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Review article

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Drug reactions: allergy and near-allergy

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CLASSIFICATION OF ADVERSE REACTIONS

A general classification of adverse drug reactions is given in Table 1, and will be discussed briefly. Most adverse reactions are toxic. Some toxic reactions mimic allergic reactions and will be discussed later. Some others are disease-associated, but are triggered by drugs and may also be misinterpreted as drug allergy. The classic reaction of this group was first described by Jarisch and Herxheimer, who observed chills, fever, localized edema, adenopathy and flareup of skin lesions during the treatment of syphilis with mercury. Penicillin treatment of these patients was associated with more severe reactions. Other drugs may produce similar reactions during treatment of spirochetal, enteric, parasitic, and fungal infections. When such reactions develop, the knowledgeable physician will continue necessary antimicrobial treatment while the reaction subsides.

Continuing with Table 1, ampicillin is associated with a high frequency of skin rashes when given to patients with infectious mononucleosis or lymphocytic leukemia, and gouty patients being treated also with allopurinol. The mechanisms involved remain speculative. The appearance of urticaria or a maculopapular skin eruption during treatment with any antimicrobial drug, especially in children, may be entirely coincidental because so many eruptions are manifestations of the illnesses being treated.

Allergy-like symptoms can be

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Table 1. Classification of Adverse Drug Reactions

Predictable Risk
1. Toxic: overdose or side effect
2. Toxic: delayed expression (teratogenicity, malignancy)
3. Superinfection
4. Drug interaction
5. Allergy-like side effects
Disease Associated
1. Increased toxicity secondary to impaired degradation and/or excretion of drugs due to organ system failure
2. Jarisch-Herxheimer reaction
3. Ampicillin reactions with infectious mononucleosis and other diseases
Coincidental
1. Infectious disease exacerbations
2. Controversial: Stevens-Johnson syndrome and other disorders with many suspected causes
3. Psychogenic
Risk to a Susceptible Subpopulation
1. Intolerance
2. Idiosyncrasy
3. Allergy

psychogenic. This is best known to those who conduct placebo-controlled clinical drug trials. Subjects may develop nasal congestion, urticaria, angioedema, or even anaphylactoid reactions while receiving only a placebo.

Two terms are used in the last section of Table 1 that need to be defined. *Intolerance* is an inherent, perhaps inborn condition in which a drug produces its expected toxic side effects at an unusually low dose. *Idiosyncrasy* is also an inherent condition in which the adverse reaction is pharmacologically unexpected (that is, different from the usual toxic reactions). Allergy will be discussed next.

ALLERGIC DRUG REACTIONS

Background

Little is known about reactions to the few specific drugs that were in use before 1900 other than their

obvious toxicity, derived (digitalis, for example) from natural poisons. Any allergic reaction would not have been recognized as such. Allergic reactions were first recognized after the introduction of horse serum antitoxins near the turn of the century. Serum sickness was the most common major manifestation of iatrogenic allergic reactions until the 1930s when new synthetic drugs then began to appear. By 1930 adverse reactions to such drugs were beginning to be reported; 3% of patients given phenobarbital, for example, developed reactions that were probably allergic. Drug allergy became a prominent problem when sulfonamides were introduced in the late 1930s. Allergic reactions to xenogenic sera and the early sulfonamides were very common (10% or more of those treated). Today, the incidence of reactions to drugs in common use is low. In the Boston Collaborative Drug Surveillance Study of hospitalized patients, the overall incidence of skin eruptions (by far the most common reactions) was about 0.3%, and exceeded 2% only for semisynthetic penicillins, trimethoprim-sulfamethoxazole, erythromycin, corticotropin, and trinitrobenzene.²

Characteristics

The allergic reaction is immunologically mediated. It differs from toxicity, intolerance, and idiosyncrasy in one fundamental characteristic; being immunologically mediated, it does not develop on first exposure to the drug. Prior treatment or several days of first exposure treatment is required for the patient to become immunologically sensitized. The terms *allergy* and *hypersensitivity* are synonymous and

will be used interchangeably in this review. The term *immune* is often applied to hematologic drug reactions. In general, the clinical features of drug allergy are restricted to a limited number of symptoms that are generally accepted as allergic. The reactions occur in a small proportion of the population, and their incidence is not significantly dose related. The risk of allergy cannot be predicted from animal testing. Ideally, allergy should be confirmed by immunologic tests but, as will be discussed, such testing has proven effective in only a few restricted circumstances. All too often, direct proof of allergy is lacking or can be provided only by readministering the suspected drug.

IMMUNOCHEMICAL PRINCIPLES

- X Foreign proteins such as horse serum-antitoxins and antithymocyte globulins are obviously complete antigens, and induce IgG antibody formation in all individuals who are capable of a normal immune response. If the titer of such antibodies is high enough, immune complexes may activate a sufficient amount of complement-derived mediators (anaphylatoxins, chemotactic factors) to produce allergic symptoms. Some individuals (not necessarily those with an atopic diathesis) will produce specific IgE antibodies, and develop typical anaphylactic manifestations. (Larger polypeptide hormones are similarly immunogenic. Molecules containing fewer than seven amino acids are not immunogenic, and most drugs in common use have molecular weights under 1000 daltons.) Such chemicals must be conjugated to a macromolecule, usually a protein or large polypeptide termed a carrier before they can become immunogenic.³ Such conjugation usually requires covalent bonding, and does not occur readily *in vivo*. A few organic compounds can form covalent bonds with carrier without synthetic manipulation. Only one of these has been firmly established as

an important reactant in man. This is the oxazolone (a type of anhydride) of penicillic acid, a metabolite of penicillin. It forms stable amide bonds with protein amino groups. This reaction was identified over twenty years ago, and is used to prepare the skin-testing conjugate, benzylpenicilloyl polylysine. Other penicillin metabolites have free -SH groups and have the potential to form stable mixed disulfides with cysteine. The immunogenicity of such conjugates has not been established in human allergy.

The penicillin experience led to considerable optimism that methods to test for allergy to other drugs would be developed by identifying and using their metabolites. Unfortunately, nothing has emerged from studies on any other drug that approaches the consistent and reproducible findings in patients with penicillin sensitivity. Acetaminophen-induced immune thrombocytopenia was shown to be due to a sulfate metabolite in one patient but such reports are rare.⁴

TYPES OF CLINICAL REACTIONS

A classification of reactions that may be caused by drug allergy is given in Table 2. Examples of drugs that may be responsible are included for each category. The clinical features of the various reactions, and complete drug listings classified by reaction are readily available in standard allergy texts.^{1,5} The best source for listings classified by drug would be, of course, pharmacology texts or drug information services. Whenever the sensitivity mechanism has been identified, the reaction usually turns out to be IgE antibody or T-cell mediated (Coombs and Gell classes I and IV). The occasional drug-induced reactions mediated by cytotoxic antibody (Type II) or immune complexes (Type III) are found in the hematologic or autoimmune categories. The following are selected topics related to the mechanisms of drug reactions.

Mast Cell-Mediated Reactions

When given to a sensitive person, an allergen reacts with specific IgE

Table 2. Classification of Allergic Drug Reactions (with Examples)

Mast Cell Mediated	
Systemic anaphylaxis:	penicillins, polypeptides, proteins
Serum sickness:	same, plus hydralazine, sulfonamides, thiazide diuretics
Urticaria and angioedema:	same, plus aminoglycosides, barbiturates
T-Lymphocyte Mediated	
Allergic eczematous contact dermatitis:	ethylenediamine, neomycin, parabens
Photodermatitis (systemic)	
Allergic:	griseofulvin, nalidixic acid, sulfonamides
Toxic:	chlorpromazine, demeclocycline, doxycycline
Other Cutaneous reactions (mechanism uncertain)	
Maculopapular or exanthematous:	most drugs
Toxic epidermal necrolysis:	allopurinol, ibuprofen, penicillin, phenytoin, sulfonamides
Fixed eruptions:	metronidazole, penicillins, phenolphthalein, sulfonamides
Drug Fever	
	Allopurinol, barbiturates, cephalosporins, penicillins
Systemic Lupus Erythematosus and Other Autoimmune Reactions	
	Hydralazine, procainamide, penicillamine
Organ Systems	
Hematologic	
Eosinophilia:	allopurinol, aminoglycosides, penicillamine, phenothiazines
Anemia-hapten-cell type:	disulfiram, penicillin; innocent bystander type: chlorpromazine; sulfonamides
autoimmune type:	methylidopa
Thrombocytopenia:	gold salts, hydantoins, quinidine, thiazide diuretics
Granulocytopenia:	gold salts, phenothiazines, sulfonamides
Hepatic	
Cholestatic:	erythromycin estolate, phenothiazines
Hepatocellular:	allopurinol, gold salts, hydantoins, valproic acid
Granulomatous:	allopurinol, quinidine
Pulmonary	
Eosinophilic pneumonitis:	gold salts, penicillins, sulfonamides
Other infiltrative:	gold salts, nitrofurantoin, thiazide diuretics
Fibrotic:	antineoplastic agents, methysergide, nitrofurantoin
Renal	
Interstitial nephritis:	cimetidine, methicillin
Mixed:	allopurinol, phenytoin
Nephrotic syndrome:	captopril, gold salts, penicillamine
Cardiac	
Eosinophilic myocarditis (rare):	methylidopa, sulfonamides

antibody on the surface of mast cells and basophils. The result is the rapid, often explosive, release or activation of potent mediators such as histamine, leukotrienes, and chemotactic factors. Antibodies can be found consistently in individuals sensitive to xenogenic sera, polypeptide hormones, and injected enzymes. As discussed earlier, antibodies to small molecular weight drugs have not been consistently identified with the exception of the penicillin group of drugs.

T-Lymphocyte-Mediated Reactions

Most of these develop after cutaneous contact, and are characterized by infiltration of lymphocytes and other mononuclear cells. Various lymphocyte mediators of inflammation (lymphokines) are responsible for the tissue injury in cell-mediated reactions. These mediators have been identified in numerous tissue culture studies on the cell responses to mitogens and proteins such as tuberculin. By inference, the same responses should take place on exposure to drugs. But tissue culture studies in which lymphocyte mitogenic responses and the generation of a standard lymphokine, migration inhibition factor, are measured in the presence of the sensitizing drug have not led to any consistent pattern of response. Our understanding in this area should become clearer with the recent identification of discrete lymphokines and monokines such as the interleukins and gamma interferon.

Photodermatitis

The photoallergic reaction appears only after the drug has been used for the period of time necessary for sensitization to develop. It is provoked by wavelengths of 320 to 450 nm. The mechanism of photoallergy is uncertain. The drug or metabolite may conjugate to dermal protein and serve as a hapten in the presence of solar energy. The phototoxic reaction will develop immediately after treatment is started, assuming there is sufficient ultraviolet light exposure. The sunburn-

like reaction is provoked by sunburn wavelengths (285 to 310 nm). Phototoxic drugs absorb and concentrate ultraviolet energy in the skin.

Autoimmune Reactions

Systemic lupus erythematosus. Most patients with symptomatic drug-induced lupus have predominantly antihistone antibodies.⁶ The prevalence of positive antinuclear antibodies increases with the duration of treatment. The drugs may render native nucleoprotein antigenic on a dose-related basis.⁷

Penicillamine has been implicated in several immune complex disorders. The most noteworthy is a myasthenia gravis-like reaction; anti-acetylcholine receptor antibodies and anti-striated muscle antibodies have been identified in the sera of some patients.⁸

Hemolytic Anemia

Three types of immune mechanisms may be responsible for red cell injury

1. *Hapten-cell or drug adsorption type.* The offending drug or its reactive intermediate binds to some portion of the red cell membrane. Since the immunogenicity of the drug relates more to its serum protein binding than to its binding to that membrane, "drug adsorption" may be the more accurate term for this category.⁹ This type was first described as a Coombs-positive anemia that developed during high-dose penicillin treatment of patients with high-titered IgG antibody which reacted with red cells having penicillin or a metabolite intercalated into their surface membranes.

2. *Immune complex type.* When IgG or IgM antibody has specificity for an epitope on a drug or drug metabolite, the antibody forms a complex with the antigen (bound to a macromolecular carrier) in the circulation. This antigen-antibody complex may come into contact with red cells only transiently, while the membrane attack complex of complement remains to produce the injury. Recently, certain receptors

for immune complexes have been identified on red cells, suggesting that active binding may occur.⁹ *Nomifensine*, an antidepressant drug (not available in the United States), causes hemolytic anemia associated with complement-fixing IgG and IgM antibodies that react primarily with its metabolites. Of most interest, the best source of these antigens was the urine from a normal person who had been given the drug. Most of these "ex vivo" metabolites have not yet been identified.¹⁰

3. *Autoimmune.* In this type of reaction, drug administration may lead to the production of an IgG autoantibody directed against an intrinsic red cell antigen with Rh specificity. The direct Coombs antiglobulin test is strongly reactive, but the anticomplement test is not. The most commonly implicated drug, *methyldopa*, inhibits the function of suppressor lymphocytes, including those that prevent the unrestrained production of autoimmune antibodies.¹¹

Renal Reactions

Interstitial nephritis is the most common drug-induced hypersensitivity reaction. The renal biopsy shows tubular degeneration and necrosis with mononuclear cell, plasma cell, and eosinophilic infiltrates. Most of these mononuclear cells are T-lymphocytes. Renal reactions have been reviewed in detail recently by Adler et al.¹²

Reactions with Inconsistent Drug Associations

Erythema multiforme and the severe mucocutaneous and bullous form known as *Stevens-Johnson syndrome* are associated most often with mycoplasma, herpetic and other infections, neoplasms, connective tissue diseases, and radiation therapy. In only a few instances has a report been published in which the offending drug was inadvertently readministered, with the reappearance of a skin eruption. *Minoxidil*, *phenolphthalein*, *rifampin*, and *trimetho-*

prim-sulfamethoxazole were the drugs involved.

About 10% of cases of *exfoliative dermatitis* are thought to be drug-induced; the remainder are associated with diseases such as psoriasis, atopic dermatitis and lymphocytic malignancies. Cutaneous or cutaneo-systemic *vasculitis* is probably an immune complex disease, and can be associated with various infections such as hepatitis B. Probably no more than 10% are drug induced. There is only one published report in which the vasculitis reappeared when the offending drug (cimetidine) was given again.¹³ No evidence other than a few anecdotal reports supports any association between drugs and either *erythema nodosum* or *Henoch-Schonlein purpura*.

PSEUDOALLERGIC REACTIONS

Allergy-like side-effects can be produced directly by certain drugs in the absence of any evidence of hypersensitivity. In contrast to true allergic reactions, these occur promptly the first time the drug is given or appear only when the dose is increased. The mediator releasers produce reactions that are similar to anaphylaxis but, not being immunologically mediated, are more properly termed *anaphylactoid reactions*. The reaction occurs most frequently when the offending substance is given rapidly intravenously, producing a *diffuse flush*, *pruritus*, *urticaria*, and *transient hypotension*, followed by *headache*. Curare drugs, opiates, polymyxins, and pentamidine are examples of such releasers. By far the most common causes of clinical reactions, though, are the iodinated radio-graphic contrast media. The risk of *anaphylactoid reactions* to these substances has been reported as high as 2.5%; most of the reported reactions occur in adults between 20 and 50 years of age.¹⁴ Contrary to a widely held belief, there is no association with iodine or seafood sen-

sitivity. The symptoms are the results of the direct release or activation of mast cell and complement-derived vasoactive mediators. A reaction is more likely to occur if the material is hyperosmolar, a large amount is given, or it is given rapidly. The incidence of reactions among those who had previous reactions is 10% to 50%. Pretreatment with antihistamines, diphenhydramine and, perhaps ephedrine can reduce the incidence to 5%.

Antihypertensive drugs may produce or aggravate respiratory symptoms. The best known is reserpine, which produces predictable dose-related nasal stuffiness and/or discharge. Others are hydralazine and alpha-adrenergic blockers. Anticholinesterase and mediator releasing drugs also may produce nasal symptoms. Asthma can be made worse by beta-adrenergic blocking agents and by anticholinesterases.

Another antihypertensive agent, captopril, blocks an angiotensin-converting enzyme. This enzyme is also a kininase, and the dose-related skin eruptions that occur with the drug are probably caused in part by the inhibition of kinin degradation.¹⁶ Enzyme inhibition may also be the mechanism by which aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) exert certain adverse effects.

At one time, aspirin reactions were thought to be among the most common examples of drug allergy. When similar reactions began to appear from anti-inflammatory drugs of significantly different chemical structure, it became clear that these drugs, although not immunochemically cross-reactive, were pharmacologically similar.¹⁷ These drugs share the property of inhibiting the enzyme cyclooxygenase, and thus the generation of prostaglandins and thromboxanes from arachidonic acid. Susceptible patients have a history of asthma and/or chronic rhinosinusitis. Many have nasal polyps and most have blood and tissue eosinophilia. Most developed their first respiratory symp-

toms as adults and are not atopic. About 4% of unselected adult asthmatic patients give a history of symptoms provoked by a NSAID, and as many more will show a drop in ventilatory function after drug challenge. Up to 40% of patients with asthma, rhinosinusitis, and nasal polyps are intolerant or will become so. Some have their symptoms for several years before intolerance develops although it is not uncommon for a patient with a history of rhinosinusitis to have the first asthma attack provoked by aspirin.¹⁸ Severe reactions can be anaphylactoid, leading to shock and death. Aspirin also aggravates symptoms in about one-third of patients with chronic urticaria, angioedema, and other skin eruptions initiated by aspirin are rare.

Another category, the sulfiting agents, are food and drug additives that delay bacterial spoilage, minimize discoloration of various foodstuffs during processing, storage and distribution, and inhibit undesirable micro-organisms during wine making and other fermentation processes. Metabisulfites are used in restaurants on lettuce, processed potatoes, and shrimp; sulfiting agents are found in a variety of other foods as well, and are used also in numerous drugs, including some bronchodilator solutions.¹⁹ The symptoms produced by sulfiting agents in susceptible people are *flushing*, *urticaria*, *angioedema*, *laryngeal edema*, *asthmatic wheezing*, and *potentially fatal anaphylactoid shock*. Sulfite reactions most likely are mediated via irritant receptors in the upper airways through neural reflexes and vagal efferent pathways. As many as 10% of asthmatic patients may be at risk for a sulfite reaction and at least four deaths have been reported to the Food and Drug Administration. The restaurant use of sulfites has been drastically curtailed over the last year.

Compared to the sulfites, two other additives, tartrazine (FDA yellow #5) and sodium benzoate are of minor significance. They produce

ure or inadequately documented
diverse reactions.

MANAGEMENT

Prevention

All would agree that reducing the incidence of drug reactions is a commendable goal. Much has been done in this regard through refinements in the manufacturing process. The absolute number of reactions can be reduced further by prescribing only drugs with a clear-cut indication for use. As an example of the need for improvement, a recent report on severe reactions to allopurinol determined that the drug was prescribed inappropriately in more than half the cases.²⁰

Taking a careful history is of paramount importance to document any previous drug reaction. It is important to find out the name and chemical nature of the drug, the symptoms, and the nature of the illness being treated at the time. It is important to be careful in selecting and prescribing any drug for someone who gives a history of allergy to several different drugs. A history of other, non-drug allergies is much less important.

In taking a history, one should ask about the use of aberrant remedies. Herbal products may be fortified with ephedrine, N.S.A.I.D.s, psychotropic agents, or thiazide diuretics. The herbal products themselves may contain a wide variety of plant allergens. Chamomile tea is prepared from flower heads that cross-react with ragweed. "Pollen" causes anaphylaxis. Ginseng can produce skin eruptions as well as toxic side effects. Anise seeds may induce a reaction similar to systemic lupus erythematosus. "Cellular therapy," consisting of injections of various animal tissues, has obvious and potentially severe risks.²¹

X Routine skin testing before treatment is appropriate before giving any xenogenic protein or large polypeptide. This includes streptokinase, which has produced some severe reactions and deaths when used

to lyse coronary artery clots. Routine testing has not proven to be necessary before treating with penicillin or its homologues.²² Premedication has been used routinely before giving the enzymes chymopain or streptokinase, but this is not as effective as routine skin testing in preventing severe reactions. Premedication is no longer used routinely before administering a radiographic contrast agent.

The Patient with a History of Drug Allergy

If the patient gives a history of allergy to the drug being considered for treatment, one should try to use a drug that is not known to cross-react with the suspect drug, but is equally effective. For example, a new β -lactam antibiotic, aztreonam, has no apparent allergic cross-reactivity with the penicillins.²³ If no alternative exists, then one should test for allergy, if a reliable test exists.

Tests. Prick and intradermal skin testing is reliable for identifying IgE-mediated allergy to xenogenic sera and large polypeptides or polysaccharides. Serologic methods for measuring IgE antibodies, namely the radioallergosorbent test (RAST) and the enzyme linked assay (ELISA) are available for testing to some agents, but are more expensive, less sensitive, take longer than skin testing, and add no additional information. Whereas routine skin testing to macromolecular agents can begin with a 1:10 dilution, it is prudent to start with a dilution of 1:1,000 if the patient gives a history of a prior allergic reaction or is about to receive an agent about which little is known. If the previous reaction was life-threatening, the first test should be a prick test using a 10⁻² dilution.

With the exception of penicillin, testing for allergy to drugs of small molecular weight or their metabolites is not, in general, reliable. The penicillin metabolite that forms a stable conjugate with macromolecular carriers was mentioned earlier.

PPL
It is commercially available as penicilloyl polylysine. Skin tests using this reagent will be positive in most patients who are truly allergic. For this reason it is called the major determinant. But it may not detect sensitivity in patients in whom reliable testing is needed the most: those at risk for anaphylactic reactions. Fortunately, almost all of them have positive skin reactions to penicillin G (PG) itself; a very small number have been found to react only to other metabolites. A standard mixture of PG and the others, called the minor determinant mixture has been tested using hospitalized patients in eight medical centers in the United States. In our study of such patients, approximately 85% of those who gave a history of penicillin allergy were no longer allergic by skin test, which was confirmed by subsequent uneventful treatment.²² A larger percentage, of course, would have given positive tests if the tests had been done 6 months or less after their reaction. We thus have been able to reduce the need to use alternative, often more toxic antimicrobial agents to a small proportion of history-positive patients.

For other drugs of low molecular weight, skin tests are not reliable (with isolated exceptions). Serologic tests are no better, except for the tests used to confirm drug-induced hematologic reactions and most of these are done reliably only in research laboratories. As mentioned earlier, T cell-mediated allergy is suspected in a large proportion of drug reactions and should be identified by demonstrating drug-induced lymphocyte stimulation in tissue culture. Despite its value as research procedure, the usefulness of lymphocyte stimulation for diagnosing drug allergy, either prospectively or retrospectively, has yet to be established. XX

Provocative Testing

The only definitive test for drug sensitivity is to give the drug again under controlled conditions. The patch

skin-test is the most commonly used **provocative-test**. This is used to identify the cause of drug-induced allergic eczematous contact dermatitis. Any positive reaction develops in 48 to 72 hours as a pruritic, erythematous, and vesicular eruption similar to the original reaction, but limited in severity and in scale. Other situations in which a provocation test may be indicated (when the offending drug is in doubt) are those in which the anticipated reaction is benign. Drug fever and the fixed eruption are good examples.

When there is a history of a more severe reaction than the above examples, the suspected agent is the best available one to use, then careful challenge testing will be necessary. This is done by giving a small dose at first, orally if possible, and increasing the dose until the therapeutic dose unless the prior reaction was a severe one, in which case, the starting amount should be 100 or 1,000-fold lower. Doses should be repeated in 10-fold increments every 15 to 30 minutes (depending on the route of administration). If any symptoms appear, the test should either be terminated or, if the need for the drug is sufficiently great, should evolve into a desensitization attempt. Properly maintained emergency resuscitative equipment must always be at hand whenever provocation testing and/or desensitization is carried out.

Desensitization

In a sense, this is an extension of provocation testing in which the goal is to allow therapy rather than simply to prove allergy. It was used with considerable success to overcome sensitivity to antituberculosis drugs in the years before alternative first-line drugs became available. Recently, reports have begun to appear describing the successful slow desensitization of patients to currently useful drugs such as carbamazepine, sulfasalazine, and even allopurinol. Sulfasalazine desensitization is most often needed because

there is no good alternative drug for the treatment of inflammatory bowel disease.²⁴ The usual starting dose is 1 mg, doubled daily until the 2-gram therapeutic dose is achieved. The dose is reduced temporarily if a reaction occurs; medication for the reaction is not usually needed.

Desensitization to other agents is done more rapidly. The patient who is sensitive to (xeno)genic serum is given 0.1 mL subcutaneously of the smallest tenfold dilution that gives a positive skin test. The dose is doubled every 15 minutes until 1 mL of the undiluted serum has been given. This dose is then given intramuscularly, followed by the full therapeutic amount.

Penicillin desensitization is most often used when there is an urgent need to treat the skin test-positive patient. Thus it should be completed as soon as possible. Desensitization can be carried out successfully by oral or parenteral routes. The oral program begins with 100 units as a rule; it is safe and takes up to five hours to complete.²⁵ In the intravenous program, a solution of benzylpenicillin or a homologue is delivered according to the method given in Table 3. Each infusion is given slowly at first, then gradually more rapidly until warning symptoms such as pruritus and flush develop. If any symptoms develop, the flow rate is reduced and the patient is given an antihistamine and a glucocorticoid drug. The flow rate is

Table 3. Intravenous Method for Penicillin Desensitization (all solutions prepared in dextrose/water: 50-mL plastic bags for piggyback delivery)

Bag #	Concentration units/mL or µg/ mL	Total dose units or µg
1†	0.01	0.5
2	0.1	5
3	1	50
4	10	500
5‡	100	5,000
6	1,000	50,000
7	10,000	500,000
8	Full dose	

* For simplicity of preparation, a unit of benzylpenicillin is equated with 1 µg rather than the actual value of 0.6 µg.

† Starting point if prick test is strongly positive.

‡ Starting point if only the intradermal test is positive.

increased again when the symptoms are gone. Thirty minutes should be sufficient to administer each dilution, and the full therapeutic dose can be reached in most cases within three hours.^{1,26}

Insulin desensitization is rarely necessary today, because human insulin is readily available as an alternative for treating allergic patients. The patient who reacts even to human insulin is rare, but does exist.²⁷ Experience with human insulin desensitization is still limited. Conventional desensitization (using pork insulin) starts with the lowest concentration that gives a positive skin test, and proceeding with tenfold increments given subcutaneously as often as every 15 minutes until a local reaction occurs. The next dose is lower, and following doses are increased at smaller increments.

Patients with rheumatoid arthritis and allied conditions who are intolerant to aspirin and other NSAIDs can be desensitized successfully.¹⁸ Usually, tolerance can be achieved in a few hours (albeit with some risk of a severe asthmatic reaction) by giving gradually increasing doses every three hours, beginning with the lowest dose that provokes symptoms (may be as little as 10 mg). Tolerance is maintained by taking the drug every day; it may lapse if drug treatment is missed for more than two days. Desensitization may reduce the underlying respiratory symptoms of aspirin-sensitive patients somewhat, but the marginal improvement is not worth the risk for most patients.

SUMMARY

In this review, allergic drug reactions are discussed in terms of their immunologic mechanisms, with an emphasis given to new information that has appeared recently in the medical literature. Because of their recent emergence as important categories to recognize and manage appropriately, the pseudoallergic reactions next receive special attention. The last section on management covers diagnostic and preven-

strategies, and concludes with a discussion of desensitization.

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ME Examination

Identification No 006-011

Questions 1-20, 305: P P VanArsdel, Jr, ND: *Ann Allergy* 1986;57: 305-312.

ME TEST QUESTIONS

1. For a therapeutic agent to be allergenic, it must have which of the following characteristics:
 - a. Contain seven or more amino acids
 - b. Be capable of forming a stable conjugate with a protein
 - c. Be converted in the body to a haptenic metabolite
 - d. All of the above
 - e. Any one of the above
2. Drug idiosyncrasy is defined as
 - a. A noncutaneous allergic reaction
 - b. A toxic reaction occurring at a low drug dose
 - c. The adverse effect of any drug interaction
 - d. A pharmacologically unanticipated nonimmunologic reaction
3. A routine history reveals a probable allergic reaction to penicillin 4 years ago. What should you do:
 - a. Arrange for skin testing with penicilloyl polylysine and penicillin G
 - b. Advise the patient that alternative antibiotics are available for most future infections. If not, skin testing can then be done
4. Tell the patient never to allow treatment with a penicillin or a cephalosporin
5. Premedicate with an antihistamine and prednisone before giving a penicillin
6. Routine skin testing of all patients before treatment is appropriate for which of the following agents:
 - a. Diatrizoate sodium
 - b. Cosyntropin

- c. Influenza vaccine
d. Penicillin G
e. Streptokinase
- 5-9. Match the following drug reactions with the most likely mechanism:
- Toxic-idiosyncratic
 - Allergic
 - Enzyme inhibition
 - Pharmacological effect
 - Intolerance
- Propranolol asthma
 - Polymixin urticaria
 - Severe drowsiness from chlorpheniramine
 - Allopurinol fever
 - Indomethacin asthma
10. Which one of the following is *least* likely to be drug-induced?
- Eosinophilic pneumonitis
 - Cholestatic hepatitis
 - Erythema multiforme
 - Fever
 - Erythema nodosum
11. The frequency of maculopapular skin rashes with ampicillin therapy is high in the presence of certain other conditions. Which of the following is *not* one of these?
- Treatment with allopurinol
 - Asthma, sinus disease, and nasal polyps
 - EB virus infection
 - Lymphocytic leukemia
12. The risk of an allergic reaction to glyburide, a new oral anti-diabetic drug, is likely to be greatest in the patient with which history?
- Severe ragweed hayfever
 - Urticarial reaction to insulin
 - Generalized pruritic skin rash from a sulfonamide
 - Jaundice from erythromycin estolate
13. The most common drug-induced hypersensitivity renal reaction is
- Nephrotic syndrome
 - Immune complex glomerulonephritis
 - Vasculitis
 - Interstitial nephritis
 - Anti-GBM nephritis
14. Which of the following drugs has *not* caused an autoimmune reaction?
- Vancomycin
 - Penicillamine
 - Methyldopa
 - Hydralazine
 - Procainamide
15. Which of the following reactions has *not* been shown to be caused by a drug metabolite:
- Penicillin urticaria
 - Nomifensine hemolytic anemia
 - Hydralazine lupus
 - Acetaminophen thrombocytopenia
16. Your patient is scheduled for a coronary angiogram using Conray 60. Which of the following is a correct statement? (one or more)
- The patient gives a history of a skin rash from an iodine antiseptic, and thus there is a substantial risk of a Conray reaction
 - The patient had a previous reaction from an intravenous pyelogram with Hypaque, but there is no additional risk since a different agent is to be used
 - The patient has had no previous reactions, but it is prudent to give a small test dose of Conray before proceeding
 - The patient reports a previous contrast medium reaction, so the angiogram cannot be done
 - The patient reports a previous contrast medium reaction, so should be given appropriate premedication before Conray is administered
17. Allergic patients have been desensitized successfully to all but one of the following. Select that one:
- Sulfasalazine
 - Iodinated radiographic contrast media
 - Insulin
 - Diphtheria antitoxin
 - Carbamazepine
18. What is the most common cause of erythema multiforme?
- Sulfonamides
 - Rifampin
 - Phenytoin
 - Penicillin
 - Mycoplasma
19. A positive skin test to penicillin G indicates that
- The risk of anaphylaxis with penicillin treatment is high
 - The RAST currently used by laboratories should be positive also
 - Desensitization to penicillin is contraindicated
 - The risk of anaphylaxis with oral amoxicillin is low
20. Anaphylactoid reactions may occur with which of the following:
- Streptokinase
 - Phenytoin
 - Polymyxin B
 - Penicillin
 - All of the above