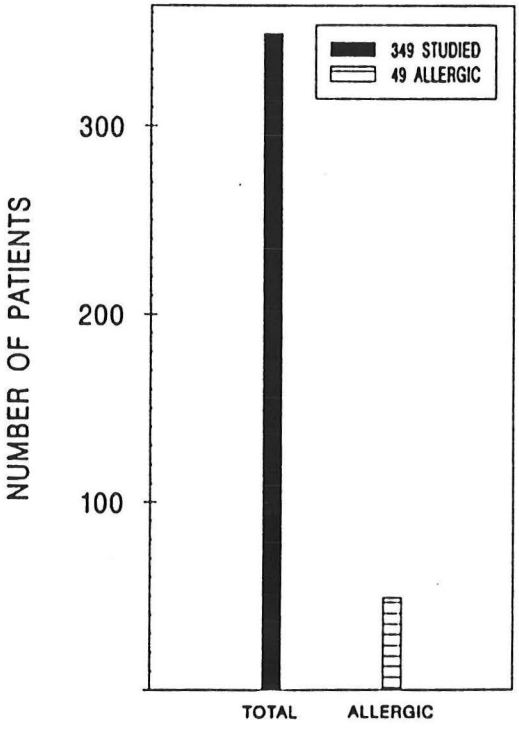
PENICILLIN ALLERGIC SUBJECTS

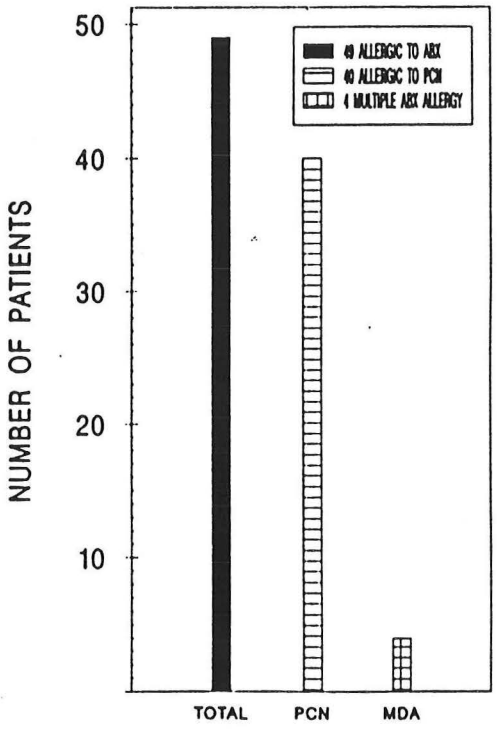


MULTIPLE DRUG ALLERGY SYNDROME

CLINICAL MANIFESTATIONS

REACTION	OCCURRENCES
CUTANEOUS	79
ANAPHYLAXIS	8
DRUG FEVER	7
TEN/S-J/EM	5
SERUM SICKNESS	4
THROMBOCYTOPENIA	1





In a followup to that study, all patients on the Internal Medicine service at PMH were studied on 3 occasions at 3 month intervals. Of the 349 studied, 49 (14%) had a documented history of drug allergy. Of these, 4 had a history of documented multiple drug allergy, approximately 1% of the patients admitted to the Internal Medicine service of Parkland Memorial Hospital.

Multiple drug allergy appears to involve antimicrobial drugs in most instances. The clinical patterns of reactions are not restricted to immediate hypersensitivity. The structures of the drugs involved are quite diverse. These observations suggest that the propensity to multiple drug allergy is not simply the consequence of a propensity to make IgE to any antigen, and is not simply an HLA associated genetic propensity to react to specific haptens.

Prospective study of multiple drug allergy. We tested the hypothesis that there is an inherent propensity to AMD allergy by prospectively comparing the incidence of allergic reactions to AMD in subjects with a history of allergy to an AMD to the incidence in patients who had tolerated AMD therapy without an allergic reaction. Screening of 2531 Parkland Memorial Hospital (PMH) patients who were beginning a course of AMD therapy detected 149 (5.9%) with a history of allergy to an AMD. The course of 37 of these subjects was followed carefully and compared to 74 nonallergic concurrent controls. Five of 37 (13.2%) of the history positive patients experienced allergic reactions. One of 74 (1.4%) of the history negative subjects reacted.

These data indicate that patients with a history of prior AMD allergy have an increased risk of reacting to unrelated classes of AMD ($P = 0.018$), a relative risk of 9.5, and would contribute 37.5% of all drug reactions at PMH while composing 5.9 % of the treated population.

Reactions in history positive patients consisted of one Stevens-Johnson reaction to norfloxacin, one fever and urticaria reaction to erythromycin, and three pruritic rash reactions during therapy with multiple antimicrobial drugs. The single reaction among history negative subjects was a pruritic rash to Unasyn.

The results of this study indicate that patients with a history of prior antimicrobial drug allergy are at markedly increased risk of developing allergic reactions to other classes of antimicrobial drugs. The structures of the drugs causing reactions and the clinical patterns of the reactions were diverse, suggesting that at least a subgroup of patients with a history of allergic reactions to antimicrobial drugs have a propensity to express multifaceted immune responses to any hapten introduced during an infection.

VI. FAMILIAL ANTIMICROBIAL DRUG ALLERGY.

In the course of evaluating and managing patients with multiple drug allergy, family histories of drug allergy appeared to be more frequent than in the general population. We investigated the hypothesis that there is a genetically defined propensity to react to drug derived haptens.

The population selected for study consisted of the families of the 292 students in grades 9-12 of a school in Dallas, from which one of the investigators had just graduated. Attempts were made to contact a randomly selected sample of 119 families by telephone. Contact was established with 42 of these families (35% of the randomly selected sample, 14% of the total population), with 41 (98% of those successfully contacted) agreeing to collect and divulge relevant medical information about both biologic parents and all biologic children.

Parents were asked to provide information about each child and their spouse. For each individual studied, the age, gender, antimicrobial drug exposures, prior apparently allergic reactions to antimicrobial drugs, nature of prior reactions, and the route of administration of the agent causing a reaction were recorded. Personal history of asthma (dyspnea associated with wheezing), allergic rhinitis (physician diagnosed), or atopic dermatitis (physician diagnosed) also was recorded. A diagnosis of an apparent allergic reaction to an antimicrobial drug was based upon an appropriate temporal relationship of onset and remission of the reaction to drug exposure (,) and upon the nature of the reaction being consistent with an immunopathologic reaction. The reactions classified as allergic reactions to antimicrobial drugs in this study consisted of pruritic erythematous cutaneous eruptions (32 subjects); fever, malaise, pruritic rash (1 adult); and contact sensitivity (1 child).

The population studied consisted of 82 biological parents of 103 children. All of the 41 fathers had been treated with antimicrobial drugs and 8 (20%) had experienced apparently allergic reactions associated with antimicrobial drug therapy. All of the 41 mothers had been treated with antimicrobial drugs and 13 (32%) had experienced apparently allergic reactions associated with antimicrobial drug therapy. The difference between males and females was not significant ($P = 0.31$). Overall, 21 of the 82 parents (26%) had histories of allergic reactions to antimicrobial drugs. At least one parent reported a history of antimicrobial drug allergy in 16 of the families (38%), and in 5 families (12%) both parents had a history of antimicrobial drug allergy. Three of the mothers (7%) had reacted to two different classes of antimicrobial drugs.

The 103 children ranged from 7 to 22 years of age with a median of age of 16 years. Sixty four were male, 39 female. All (100%) of the female children and 63 (98%) of the males had been treated with antimicrobial drugs. The single unexposed child, an 18 year old boy with allergic rhinitis, was the offspring of non-atopic, non-drug

allergic parents. Both parents and a 21 year old sister had been treated with antimicrobial drugs. Apparently allergic reactions to antimicrobial drugs had occurred in 5 (8%) of the male and 7 (18%) of the female antimicrobial drug treated children. The difference between males and females was not significant (P = 0.20). Overall 12 of 102 (12%) of the children treated with antimicrobial drugs had reacted. Children in 9 of the 41 families (22%) had experienced antimicrobial drug allergy.

When the children were stratified according to the antimicrobial drug allergy history of their parents to test the first hypothesis regarding familial antimicrobial drug allergy, a striking familial association was detected. Among children of parents with no history of antimicrobial drug allergy, 1 of 22 female and 0 of 37 male treated children had experienced antimicrobial drug allergy (1 of 59, 1.7% overall).

In contrast, among children of parents with a history of antimicrobial drug allergy 5 of 26 (19%) of the male children and 6 of 17 (35%) of the female children had experienced antimicrobial drug allergy. The difference between males and females was not significant (P = 0.30). Overall, 11 (25.6%) of the 43 children of parents with antimicrobial drug allergy had reacted to an antimicrobial drug.

The difference in rates of antimicrobial drug allergy for the children with a parental history of antimicrobial drug allergy compared to those without such a parental history was highly significant (P = 0.00024). The relative risk of having had an allergic reaction to an antimicrobial drug was 15.1 for children with a parental history compared to children without a positive parental history (25.6% vs 1.7%).

A history of asthma, allergic rhinitis, or atopic dermatitis was present in 17 of the 41 fathers (41%) and in 13 of the 41 (32%) of the mothers. A history of drug allergy was present in 4 of the 17 atopic fathers and 4 of the 24 nonatopic fathers: an insignificant difference (P = 0.70). A history of drug allergy was present in 5 of the 13 atopic mothers and 8 of the 28 nonatopic mothers: an insignificant difference (P = 0.72). Overall, 9 of 30 atopic parents (30%) had a history of drug allergy compared to 12 of 52 nonatopic parents (23%): an insignificant difference (P = 0.60) with a nominal 1.3 relative risk. A history of atopy in the parents was not associated with an increased incidence of antimicrobial drug allergy in parents.

Parental atopy was not associated with a significantly increased risk of antimicrobial drug allergy in their offspring. In contrast to the observations in parents, a personal history of atopy was significantly associated with antimicrobial drug allergy in the children. Three of the 5 male children (60%) and 6 of the 7 female children (86%) with a history of antimicrobial drug allergy had a history of atopic disease. Nine of 33 antimicrobial drug treated children with a personal history of atopy also had a history of drug allergy: 3 of 69 with no history of atopy had a history of drug allergy. The association of drug allergy with atopy in children was significant (P = 0.00167) with

a relative risk of 6.3 (27.3% vs 4.3%).

All of the reactions reported included the expression of a pruritic cutaneous eruption. In one instance urticaria and facial angioedema were noted during penicillin therapy, and in one other the reaction to erythromycin consisted of urticaria, fever, and malaise.

The majority of reactions were caused by penicillins (39%) and sulfonamide containing preparations (31%). Reactions to therapy with sulfamethoxazole/ trimethoprim and to sulfisoxazole/ erythromycin combinations were classified as reactions to sulfonamides for convenience, but the causal agent was not established. The reaction to topical Cortisporin consisted of a contact dermatitis. In all instances, the agent associated with apparent allergic reactions to antimicrobial drugs in children was known. In five instances, the parents were able to describe an antimicrobial drug related apparent allergic reaction in themselves, while not being able to remember with certainty the specific agent.

In 5 instances the classes of antimicrobial drugs causing reactions in specific parents and children were the same in parent and child, and in 6 instances the classes were are structurally dissimilar, indicating that the hereditary disposition was not restricted to specific classes of antimicrobial drugs.

No consistent pattern of familial association was detected that would permit assignment of the genetic disposition to antimicrobial drug allergy to a single Mendelian dominant or recessive gene.

In summary, a medically unselected population of children was studied by randomly selecting 42 families that had a child attending a single high school. Drug allergy and atopic history were obtained on the biologic parents and all children in 41 of the 42 (98%). The 82 parents had a median age of 47, the 103 children had a median age of 16. All parents and 102 children had been exposed to oral antimicrobial drugs (AMD). A convincing history of AMD allergy was present in 21 parents (26%), multiple AMD allergy in 4 (5%), and in 12 children (12%). Eleven of 43 offspring of AMD allergic parents (25.6%) were allergic to AMD vs 1 of 59 children (1.7%) of non-allergic parents ($P = 0.00026$), a relative risk of 15.1.

Atopy and familial drug allergy. We performed a second study to confirm the existence of a familial factor in drug allergy and to control for the possible influence of the inheritance of the atopy gene. All of the 2615 active records of a Pediatric Allergy and Immunology clinical faculty member were reviewed for histories of drug allergy. A positive history of drug associated rash, urticaria, angioedema, pruritus, anaphylaxis, or cytopenias was present in 262 (10%). Controls were selected by calling every 5th drug allergy history-negative atopic patient on an alphabetical listing.

Seventy four (74) of the 262 patients with apparent drug allergy were successfully contacted by phone. Complete histories were obtained on 42 acceptable atopic drug allergic patients. Exclusion criteria were: a negative history of atopy, an unconvincing history of drug allergy, or an incomplete family history due adoption, divorce, or poor memory. Attempts were made to contact 458 control patients by phone: 84 patients were contacted. Complete histories were obtained on 60 acceptable atopic control patients who had no history of drug allergy.

Twenty of the 84 parents (24%) of the drug allergic patients had experienced allergic reactions to antimicrobial drugs. Fifteen of 60 (12.5%) of the parents of the control patients had experienced allergic reactions to drugs. (P value =.04 by Fisher Exact Test)

Of the 19 drug allergic patients with a drug allergic parent, 47% (9/19) had an allergic reaction to the same class of drug as their parent. Ten of 19 (53%) reacted to a different class of drug.

The median age of the drug allergic children was 5.5 years. The median age of the non drug allergic child was 8.0 years. The relative risk of drug allergy was 1.9 for atopic children of drug allergic parents.

VII. DRUG ALLERGY AS A CHRONIC DISEASE RATHER THAN AN EVENT.

The data presented above suggest strongly that in general drug allergy is not a random event, and that the rules dictating who will react are not completely different for each class of drug. Rather, the data suggest that there is a group of people who have a propensity to react to antigenic drugs in general.

If we accept the estimates that 13% of patients who have reacted to a drug in the past will react to the next course of in hospital antimicrobial drug therapy, and that 1.4% of the patients who have tolerated antimicrobial drug therapy in the past will react, the relative importance of this propensity can be estimated. Taking all PMH patients together, 6% have a history of drug allergy: 38% of all reactions to antimicrobial drugs would occur in this group. Internal Medicine patients at PMH had a 14% incidence of antimicrobial drug allergy: 60% of all reactions to antimicrobial drugs would occur in this group. Upper and middle class adults in Dallas had a 26% incidence of antimicrobial drug allergy: 76% of all reactions to antimicrobial drugs in this population would occur in this prior allergy group. These estimates are not corrected for the patients who have a propensity to react to antigenic drugs, but who have not yet had a clinical reaction.

These considerations suggest that the majority of the patients who express allergic reactions to antimicrobial drugs, have a fundamental propensity to react to

antigenic drugs. A normal decision by an immune system presented with potentially antigenic drugs would be to make no response. In those individuals with a genetic or acquired propensity to react to haptens, a response is made setting the stage for clinical drug allergy. Drug allergy would represent an abnormal, inappropriate immune response. From this perspective, drug allergy could be regarded as a chronic disease than a random event.

The data presented are consistent with a genetic or acquired propensity to react to haptens: no specificity for specific structures or for specific immunopathologic mechanisms is evident in this disorder. The apparent level of dysregulation is after antigen presentation and before commitment to specific forms of immune responses.

One abnormality that could explain this phenomenon would be a propensity to express high levels of IL-6 during infections (or even constituitively elevated levels). IL-6 is a potent stimulus to the proliferation and differentiation of antigen activated B lymphocytes and enhances the production of all isotypes of antibodies (55). IL-6 also is a potent cofactor for antigen activated T lymphocyte proliferation and cytolytic T cell differentiation. Human serum IL-6 levels are known to be increased by endotoxin to a quite variable extent (56). Excessive production of IL-6 linked to ineffective counterregulation (44,50,52) could account for the immunoregulatory abnormality apparently present in the drug allergy prone patients.

Studies of AIDS patients are consistent with this hypothesis. AIDS patients are known to have a very high rate of allergic reactions to sulfonamides, sulfones, rifampin, INH, and other drugs (57,58). A recent study of IL-6 levels in the serum of AIDS patients (59) revealed the following:

Clinical Status	IL-6 (pg/ml)
Normal	9.5
HIV+	55.5
ARC	106.8
AIDS	283.0

These data demonstrate increased IL-6 levels in patients at increased risk for drug allergy and support the concept that elevated IL-6 levels could lead to a propensity to react to haptens.

Experiments to test the validity of the IL-6 hypothesis to explain multiple drug allergy are in progress. This or a related cytokine mediated effect seems a likely explanation for this disorder.

VIII. MANAGEMENT OF PATIENTS WITH ANTIMICROBIAL DRUG ALLERGY.

One of the implications of the recognition of the propensity to multiple drug allergy is that a comprehensive plan for future management should be constructed when the diagnosis is made. The problem should be approached as a chronic, potentially life-endangering disease.

The principles of management can be grouped into six major groups:

Strategies to avoid future infections. This includes immunization, altered child care, surgical and medical eradication of predisposing factors, and possible prophylactic antibiotics.

Avoidance of classes of drugs associated with prior reactions. Selection of alternatives based upon drugs not used in prior therapy, tolerated drugs, and a consideration of all agents appropriate for site specific infections.

Caution when using a drug that has been used in prior therapy. The propensity to drug allergy increases the risk of silent sensitization by prior therapy and a risk of anaphylaxis or some other reaction on readministration.

Immunodiagnostic tests. Tests for IgE can be used to screen for sensitivity (2). Penicillin skin tests can be used to predict absence of sensitivity (14).

Acute desensitization. Feasible with a wide range of drugs. Restricted to patients with isolated immediate hypersensitivity to the drug (60).

Careful monitoring. The first dose of an antimicrobial drug should be given under direct supervision, by mouth when possible. Careful monitoring during the course of therapy should be employed with emphasis on early detection of TEN/Stevens-Johnson/EM reactions.

IX. SUMMARY

This review of drug allergy has focused on the development of knowledge of the pathophysiology of immunologically mediated drug reactions, the development of new immunodiagnostic methods, and the recognition of the existence of immunologic abnormalities that dispose to drug allergy. Combinations of new immunodiagnostic tests and assessments of immunoregulatory cytokine arrays should permit much more accurate identification of patients at risk for drug allergy. The recognition of the existence of an underlying immunoregulatory disorder that permits some patients to make immune responses to antigenic drugs raises the possibility of developing pharmacologic interventions that can prevent drug allergy.

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