MEDICAL GRAND ROUNDS

PENICILLIN ALLERGY

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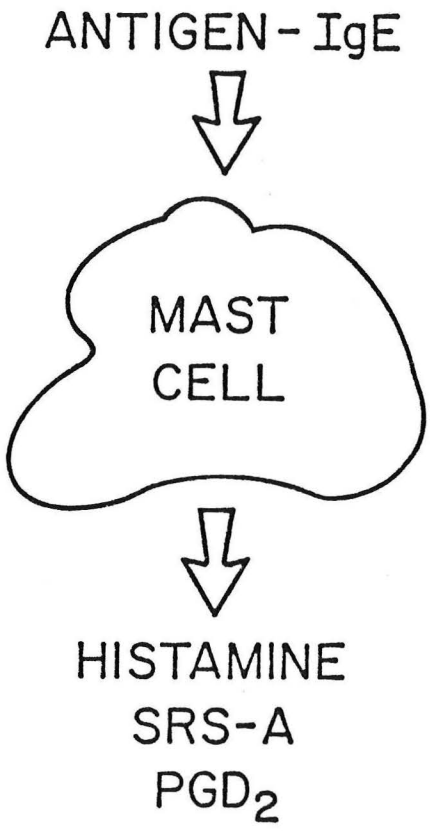

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INTRODUCTION

The discovery of penicillin led to immeasureably beneficial clinical interventions and to a revolution in thought about approaches to infectious diseases. Emphasis on serotherapy and immunization was replaced by emphasis on empirical searches for other antibiotics and then systematic chemical modification of naturally occurring antibiotics (1). Recently the molecular basis for the actions of penicillins has been defined in progressively better detail (2-5).

Unfortunately penicillin therapy is accompanied by severe, even fatal, immunologically-mediated reactions in a significant proportion of patients. Our understanding of these reactions has progressed through stages similar to those for knowledge of penicillin itself. The phenomena of penicillin allergy were defined, empirical aproaches were developed to detect and to deal with these reactions, and then our perception of the phenomena in pathophysiologic and molecular terms increased markedly.

Today we can identify patients at risk for allergic reactions to penicillin, and those not at risk, with a high degree of precision. We can administer this agent to patients known to be allergic with an acceptable level of safety. Effective use of this new knowledge, however, requires a thorough understanding of this group of antibiotics and immune reactions against them.

EPIDEMIOLOGY OF PENICILLIN ALLERGY

General considerations - Approximately 5 per cent of hospital admissions in this country are the result of adverse reactions to drugs and at least 15 percent of hospitalized patients experience untoward reactions to drugs (6-9). A significant proportion of these instances are immunologically mediated reactions to β-lactam antibiotics: penicillin, the closely related semisynthetic penicillins and cephalosporins (6, 10-12).

The population receiving these agents is quite large. At least one-third of the patients hospitalized in this country receive antibiotic therapy and a majority of these individuals receive β-lactam antibiotics (13,14). A much larger population of outpatients receives these drugs each year.

Immunologically mediated reactions to penicillin can be defined and stratified effectively according to the Gell and Coombs classification system.

Table I

Immunopathologic mechanisms

Type I - IgE-mediated reactions.

Type II - Cytotoxic IgM or IgG antibody mediated reactions.

Type III - Immune complex reactions.

Type IV - Lymphocyte-mediated reactions.

Type I IgE-mediated reactions are manifested clinically as typical allergic responses: anaphylaxis, urticaria, angioedema, asthma, rhinitis. These problems will be addressed in detail below.

Type II reactions to penicillin are clinically evident in the hemolytic anemia sometimes seen in subjects receiving β-lactam antibiotics. Positive direct Coombs reactions are detectable in approximately 10% of all patients treated with these antibiotics (15). Clinically relevant hemolysis usually occurs only when daily doses of penicillin exceed 5 grams (10 million units). Penicillin readily couples to the surface of erythrocytes and at high concentrations achieves a density of hapten substitution sufficient to permit IgM or IgG mediated hemolysis. Hemolysis varies from detectable but insignificant to rapidly fatal (16,17). Cessation of therapy leads to prompt cessation of hemolysis. The choice of alternative antibiotics in the rare circumstance of marked hemolysis should be guided by an awareness that the antibodies involved usually crossreact efficiently with erythocytes exposed to other β-lactam antibiotics (15,18).

Type III immune complex or serum sickness reactions to β-lactam antibiotics are manifested clinically as fever, rash, arthralgia, lymphadenopathy and occasionally nephritis, typically appearing 1 to 3 weeks after cessation of therapy (19). These reactions are more common than significant hemolytic reactions and contact sensitivity reactions (see below) but are considerably less frequent than Type I reactions (12).

Type IV reactions (20) against β-lactam antibiotics are almost completely limited to contact sensitivity reactions among nursing, pharmacy and medical personnel and among individuals involved in the manufacture of these agents (21).

Penicillin allergy. This term can be used to represent all immunologically-mediated reactions against penicillin, but usually it is used to denote IgE-mediated reactions.

Recent estimates of the frequency of IgE-mediated systemic allergic reactions to penicillin and other β-lactam antibiotics during a single course of therapy have ranged from 0.7 to 8 percent in large groups of patients (6, 12, 22, 23). Several investigators have reported incidences greater than 2 percent. In an ongoing drug allergy study conducted by the Boston Collaborative Drug Surveillance Program (6, 12) the following incidences of allergic cutaneous reactions have been observed.

Table II

Incidence of Cutaneous Allergic Reactions

Drug	Total number of patients treated	Percentage of allergic reactions
Penicillin G	3286	1.6%
Ampicillin	2988	5.2%
Cephalosporins	1308	1.3%

Approximately 10% of these systemic responses are anaphylactic reactions; approximately 1 to 4 per thousand treated patients (6, 12, 22). IgE-mediated reactions usually are termed anaphylactic if they are potentially life-threatening.

Hypotension, laryngeal edema, bronchospasm, cardiac dysfunction or combinations of these disorders can lead to life-endangering or fatal reactions (24-27). Anaphylactic reactions are fatal in 3 to 10 percent of cases resulting in an overall mortality rate of approximately 2 deaths per 100,000 treated patients. Reported deaths from drug induced anaphylaxis vastly underestimate actual occurrence (28). Nevertheless 100 to 300 fatal cases are reported each year in this country (29).

Waldbott's description of the first known death from penicillin anaphylaxis illustrates several important aspects of the phenomenology of penicillin allergy (30).

> A 39 year old asthmatic woman had received three courses of intramuscular penicillin therapy. Beginning one week after her third course of penicillin therapy she experienced an episode of fever, arthralgia, urticaria and worsening of her asthma. Approximately one month after this reaction she developed fever and malaise. The patient was given penicillin for administratio at home. Her sister, an R.N., injected 50,000 units of penicillin I.M. in the gluteal region. Within 5 seconds the patient complained of a strange taste in her mouth and a sensation of swelling and tightness in her throat. She became flushed and cyanotic and complained of generalized itching. The patient asked for a glass of water, then collapsed and died "immediately".

In their review of 151 fatal anaphylactic reactions to penicillin, Idsoe and co-workers drew together most of the principles of therapy that analysis of the phenomenology of these reactions has generated (22). A summary of these observations is presented in Table 3.

Table III

Epidemiology of Fatal Penicillin Anaphylaxis

Age: 3 months to 65 years

Sex: 77 women, 74 men

History of allergic disease: 28%

History of asthma: 14%

Previous allergic reaction: 25%

Interval since last drug exposure: 10 days to 7 years

Interval from drug administration to onset of anaphylaxis:

Immediate	49%
Less than 15 minutes	85%
Less than 60 minutes	96%
Less than 24 hours	100%

Interval from drug administration to death:

Less than 15 minutes	57%
Less than 60 minutes	79%
Less than 24 hours	90%

Treatment: 71 of 151 (46%)

This review and numerous subsequent reports have come to the following general conclusions. Fatal anaphylaxis is less common in the extremes of life but age is not a determining factor in assessing the risk of an allergic reaction to penicillin. Sex also does not appear to influence the expression of penicillin allergy. A careful review of the records of patients dying of penicillin-induced anaphylaxis reveals that some had experienced previous reactions that might have been allergic in nature, but the vast majority had experienced no previous clinical reaction. The onset

of anaphylaxis is within 15 minutes in most instances, but a delayed onset (over 60 minutes) of fatal reactions definitely can occur. Many patients who experience anaphylaxis outside of a medical facility die before therapy can be instituted. Patients brought to hospitals because of anaphylaxis often are unconscious, making the diagnosis a challenging undertaking (31). Several case reports indicate existing therapy may be to no avail in some instances.

Patients prone to making IgE responses to inhalant antigens may be slightly more prone to develop IgE antibodies against penicillin (10) but this issue is controversial (32, 33). Asthmatic patients who do experience anaphylaxis appear to have a higher mortality rate than nonasthmatics (22).

Two lines of epidemiologic evidence indicate that oral administration of β-lactam antibiotics is considerably safer than parenteral administration. First, only 6 deaths from anaphylaxis induced by oral penicillin have been reported (25, 34-36). While this number serves only as an index, death from orally administered β-lactam antibiotics appears to be exceedingly rare. Second, the frequency of nonfatal allergic reactions appears to be lower after oral administration (37, 38).

Table IV

Rates of Cutaneous Allergic Reactions for Orally and Parenterally Administered β-lactam Drugs

Agent and Route	Total Recipients	Skin Reactions	%
Penicillin G			
Parenteral	893	24	2.7
Oral	362	5	1.4
Total	1255	29	2.3
Ampicillin			
Parenteral	486	35	7.2
Oral	977	34	3.5
Total	1463	69	4.7
Other Semisynthetics			
Parenteral	180	8	4.4
Oral	148	4	2.7
Total	328	12	3.7

From reference 40

The absolute amounts of antibiotics administered orally usually are smaller than those delivered parenterally, but as discussed below other important factors may be active.

Since topically applied penicillin sensitizes a huge proportion of subjects, this route has been abandoned.

Taken together these epidemiologic features of β-lactam antibiotic allergy have led to several widely held conclusions.

TABLE V

Epidemiology of Penicillin Allergy

1. Careful inquiry into possible allergic reactions associated with earlier exposures to β-lactam antibiotics is mandatory.

2. Most patients who experience allergic reactions have no history of previous reactions.

3. Direct observation of patients for a minimum of 15 minutes after the administration of the first dose of β-lactam antibiotics is mandatory.

4. The onset of severe or potentially fatal allergic reactions can be delayed for hours.

5. Patients experiencing severe reactions often are unconscious when they arrive at a medical facility.

6. Particular care should be exercised when administering β-lactam antibiotics to asthmatics or patients with other illnesses that would be likely to exaggerate the impact of an allergic reaction.

7. When possible, β-lactam antibiotics should be administered orally.

MECHANISMS OF SENSITIZATION BY β-LACTAM ANTIBIOTICS

Penicillin G, semisynthetic penicillins and cephalosporins inhibit bacterial growth by inhibiting the synthesis of cell wall peptidoglycans (2-5). Synthesis of linear peptidoglycans is not affected by β-lactam

agents, but crosslinking of these subunits by peptidoglycan transpeptidase is specifically blocked (2-3). Ghuysen and coworkers have presented data suggesting that penicillin might act as a competitive inhibitor of the transpeptidase (39). Recent studies by Strominger and his colleagues have presented compelling evidence, however, that an entirely different mechanism is operative. Penicillin appears to act as an analog of the acyl-D-Ala-D-Ala terminal portion of the pentapeptide side chain of peptidoglycan monomers (3). The antibiotic binds to the reactive site on the transpeptidase enzyme and the unstable β-lactam ring irreversibly acylates the active site of the enzyme (3,4).

The marked tendency of β-lactam antibiotics to become covalently bound to proteins in vitro and in vivo leads to the generation of molecules capable of stimulating immune responses (22, 40-43). The fermentation processes used to produce β-lactam antibiotics yield very high concentrations of these agents (43). Under these conditions soluble mold proteins may become substituted with 30 or more antibiotic molecules per carrier molecule. The predominant form of substitution is the penicilloyl group coupled to epsilon amino groups of lysine residues (44). Recent studies in experimental animals have suggested that the preformed conjugates may play a central role in provoking immune responses against β-lactam antibiotics (43,45). Conjugation of β-lactam antibiotics to carrier molecules in vivo also appears to contribute immunogenic molecules. Polymers do not appear to be an efficient form for sensitization (43).

Immune responses against β-lactam antibiotic derived antigens occur in virtually all patients treated with a full course of therapy with these agents (17, 18, 22, 39-43). IgM and IgG responses can be detected in over 90% of such patients if sensitive assays are used (46). In vitro evidence of cell mediated immune responses has been reported in a variable percent of treated patients. High level, persistent IgE antibody responses are less common, but these responses are of much greater clinical importance. No satisfactory prospective studies of the incidence of IgE responses after therapy has been reported. Minimum estimates, based on positive skin test reactions in hospitalized patients requiring antibiotic therapy, are that 2 to 5% of treated subjects develop persistent IgE responses (33, and unpublished data from a National Institute of Allergy and Infectious Diseases study still in progress).

The factors that determine which patients make a vigorous, sustained IgE response to β-lactam antigens are not entirely clear, although some determinants are known. The route of presentation of antigen is important: IgE sensitization is most likely after topical > parenteral > oral administration. Small doses of antigen favor IgE production in experimental animals while large doses favor IgG and IgM responses. Human IgE responses against pollen allergens are controlled in part by genes in the HLA-A region of the 6th chromosome (47) indicating that immune response genes exist and suggesting that they may also influence IgE responses against β-lactam antibiotics.

Experiments using human tissues have demonstrated that IgE responses are T cell dependent processes (48-540. As in experimental animal systems, human IgE responses appear to be regulated by a dominant suppressive mechanism (49, 51-53). These studies indicate that patients who make vigorous and sustained IgE responses against penicillin may differ from other patients by not actively suppressing the response (54-56).

Table VI sumarizes this section.

TABLE VI

Sensitization by β-lactam Antibiotics

1. β-lactam antibiotics act on bacterial enzymes by acylating the reactive sites. This ability to covalently attach to macromolecules leads to *in vitro* and *in vivo* substitution of carrier molecule in an immunogenic form.

2. Virtually all patients treated with β-lactam antibiotics make an immune response of some kind against the coupled forms of the drugs.

3. IgE antibody responses persist in detectable amounts only in a small subpopulation of patients (2 to 5%).

4. Failure to suppress an IgE response rather than a special ability to make an IgE response seem to distinguish IgE responders from "nonresponders".

IgE-MEDIATED REACTIONS

Immedate hypersensitivity reactions (acute IgE-mediated allergic reactions) ensue when antigen-IgE interactions on the surface of mast cells and basophils stimulate the release of inflammatory mediators (24). These mediators alter the function of nearby cells resulting in clinical manifestations such as hypotension, bronchospasm, urticaria, angioedema and laryngeal edema.

The first evidence that a specific class of immunoglobulin mediates allergic reactions was provided by Prausnitz and Kustner (57). Injection of serum from a fish-allergic donor (Kustner) into the skin of a non-allergic recipient (Prausnitz) followed 2 days later by injection of the site with a solution containing fish allergen resulted in a wheal and flare response. The discovery of this PK or passive transfer test

permitted identification of the physicochemical properties of the responsible molecules and ultimately guided the purification of IgE by Ishizaka and coworkers (58, 59).

IgE is a 2 heavy chain (epsilon), 2 light chain (kappa or lambda) glycoprotein with a molecular weight of 188,000 to 196,000 daltons (24). This antibody has two antigen combining sites, similar to IgG, and has a highly specialized Fc region that binds with high affinity to receptors on tissue mast cells and blood basophils. The IgE receptor is a plasma membrane glycoprotein of approximately 50,000 daltons. Mast cells express approximately 1 million IgE receptors, basophils approximately 100,000 (24).

Administration of penicillin to patients bearing specific IgE on their mast cells and basophils leads to the release of mediators and clinically apparent inflammation (60). Recent studies by Ishizaka et al. (61) and Isersky et al. (62) indicate that cross-linking of IgE-Fc receptors on rat mast cells or leukemic basophils is a sufficient signal to cause mediator release. These results are in accord with many previous studies which have indicated that antigens provoking IgE-mediated reactions usually must be immunologically multivalent (63). Mediator release also can be provoked by intact antibodies directed against the IgE molecule but does not occur when univalent antibody fragments are used (63). Existing information strongly suggests that antigen induced mediator release occurs primarily following multivalent interaction of antigen with IgE bound to cell surface IgE-Fc receptors; IgE appears to act as an acquired, specific receptor which permits antigen dependent cross-linking of IgE-Fc receptors which in turn initiates mast cell or basophil secretion.

While much work remains to be done to clarify the details of antigen-induced mediator release, studies in a variety of species and antigen systems consistently have indicated that univalent ligands can block immediate hypersensitivity responses to multivalent antigens. This principle, initially called a state of antianaphylaxis, was first described by Landsteiner (64). Guinea pigs sensitized by repeated injections of horse serum substituted with diazotized para-arsanilic acid experienced anaphylaxis after intravenous challenge with chicken serum substituted with the same determinants. Sensitized animals injected with para-amino-phenyl-arsanilic acid or with phenyl-4-arsonic acid-azo-tyrosine did not react to these compounds but they were completely protected from anaphylaxis after subsequent injections of the chicken serum azoproteins. Inhibition of immediate hypersensitivity reactions by univalent ligands has been observed in the human leukocyte system using multivalent and univalent penicillin derivatives (65), the sensitized guinea pig uterus system using trinitro-phenyl-methylnitramine-protein sensitive tissue and pycrylglycine as an inhibitor (66), and the human direct skin test system using dinitrophenyl or penicillin sensitive subjects and specific monovalent inhibitors (67-69). In these and similar studies multivalent hapten-carrier stimuli have usually been required to provoke mediator release and appropriate

monovalent ligands have been protent inhibitors. When univalent and multivalent ligands have been added simultaneously, a 100 to 5000-fold molar excess of univalent material has usually been required for 100 percent inhibition of mediator release. When penicilloyl sensitive rabbit leukocytes were exposed to univalent benzylpenicilloyl-n-propylamine and then were challenged with multivalent penicilloyl-haptenated proteins, however, equimolar concentrations of inhibitor were sufficient to achieve 100 percent inhibition (70). Equimolar concentrations of univalent inhibitors injected simultaneously with bivalent antigens also have been reported to completely inhibit immediate hypersensitivity responses in calf skin (71).

Several important implications can be drawn from these general studies of antigen-IgE interactions in regard to β-lactam allergy.

TABLE VII

Antigen-IgE Interactions

1. Free drug binds to specific IgE antibody, but can not trigger an allergic reaction.

2. Drug conjugated to a single site on a carrier molecule (univalent conjugate) binds to IgE but can not stimulate an allergic reaction.

3. Multivalent conjugates (or drug polymers) are necessary to crosslink IgE molecules and thereby to initiate an allergic reaction.

4. In vivo the degree of mediator release will be a function of the specificities and affinities of the IgE present and the relative concentrations of free drug, univalent conjugates and multivalent conjugates.

Stable crosslinking of IgE receptors leads to a series of intracellular biochemical reactions culminating in the fusion of the membranes surrounding cytoplasmic granules with the plasma membrane (24, 60, 72-74). This exocytosis process releases a diverse group of preformed mediators including histamine, heparin, eosinophil chemotactic factors, proteases and glycosidases. Concommitant with the release of preformed mediators, arachidonic acid is cleaved from membrane lipids and converted through lipoxygenase or cyclo-oxygenase pathways to a family of newly formed inflammatory mediators. SRS-A, PGD_2, 5-HETE and 12-HETE are included in this group of mediators.

Histamine can cause most of the clinical phenomena of anaphylaxis (75). This agent can induce hypotension, bronchospasm, vasodilation,

increased vascular permeability, cutaneous pruritus, rhinorrhea, lacrimation, colic and diarrhea (24,75). These effects are mediated by activation of H_1 and H_2 receptors on the plasma membranes of target cells. H_1 receptors mediate most of the recognized manifestations of allergic reactions (75-76). H_2 receptors also may contribute to the vascular effects of histamine (77,78).

The wheal and flare response that occurs after intracutaneous administration of histamine appears to result from local vasodilation and increased capillary permeability surrounded by an area of vasodilation mediated by antidromic reflexes (79,80). This response appears to be mediated primarily by H_1 receptors with a small but detectable contribution from H_2 receptors (77,78,81,82). Antigen-induced cutaneous wheal and flare responses also are inhibited by histamine receptor blocking agents indicating that histamine is the principal mediator of acute allergic reactions in skin (83).

While the known actions of histamine appear to be sufficient to account for acute allergic reactions, other potent mediators are known to be released that may play important roles. Slow reacting substance of anaphylaxis (SRS-A) activity is now known to reside in 3 closely related arachidonic acid derivatives. Arachidonic acid is modified by a 5-lipoxygenase system to yield molecules with a hydroxyl group at the C-5 position and a C-6 thio ether linkage to cysteine, cysteinylglycine or glutathione (84-86). These molecules, also called leukotrienes, are capable of causing vasodilation and bronchoconstriction.

The principal oxygenated derivative of arachidonic acid produced by stimulated mast cells is PGD_2 (87). This agent also is capable of causing vasodilation and bronchoconstriction. A recent study indicates that PGD_2 exerts an important force in the flushing and hypotension seen in some patients with systemic mastocytosis, raising the possibility that PGD_2 plays a similar role in antigen-induced anaphylaxis (87).

Increasing evidence indicates that immediate hypersensitivity reactions are of major importance in the orchestration of protective responses against some parasites, and perhaps other infectious organisms (88). Many parasites evoke marked IgE responses, in contrast to most bacterial, fungal, rickettsial or viral infections (89,90). These antibodies provide mast cells with receptors for parasite antigens. Mast cells are ideally positioned in the dermis, respiratory epithelium and gastrointestinal epithelium to detect the presence of an invading organism. Histamine, SRS-A, and PGD_2 released in response to antigen-IgE interactions increase local vascular caliber and permeabililty resulting in an influx of IgG and complement, among other factors. Eosinophil chemotactic factors released by mast cells cause an influx of eosinophils (88).

Eosinophils can bind to parasites and/or nucleated mammalian cells through IgG_{Fc} or C3b receptors and can kill the target organism or cell (88,81). Histamine and the eosinophil chemotactic factor of anaphylaxis (ECF-A) peptides rapidly increase the expression of IgG_{Fc} receptors and C3b receptors on the surface of eosinophils (92). These same mast cell mediators markedly increase the capacity of eosinophils to kill target organisms (92). Thus, mast cell mediators recruit eosinophils into the region of invading organisms and then arm them for efficient killing.

Recent studies by Butterworth, David and their colleagues have demonstrated that if schistosome parasite larvae are coated with parasite specific IgG or with C3b, eosinophils can bind and can kill the organism (93-94). This is in accord with *in vivo* studies in primates that demonstrate wheals at the site of cercarial penetration of the skin of protectively immune animals and mast cell degranulation at the site (95). Penetrating larvae are soon surrounded by eosinophils and are destroyed (95). These reactions do not occur in animals lacking protective immunity. Apparently parasite specific IgE, normal mast cells, specific IgG and normal eosinophils all are essential for successful killing in vivo (88,96).

When IgE responses are made against pollen antigens and the individual is re-exposed to pollen landing on the conjunctivae or respiratory epithelium, these anti-parasite defenses are mobilized. Mast cell mediators alter local tissue function and cause an influx of eosinophils. Diseases of immediate hypersensitivity can result from these inappropriate IgE responses and the inappropriate release of mast cell mediators. Eosinophils may be irrelevant (88), may decrease the intensity of the reactions (97), or may contribute to the inflammation (98) in these reaction sites. Organ specificity of diseases of immediate hypersensitivity appears to be related partially to the sites of antigen entry.

Systemic allergic reactions occur after hematogenous dissemination of antigen. These explosive immediate hypersensitivity events occur when a large amount of antigen is abruptly introduced into the system. This is an enormous exaggeration of the focal anti-parasite response that normally occurs. Antigen-IgE reactions on the surface of basophils would be expected to accelerate the delivery of antigen to perivascular mast cells and then to mast cells throughout the connective tissue. The clinical manifestations of anaphylaxis can vary depending upon the route of administration (inhalation; ingestion, injection), the rate and amount of antigen delivery to specific tissues and the local responsiveness of mast cells and target tissues. Knowledge of the forces that determine the nature and magnitude of these reactions is far from complete.

IDENTIFICATION OF PATIENTS AT RISK, OR NOT AT RISK, FOR ALLERGIC REACTIONS TO PENICILLIN

The clinical manifestations of penicillin allergy (hypotension, urticaria, angioedema, bronchospasm) are indistinguishable from reactions provoked by antigen-IgE interactions (24). Immunologic assessment of patients before and after allergic reactions to penicillin has clearly documented the presence of IgE anti-penicillin antibodies in patients at risk for allergic reaactions and an absence of acute allergic reactions in patients not expressing such antibodies (99).

In the late 1950's Charles Parker at Washington University in St. Louis and Bernard Levine at New York University independently embarked on systematic inquiries into penicillin allergy. The strategy adopted was 1.) to determine the chemical nature of the forms in which penicillin conjugates to carrier molecules, 2.) to develop assays to detect antibodies or lymphocytes capable of binding these haptens, 3.) to correlate these immunologic parameters with clinical allergic reactions, and 4.) to refine immunodiagnostic methods to identify patients at risk for allergic reactions.

As illustrated in Figure 1 the immunochemistry of penicillin haptens has been clarified in some detail (100). Approximately 95% of the penicillin molecules that become conjugated to carriers are in the penicilloyl configuration. The peniciloyl determinant is therefore called the major determinant. The remaining 5% of conjugates are in a variety of forms, collectively referred to as minor determinants. The terms major and minor refer to the abundance of the determinants.

Hemagglutination assays, lymphocyte transformation assays, other in vitro assays and direct skin tests were developed to detect reactions against these determinants (100,101). The presence or absence of serum IgG and IgM antibodies was found to be of no value for predicting allergic reactions - such antibodies can be found in the sera of over 90% of patients in this country (102,103). Delayed skin test reactions and lymphocyte transformation assays also were not of predictive value (104). Immediate wheal and flare skin test procedures were developed that reflect the presence of IgE and that do have predictive value (105-107).

Detection of IgE anti-penicillin antibodies. Antigen-specific IgE antibodies can be demonstrated by skin testing; immunoassay; radioallergosorbent (RAST) tests; peripheral blood leukocyte histamine release assays; passive transfer (PK) tests using the skin of nonimmune humans or primates; or passive sensitization of human leukocytes, lung fragments, or skin fragments.

To be clinically useful a test must be rapid, specific, sensitive, and safe. Leukocyte histamine release and in vitro passive sensitization tests

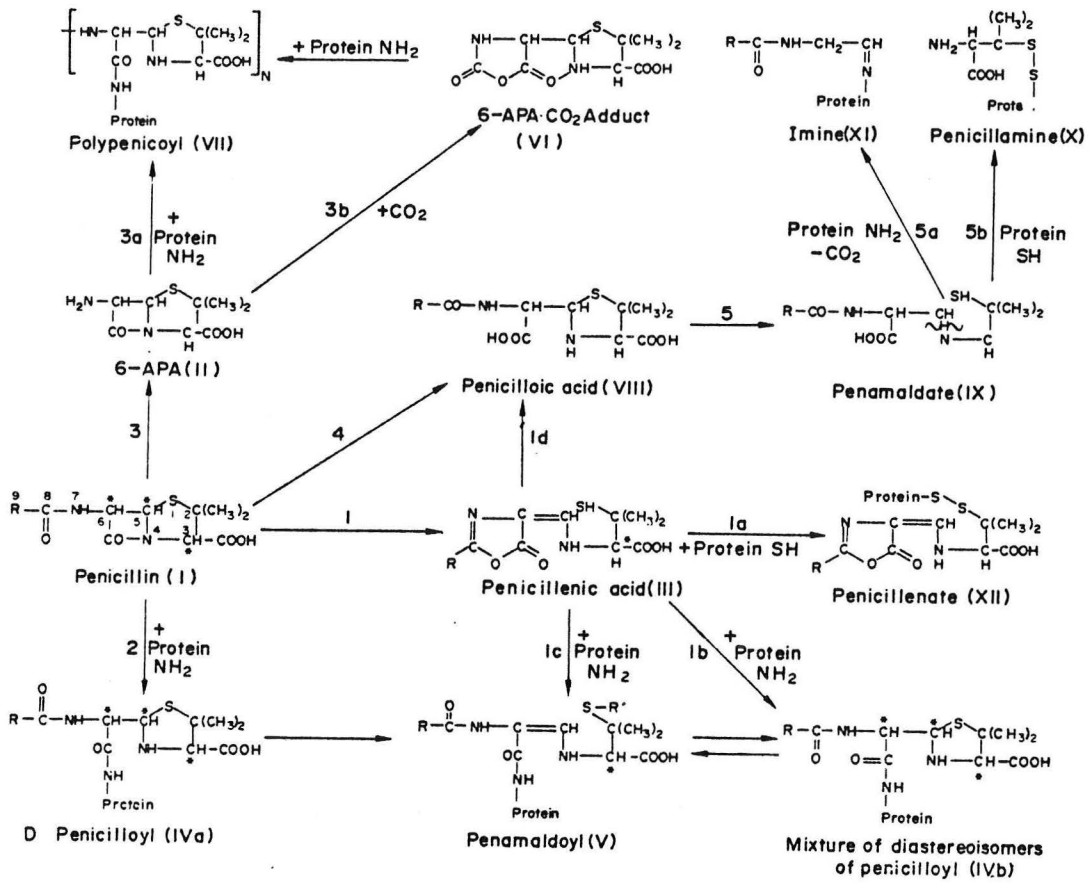

Fig. 1. Proposed mechanism for formation of antigen in penicillin allergy. In VII the group in brackets may be polymerized. The asterisk refers to asymmetric carbons. 6-APA is 6-aminopenicillanic acid.

From reference 100

are cumbersome, slow, incompletely characterized methods for the diagnosis of drug allergy and are not in use outside research laboratories. The danger of transmission of disease in PK tests and the availability of alternatives has virtually ended the use of this procedure. These functional in vitro assays and PK tests are not viable options for routinely detecting patients with IgE anti-penicillin antibodies.

RAST methods for detection of circulating specific IgE show good correlations with skin tests and clinical penicillin allergy (108-110). ELISA assays also show promise (111). Three major problems limit the usefulness of these assays for most clinical situations, however. First, the procedures take two days to complete. Second, the sensitivity of the

assays is less than that of skin tests. Third and most important, all of the relevant conjugated forms of penicillin must be known and present. Currently only the penicilloyl determinant is used. A positive test indicates the presence of specific IgE and the presence of risk of an allergic reaction. A negative test is of no value. Exquisite sensitivity still could be present.

At the present time skin testing is the only method available that can effectively stratify patients according to the presence or absence of significant risk of an allergic reaction (105-107). Knowledge of the major features of the immuno chemistry of penicillin reactions permitted the development of reagents that could elicit immediate wheal and flare reactions when injected into the skin of patients with IgE anti-penicillin antibodies. Anti-penicilloyl antibodies are detected by injecting penicilloyl poly-L-lysine, marketed as Pre-Pen, a preformed nonimmunogenic conjugate. Antibodies of other specificities are detected by injecting penicillin G and penicilloic acid. These latter agents conjugate to endogenous carriers in many different configurations. These conjugates trigger local mast cell secretion and a visible wheal and flare reaction if specific IgE antibodies are present. If no such antibodies are present, no reaction occurs. Testing with these three reagents appears to be sufficient to detect patients at risk although occasionally stronger reactions can be provoked by injecting other derivatives of penicillin such as penicillenic acid (99, 107).

TABLE VIII

Skin Test Reagents

Penicilloyl poly-L-lysine

Concentrated (6×10^{-5} M)
1:100
1:10,000

Penicillin G

Concentrated (5000 u/ml, 10^{-2} M)
1:100
1:10,000

Penicilloic acid

Concentrated (10^{-2} M)
1:100
1:10,000

During the development of skin test procedures systemic reactions and one death from anaphylaxis occurred (112,113). To guard against this possibility our skin tests have been initiated by placing a very dilute solution of the test reagent on the forearm and pricking the underlying skin with a 26 guage needle. If no wheal and flare response occurs within 15 minutes, a 100-fold higher concentration is tested. If negative the reagent is tested at a concentration 10,000-fold higher than the initial solution. If these percutaneous tests are negative intradermal injections are made in a similar progressive manner. Investigators using this protocol or similar procedures on several thousand patients over fifteen years have provoked no serious allergic reactions (99, 100, 107). Allergic reactions stimulated by skin testing are likely to be easier to reverse than a reaction in the same patient after a full therapeutic dose of penicillin administered without knowledge of the subjects immune status.

Skin testing has the advantages of speed, simplicity, sensitivity, specificity and extensive characterization of its relationship to clinical allergy. This approach has the disadvantages of in vivo bioassays - a small degree of risk, obstruction by extensive skin disease, obstruction by antiallergic drugs. If properly performed with defined reagents and with positive controls with histamine and negative controls with diluent, this approach to detecting IgE anti-penicillin antibodies is the most satisfactory method available.

Predictive value of positive penicillin skin tests. Approximately two-thirds of patients who have positive reactions to penicillin skin test reagents will experience an acute allergic reaction if penicillin is administered in usual doses (33, 100,107). Levine and coworkers have reported an increased frequency of positive reactions to minor determinants and negative reactions to penicilloyl determinants in patients who have anaphylactic reactions suggesting that antibodies against these determinants predispose to anaphylaxis (102). Parker and coworkers, on the other hand found penicilloyl reactivity in 12 of 17 patients who had experienced anaphylaxis (100). At this time neither the pattern nor the intensity of the positive skin test reactions appears to accurately predict the nature or severity of a clinical reaction. A positive skin test simply demonstrates the presence of anti-penicillin IgE and identifies the patient as being at risk for an allergic reaction.

Penicillin skin tests appear to be adequately sensitive assays of specific IgE since antibodies can be detected in some patients (one-third of positive patients) who do not experience clinical allergic reactions during treatment. Negative skin tests indicate virtually no risk of allergic reaction (see below). The forces that govern which patients have clinical reactions currently are not known.

Predictive value of a negative skin test. During the 1960's a large number of studies addressed the issue of which reagents were necessary to demonstrate anti-penicillin IgE and how skin test reactions correlated with clinical reactions. When penicilloyl poly-L-lysine, penicillin G, penicilloic acid and other minor determinants began to be used in concert a remarkable ability to identify patients not at risk for allergic reactions emerged (99, 107, 114). To date no anaphylactic or other serious allergic reaction has been reported in such skin test negative patients. An acute urticarial reaction has been noted in 3 skin test negative subjects followed by Dr. Levine and no allergic reactions have occurred within 48 hours in Dr. Parker's skin test negative patients, a combined experience of several thousand skin test negative, β-lactam antibiotic treated patients.

Taken together these observations indicate that patients expressing IgE anti-penicillin antibodies can be detected by several methods. Skin testing appears to be able to detect virtually all patients at risk for allergic reactions. Skin test negative patients appear to be at virtually no risk of serious allergic reactions.

CROSS-REACTIONS OF β-LACTAM ANTIBIOTICS WITH IgE ANTI-PENICILLIN ANTIBODIES

Many physicians believe that cephalosporins or semisynthetic penicillins can be administered to patients allergic to penicillin with little or no risk of an allergic reaction. This belief is not based upon clinical or immunologic studies. In fact the clinical and immunological evidence that cross-reactivity can occur is so overwhelming this issue would not be addressed if it were not for the widespread misconception that no cross-reactions occur. The real issue is the extent to which the β-lactam antibiotics cross-react.

The similarity in the structures of these agents and the recognition that they all readily acylate proteins (4,5) would lead an immunologist to predict that all β-lactam antibiotics would be allergenic and that they would cross-react to some degree. Reports of the outcome of administering cephalosporins or semisynthetic penicillins to penicillin allergic patients are not adequate to make precise extimates of the frequency or intensity of cross-reactions, but they do clearly document the phenomenon of cross reactions (115-122). Immunologic studies also have demonstrated frequent cross-reactivity (99, 121, 122-125).

A recent report of skin test reactions to cephalothin, ampicillin and carbenicillin in penicillin skin test positive patients (99) indicates that cross-reactions are frequent with cephalothin and ampicillin and increase with the intensity of reactivity to penicillin reagents (Table IX).

TABLE IX

Skin Test Reactivity to Ampicillin, Cephalothin and Carbenicillin in Patients Also Skin Tested for Penicillin Reactivity

Degree of Penicillin Reactivity	Skin Test Results[a]					
	Ampicillin		Cephalothin		Carbenicillin	
	+	-	+	-	+	-
Negative	0	14	4	45	1	7
Intradermal Positive	25	15	26	35	1	3
Percutaneous Positive	16	0	12	1	0	2

a. Skin tests with these agents were performed using the same concentrations that were selected for skin tests with Pen G. Reactions to percutaneous or intradermal tests were combined as a total.

These studies clearly document the existence of immunologic and clinical crossreactivity. The degree of cross-reactivity is unknown, but studies are in progress to address this issue. Two recent experiences at this hospital illustrate the polar poossibilities. One 67 year old man with a history of penicillin allergy and very strongly positive penicillin skin tests received 2 gm of cephalothin I.V. and then continued therapy without an allergic reaction. The second patient, a 36 year old penicillin allergic man ingested one Keflex capsule and experienced near-fatal anaphylaxis within 1 hour. While other β-lactam antibiotics may cause fewer or less severe reactions than penicillin, no methods exist to characterize the degree of risk. Penicillin allergic patients must be regarded as being at risk for allergic reactions if exposed to any β-lactam antibiotic.

Penicillamine may cause an allergic reaction in penicillin sensitive individuals but the degree of risk is unclear (126).

PENICILLIN SKIN TESTING IN A UNIVERSITY HOSPITAL SETTING

The prevalence of positive penicillin skin tests in patients with a history of an allergic reaction to penicillin typically ranges from 36% to

75% (99, 127). To date 14 of 29 patients (48%) history positive patients studied at Parkland Hospital were skin test positive. The specific clinical manifestations of previous allergic reactions (hypotension, urticaria, angioedema, bronchospasm) do not appear to be related to an unusual prevalence of positive reactions or to the specific pattern or intensity of the positive skin test reactions (99).

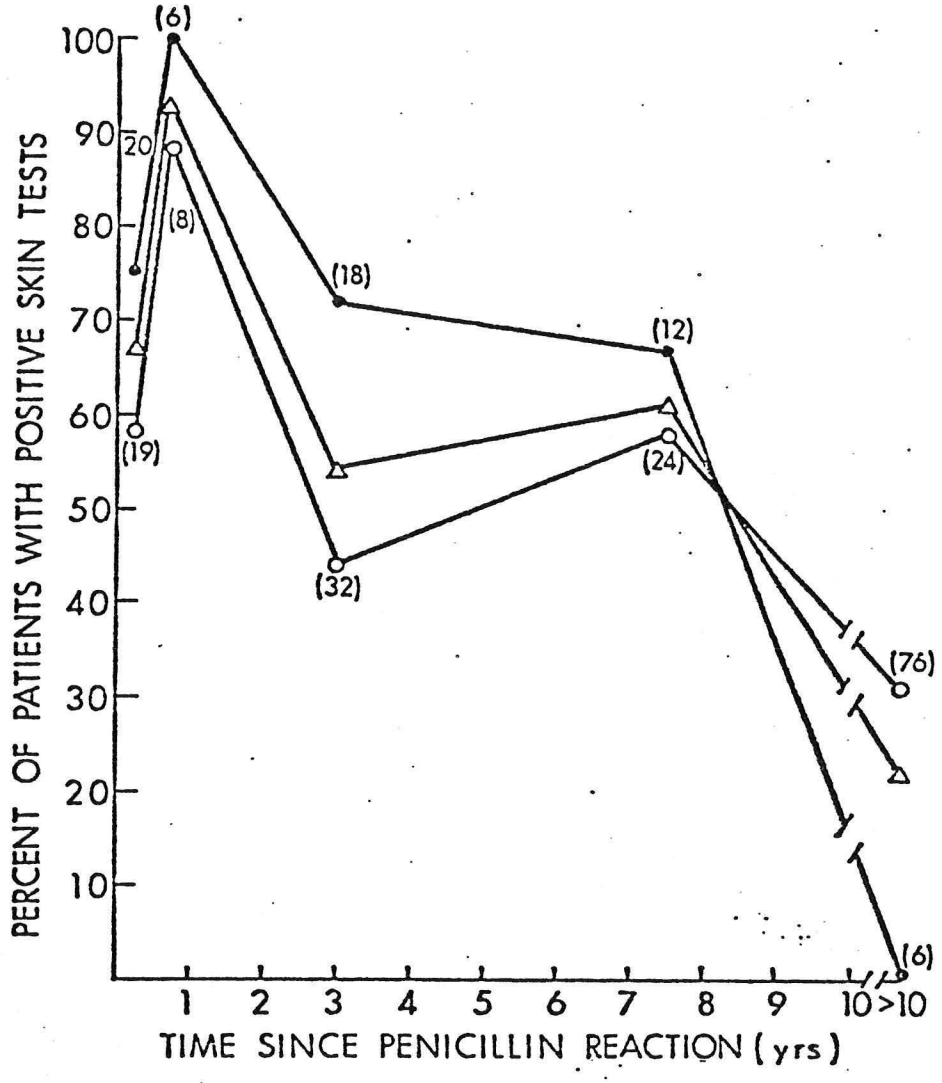

Fig. 2. Relationship of positive penicillin skin test reactions to the time since penicillin reactions. The percent of children (●——●), adults (○——○) and of the total group (△——△) skin test positive at each time is presented. The number of patients tested falling into each group appears in brackets next to the data points. The time intervals selected were 0-6 months, 6-12 months, 1 to 5 years, 6-10 years, and over 10 years.

Two aspects of histories of adverse reactions to penicillin deserve special emphasis. First, pruritic macular rashes can be an indication of an allergic reaction to penicillin. For example one recent study reported positive skin tests in 48 of 106 (45%) patients with a history of pruritic macular rashes (99). At Parkland Hospital 5 of 7 (71%) such patients were skin test positive. Emphasis on the nonallergic macular rash associated with ampicillin therapy has led some physicians to regard any macular rash as nonallergic. Clearly this is not warranted for pruritic macular rashes. Second, as illustrated in the case description above (30) and as documented in published series (99), patients who experience serum sickness often have persistent IgE responses. Serum sickness is mediated by immune complexes, but this clinical phenomenon is a marker of patients who make IgE anti-penicillin antibodies and who may be at risk for an allergic reaction in the future when treated with penicillin.

The prevalence of positive skin test reactions changes dramatically with increasing time after the last known exposure to β-lactam drugs (99 and Fig. 2). Fourty-six of 63 subjects (73%) tested within 1 year after an apparent allergic reaction to penicillin were skin-test positive. Of those tested within 6 months of a reaction, 33 or 49 (67%) were positive; 13 of 14 (93%) of those tested between 6 and 12 months after a reaction were positive. These were not statistically significantly different ($p > 0.06$). The prevalence of positive skin tests 1 to 10 years distant from allergic reactions declined to 57%, a significant difference from 0 to 1 years after reactions ($p < .05$). Twenty-two percent of the subjects tested 10 years or more after a reaction were skin test positive, a significant decline from the prevalence 1 to 5 or 5 to 10 years after reactions ($p < .01$). Children were not significantly different from adults at any interval studied.

TABLE X

Patterns of Positive Penicillin Skin Test Reactions:
Method of Testing and Concentration of Reagents

Route and Concentration	Number of patients (% of total)
Percutaneous	
1:10,000	11 (2.3%)
1:100	25 (5.3%)
Concentrated	59 (12.6%)
Intradermal	
1:10,000	41 (8.7%)
1:100	83 (17.7%)
Concentrated	250 (53.3%)

From reference 107

As illustrated in Table X, a broad range of sensitivities is encountered among skin test positive subjects. Testing with concentrated reagents intradermally might cause serious difficulties in subjects who react to a 10,000-fold dilution by prick testing (2% of all tested). The use of dilutions adds time to the procedure, but provides ameasure of safety.

TABLE XI
Patterns of Positive Penicillin Skin Test Reactions:
Responses to Specific Reagents

Reagents Positive[a]	Number of Patients Positive [b]
Pen G	29 (6.2%)
PPL	120 (25.6%)
PA	34 (7.2%)
PA + Pen G	48 (10.2%)
PA + PPL	47 (10.0%)
Pen G + PPL	60 (12.8%)
Pen G + PPL+ PA	131 (27.9%)
TOTAL	469

a. Patients with 1+ or greater responses to percutaneous or intradermal testing with penicillin G (Pen G), penicilloyl-poly-L-lysine (PPL) or penicilloic acid (PA).

b. The data are presented as the number of patients and the percent of total patients.

From reference 99

The patterns of responses to specific reagents are illustrated in Table XI. Of particular interest is the observation that testing with penicillin G alone, penicilloyl poly-L-lysine alone or penicilloyl poly-L-lysine alone or penicilloic acid alone would have detected only 57%,

76% and 55% of the allergic subjects respectively. Omission of penicillin G, penicilloyl poly-L-lysine or penicilloic acid would have resulted in failure to detect 6%, 26% and 7% of the positive subjects.

In combination these agents define a group of subjects at risk for allergic reactions. Skin test negative patients are presumed to be free of IgE anti-penicillin antibodies and therefore free of risk of an allergic reaction. As discussed above skin test negative patients are at very low risk regardless of a history of previous allergic reactions. Table XII illustrates the Washington University experience from with skin-test negative patients from 1977-1979 (99).

TABLE XII

Results of β-lactam Antibiotic Therapy in History-Positive, Skin Test-Negative Patients

Treatment	Number of Patients	Reactions	
		Acute	Late
None	36	--	--
Penicillin G	32	0	0
Semisynthetic Penicillins	29	0	2
Cephalothins	23	0	0
Unknown	24	--	--

a. Acute reactions were designated as responses occurring within the first 48 hours of therapy.

DESENSITIZATION OF HISTORY-POSITIVE, SKIN TEST-POSITIVE PATIENTS

Alternative antibiotics are used when possible in β-lactam antibiotic allergic subjects who require antibiotics. Occasionally the risk of not administering β-lactam drugs is greater than the risk of an allergic reaction. If two-thirds of skin test positive patients react, and 10% of these will be anaphylactic reactions, and 10% of anaphylactic reactions are fatal the administration of conventional doses of β-lactam drugs to these patients could carry as high as a 0.7% mortality rate. In some instances of bacerial endocarditis, Pseudomonas sepsis or other infections, avoidance of β-lactam drugs carries a greater than 0.7% chance of contributing to a fatal outcome. Under these circumstances desensitization is considered.

In a word, premedication with currently available anti-allergic drugs is not sufficient to assure suppression of anaphylaxis.

The concepts that cross-linking of IgE molecules is obligatory for immediate hypersensitivity reactions to occur and that administration of appropriate concentrations of selected univalent ligands would prevent such reactions have been applied to the care of patients allergic to penicillin with an encouraging amount of success (128, 129). Fifteen patients presenting symptoms and signs of penicillin induced IgE mediated reactions, serum sickness reactions or hemolytic anemia were treated with benzylpenicilloyl-formyllysine (BPO-FLYS). Among 8 patients with immediate skin test reactions to penicilloyl-poly-L-lysine, all skin tests reverted to negative during BPO-FLYS therapy. Four of these skin test-positive patients had experienced what appeared to be pure IgE-mediated reactions during penicillin therapy. In three of these patients treated with BPO-FLYS, allergic signs remitted within 2 days and penicillin therapy was continued without incident. A fourth patient had a recurrence of allergic symptoms on low doses of BPO-FLYS which remitted when the dose was increased. Serum sickness and hemolytic anemia reactions also appeared to respond in other patients. A total of 12 of 13 treated patients tolerated continued penicillin therapy. Enthusiasm for this approach to penicillin allergic patients was dampened by Basomba et al. (130) when anaphylaxis was observed during penicillin therapy despite BPO-FLYS treatment. This reaction appeared to have been mediated by IgE antibodies directed against penicillin determinants which were not cross-reactive with BPO-FLYS. de Weck has presented evidence that univalent ligands can suppress human allergic reactions, but the known multiplicity of IgE responses against penicillin determinants limits the usefulness of a single inhibitor. A variety of univalent inhibitors appear to be necessary if this approach is to be routinely successful in penicillin sensitive patients.

Knowledge of the apparent relative safety of the oral route led Parker to use oral penicillin for the rapid desensitization of penicillin allergic patients (100). Skin test-positive patients with life-threatening infections for which alternative antibiotics were not available were treated without significant acute allergic complications. These results are in sharp contrast to the results of parenteral desensitization procedures. The experience of investigators attempting to "desensitize" history-positive patients (reviewed by Pedersen-Bjergaard, ref. 131) indicated that acute systemic allergic reactions occurred in the majority of instances despite the probability that a number of these patients were no longer sensitive to penicillin. Among skin test-positive patients desensitized by the parenteral route a similar frequency of severe reactions has been reported. Review of the results of the parenteral procedures applied to 22 patients (107, 132-144) indicates that 12 of the patients experienced acute systemic allergic reactions, at least 5 of which were life-threatening and 1 patient did die of laryngeal edema. Allusion has been made to an unreported death during attempted desensitization (134). This frequency of severe reactions approximates the expected frequency of reactions to full therapeutic doses in skin test-positive

patients. Thus oral β-lactam antibiotic therapy appears to be markedly safer than parenteral therapy and when these agents must be administered to skin test-positive patients, initial presentation by the oral route appears to minimize reactions to subsequent parenteral therapy.

In 1962, Dr. Charles Parker at Washington University in St. Louis began studies of oral desensitization in skin test-positive patients with an urgent need for penicillin. A brief report of his experience with the first patients has been presented (108). In all, 30 additional well characterized patients have been treated using the oral route for initial presentation of the drugs according to a set protocol. The increasing availability of alternative antibiotics has reduced the need for β-lactam antibiotics in some situations such as many cases of bacterial endocarditis. At the same time evolution of the β-lactam antibiotics themselves has broadened their usefulness and increased the number of situations where their use may be urgently needed, as for example in some cases of Pseudomonas sepsis.

The patients studied to date have been skin test positive to one or more penicillin reagent, have had proven life-threatening infections with in vitro culture sensitivities established, and have had deteriorating clinical courses on alternative antibiotics (if any were available). Bactaerial endocarditis (19 patients - penicillin therapy), Pseudomonas infections (9 patients - carbinicillin therapy), and Staphylococcal infections (2 patients - oxacillin therapy) have been the underlying illnesses and the drugs used to treat them.

Once the presence of IgE anti-penicillin antibodies have been demonstrated in patients with a definitive need for penicillin or a related β-lactam antibiotic, a constant procedure has been used. All physicians involved in the patient's care are consulted about the decision to proceed with desensitization. If they concur the patient and the patient's family are consulted and the situation with all alternative courses of action is discussed. If the patient and family agree to the procedure an intravenous line is established, epinephrine and aminophylline are drawn up for possible injection, and all adjunctive emergency medication and equipment is brought to the bedside. A physician is in attendance at all times during the procedure and the physicians and nursing personnel are warned about possible late reactions. The protocol for penicillin administration is presented below. If an oral form of the specific antibiotic is available, this is used in place of penicillin G, usually in the pediatric liquid form. Since most of these patients have been sensitized by penicillin G, other drugs would be expected to interact with the anti-penicillin antibodies less avidly.

PROTOCOL

Dose	Units	Route
1	100	P.O.
2	200	P.O.
3	400	P.O.
4	800	P.O.
5	1,600	P.O.
6	3,200	P.O.
7	6,400	P.O.
8	12,800	P.O.
9	25,000	P.O.
10	50,000	P.O.
11	100,000	P.O.
12	200,000	P.O.
13	400,000	P.O.
14	200,000	S.C.
15	400,000	S.C.
16	800,000	S.C.
17	1,000,000	I.M.

These doses are administered every 15 minutes during continuous monitoring for allergic reactions. Therapy is then conducted according to usual clinical practices. The responsible personnel are warned against any lapses in therapy (over 8 hours) which might permit an anaphylactic sensitivity to reappear. Any allergic reactions are carefully monitored and if necessary are pharmacologically suppressed.

Complications of oral desensitization of penicillin allergic patients

Deaths: None
Anapylaxis: None
Severe systemic reactions: None
Mild systemic reactions:
    Urticaria: 7
    Pruritic macular rash: 1
Late complications:
    Immune complex nephritis: 1

None of the cutaneous reactions were severe and were easily controlled with H-1 antihistamines. These responses appeared between 1 and 48 hours after exposure to penicillin. One patient developed hematuria, proteinuria, sterile pyuria and falling creatinine clearance from 112 to 62 ml/minute

beginning 3 weeks into penicillin G therapy for bacterial endocarditis. Therapy was halted. The renal abnormalities quickly reversed to normal, and the patient did not require additional therapy of any kind.

These results with oral penicillin desensitization are in accord with the clinical inferences of fewer and generally less severe allergic reactions associated with oral therapy. The contrast with results of parenteral desensitization are striking. Although it is difficult to design a reliable protocol to compare the two approaches because of marked patient variability, the data available indicate that the oral desensitization method may be quite effective in avoiding life-threatening allergic reactions to β-lactam antibiotics and may be vastly safer than the currently recommended parenteral approach.

Oral presentation has theoretical advantages over parenteral administration. First, preformed conjugates or polymers would be expected to be degraded and only a minute fraction of surviving molecules would be expected to be absorbed. Acute reactions would be reduced to the extent these molecules contribute to the reactions. Second, blood levels of reactive β-lactam agents would gradually rise after oral administration. This would favor the formation of univalent conjugates and would favor binding of free drug and univalent conjugates to cell bound IgE before the appearance of newly formed multivalent conjugates or injected multivalent conjugates or polymers. The more gradual binding of multivalent conjugates to IgE would favor desensitization rather than mediator release.

Mechanism of penicillin desensitization. Studies performed recently on two patients at Parkland Memorial Hospital have clarified the means by which subjects allergic to β-lactam drugs by history and on skin testing can tolerate these agents after oral desensitization. These patients were skin tested with penicillin reagents, histamine, a chemical mast cell stimulating agent 48/80, and a group of pollen allergens before and after desensitization. Several pollen skin tests were positive in each patient. Dose related responses to penicillin reagents diminished or vanished while histamine, 48/80 and pollen allergen dose response curves were unchanged. This pattern of change demonstrates that after desensitization 1.) cutaneous tissues remain responsive to histamine; 2.) mast cells retain abundant mediators that can be liberated by 48/80 and pollen allergens; 3.) there is specific unresponsiveness to penicillin determinants. Thus this penicillin desensitization procedure appears to result in a state of antigen specific unresponsiveness at the level of the mast cell.

This unresponsiveness could result from failure of multivalent conjugates to crosslink specific IgE because of competing univalent materials (hapten inhibition) or from a failure of crosslinked anti-penicillin IgE to deliver an effective signal for mediator release (specific mast cell desensitization). We were able to obtain evidence that hapten inhibition is at least partially responsible for this phenomenon. Skin testing was performed on one subject 30 minutes before and 30 minutes after intravenous infusions of 2 million units of penicillin G on 4 occasions. Penicillin skin test reactions were positive just before a dose of drug and became negative or markedly diminished immediately after a

dose. Much work remians to clarify these reactions and to determine the generality of these observations. Assuming the cutaneous response to be an appropriate model of systemic alterations, oral desensitization appears to lead to antigen specific unresponsiveness at the level of the mast cell. Hapten inhibition appears to contribute to the unresponsive state. It remains to be seen if actual abrogation of intracellular responses to IgE crosslinking also is active.

AN APPROACH TO PATIENTS REQUIRING β-LACTAM ANTIBIOTIC THERAPY

The information and concepts reviewed to this point indicate that ideally all patients should be skin tested before receiving β-lactam drugs. Currently this is impractical for two reasons: a period of at least 30 minutes usually is required to test each patient with most protocols and penicilloic acid is not commercially available. The National Institute of Allergy and Infectious Diseases is conducting a multicenter trial of penicillin skin testing in a vigorous attempt to persuade the F.D.A. to approve manufacture and use of the minor determinants. If N.I.A.I.D. is successful, penicillin skin testing reagents will be generally available and we may face a medico-legal obligation to screen all patients before therapy.

A compromise approach we currently recommend is:

1.) Patients requiring β-lactam antibiotic therapy should be questioned carefully about previous untoward reactions to this class of drug.

2.) History-negative subjects should receive their first dose by mouth if possible (meningococcal disease excepted). Anaphylaxis induced by an oral challenge should be manageable. Certainly such anaphylaxis would be milder than that following a parenteral injection. If no reaction occurs within 60 minutes, conventional therapy can be initiated. This maneuver alone might reduce death from β-lactam drug induced anaphylaxis to near zero. No direct data is available to assess this position at the present time, however.

3.) History-positive subjects should be skin tested. Many of these patients will be skin test negative and can be treated as if they were history-negative patients.

4.) Skin-test positive patients can receive alternative antibiotics or can be desensitized.

Skin testing of all patients before penicillin therapy would be expected to eliminate virtually all allergic reactions and even more likely would be expected to eliminate deaths from anaphylaxis. Skin testing also would permit use of the drugs of choice in the many patients who no longer are allergic to β-lactam drugs. The approach outlined above would be likely to minimize fatal reactions while not significantly reducing the incidence of allergic reactions in history-negative patients who are not skin tested.

The approach most physicians employ depends solely upon a drug allergy history. History-positive patients usually are given alternative (often toxic) antibiotics. History-negative patients receive full therapy. As noted above, this approach results in a disturbing frequency of allergic reactions and an unacceptable number of deaths.

TREATMENT OF ANAPHYLAXIS

Anaphylactic reactions can lead to death through hypotension resulting from peripheral vasodilation, laryngeal edema, severe bronchospasm or cardiac dysfunction (25-27). The strategy usually employed to reverse these reactions is to repeatedly administer epinephrine to arrest mediator release and reverse end organ responses to mediators, and to employ specific therapy to reverse any remaining life threatening respiratory or cardiovascular manifestations (145).

Treatment of anaphylaxis is based upon knowledge of the pathologic forces involved and fragmented experience. No controlled studies have been performed in man. The following is the approach in widest use in academic centers.

TABLE XIII

A General Approach to the Treatment of Anaphylaxis

Initial Management

1. Administer epinephrine, usually 0.3 ml of 1:1000 (300 micrograms) S.C.

2. Assess respiratory and cardiovascular status.

Specific Management

1. Protect the patency of the airway with vigilance, an endotracheal tube, airway needles or tracheotomy.

2. Administer aminophylline to relieve persistent bronchospasm - 7 mg/kg of body weight I.V. over 20 minutes followed by 0.9 mg/kg/hour.

3. Hypotension should be addressed with abundant isotonic fluids and with a norepinephrine drug if necessary.

4. Cardiac rhythm should be monitored. Arrhythmias are managed with conventional approaches.

5. A second resurgence of anaphylaxis 6 to 10 hours later should be anticipated with vigilance and glucocorticoid administration.

Epinephrine, the drug of choice, must be used carefully. A large bolus I.V. (in a hypotensive, hypoxic patient in whom an arrythmogenic intracardiac allergic reaction is in progress) can lead to serious ventricular arrhythmias. When possible (systolic pressure above 70) epinephrine is given S.C. If the patient has been treated with β adrenergic blocking agents for cardiovascular disease or β agonists for asthma (tachyphylaxis occurs) larger doses of epinephrine will be required. Doses can be repeated every 10 to 15 minutes if required.

Hypotension usually responds to epinephrine alone. Refractory hypotension can be reversed by the administration of fluids and norepinephrine. Dopamine has been ineffective in most instances in which it has been used in anaphylaxis.

Benadryl (100 mg) usually is given parenterally early in treatment to block H_1 receptors. This maneuver is logical, but it is considered to be of secondary importance to other measures because the impact of the drug appears to be modest in anaphylaxis compared to epinephrine. Recently, however, the administration of this H_1 blocking agent in combination with the H_2 blocking drug cimetidine (300 mg I.V. over 10 minutes) has appeared to reverse refractory hypotension during anaphylaxis (1 Parkland Memorial Hospital patient and 2 patients at the N.I.H.). This approach is unproven but may prove to be an effective means of suppressing histamine mediated cardiac and peripheral vascular derangements. In patients receiving β adrenergic blocking agents this approach should be considered promptly.

Recently several investigators have noted that a severe acute anaphylactic reaction often is followed by a resurgence of anaphylaxis 6 to 10 hours later. This must be anticipated with careful direct observation. Since glucocorticoids suppress late phase allergic reactions in the skin and the lung, a dose of 60 mg of prednisone or its equivalent is given once the patient is stabilized in an attempt to suppress late anaphylaxis.

Careful observation of patients after the administration of β-lactam antibiotics, administration of epinephrine at the first sign of a systemic allergic reaction and aggressive monitoring and management of complications should permit the rescue of at least 97% of patients experiencing anaphylaxis.

CONCLUSIONS

Studies of penicillin allergy have revealed many important aspects of human IgE-mediated reactions. Basic and clinical studies of immediate hypersensitivity in turn have led to improved management of penicillin allergy. We have new, effective methods to identify and to manage patients allergic to penicillin, but there are many unsolved problems.
blems.

The near future holds several exciting possibilities for new approaches. As the actions of SRS-A, PGD_2, histamine and other mast cell mediators on human tissue are clarified and more effective blocking agents are developed, new aproaches to anaphylaxis will emerge. We may become able to premedicate patients with potent mast cell suppressing agents and mediator blocking agents and not be concerned about desensitization. Several laboratories are developing methods to suppress IgE anti-penicillin antibody synthesis using suppressive conjugates and anti-ideotypic antibodies. Ten years from now at these rounds I hope to be able to describe maneuvers employed at the time of β-lactam antibiotic administration that suppress IgE responses to the drugs. For those patients who already are sensitized I hope to be able to describe therapy completely effective in blocking acute allergic reactions. Today we are capable of minimizing allergic reactions to penicillin. We look to the day when none occur.

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