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Drug allergy—Problems and strategies

Richard D. DeSwarte, M.D. Rockford, Ill.

Today, the physician is confronted with a large and growing number of pharmacologic agents with which to diagnose, treat, and prevent human illnesses. This admittedly desirable circumstance has been associated with an increased incidence of adverse reactions to these agents that may produce additional morbidity and, on occasion, mortality. It is a sobering fact that adverse drug reactions probably account for the majority of iatrogenic illnesses. This should serve as a warning to physicians not to prescribe potent and often unnecessary drugs for treatment of minor illnesses. On the other hand, a clinician should not deprive a patient of indicated therapy for fear of a reaction.

The overall incidence of adverse drug reactions in the general population is unknown. However, some indication of the problem is obtained from surveys of hospitalized medical patients where the prevalence ranges from 6% to 15%. The incidence on other hospital services appears to be much lower. Approximately 3% of all acute care medical ward admissions and 0.3% of general hospital admissions are attributed to adverse drug reactions. Fortunately, fatal drug reactions are rare.¹ Unfortunately, only a small pro-

Abbreviations used

SLE:	Systemic lupus erythematosus
PPL:	Penicilloyl polylysine
BP:	Benzylpenicillin
MDM:	Minor determinant mixture
RCM:	Radiographic contrast media

portion of adverse drug reactions occurring in outpatients are voluntarily reported to pharmaceutical companies and appropriate national registries.

It is clear that the above information provides only a rough guide to the incidence of adverse drug reactions. Surveys are complicated by the problem of differentiating between signs and symptoms caused by the natural disease and those related to its treatment. Adverse drug reactions may mimic virtually every disease, now replacing syphilis as the "great imitator" of the modern era. The challenge of monitoring adverse drug reactions is further complicated by multiple drug prescribing and the frequent use of nonprescription medications.

This discussion is primarily concerned with *allergic drug reactions* that account for 6% to 10% of all observed adverse drug reactions; fortunately, death from an allergic drug reaction is rare with an esti-

Reprint requests: Richard D. DeSwarte, M.D., Rockford Clinic, Ltd., 2300 North Rockton Ave., Rockford, IL 61103.

mated risk based on hospital surveys of 1 in 10,000.² Obviously, one cannot cover all aspects of drug hypersensitivity, but several excellent reviews are available that will be liberally drawn on for this discussion and will provide readers with more in depth information and excellent bibliographies.³⁻⁷

It is estimated that approximately 5% of the adults in the United States may be allergic to one or more drugs. However, as many as 15% believe themselves to be allergic to medication(s), and therefore may be denied treatment with an indicated drug. On occasion it may be imperative to establish the presence or absence of allergy to a drug when it is necessary, and there are no safer alternatives. The *problems* inherent in defining drug allergy will be discussed. Recognizing that such is often impossible to accomplish with certainty (for reasons to be cited), a review of management *strategies* that have evolved to deal with these problems will be presented.

CLASSIFICATION OF ADVERSE DRUG REACTIONS

Before proceeding with a discussion of drug hypersensitivity, it is useful to place this in perspective with other adverse drug reactions. Adverse drug reactions can logically be divided into two major groups: (1) those which are *predictable*, usually dose-dependent and related to the pharmacologic actions of the drug(s) and thus occur in otherwise normal patients, and (2) those that are *unpredictable*, often dose-independent and are related to the individual's immunologic response (allergy or hypersensitivity) or, on occasion, to genetic differences in susceptible patients (idiosyncrasy and, perhaps, intolerance). It is estimated that 80% of adverse drug reactions are predictable. Although it may be difficult to categorize a particular drug reaction, the following provides a useful classification.⁶

Predictable adverse reactions occurring in normal patients

Adverse reactions are (1) overdosage or toxicity, (2) side-effects of immediate expression or delayed expression (carcinogenicity and teratogenicity), (3) secondary or indirect effects, and (4) drug interactions.

Unpredictable adverse reactions occurring in susceptible patients

Adverse reactions are (1) intolerance, (2) idiosyncratic reactions (pharmacogenetics), and (3) allergic and pseudo-allergic reactions.

Not included in this classification are those reactions that are unrelated to the drug itself but are attributable to events associated with and during its

administration. *Psychophysiologic reactions* in the form of hysteria or hyperventilation may follow parenteral administration of a drug. *Coincidental reactions* as a result of the disease may be incorrectly attributed to the drug, e.g., the appearance of a viral exanthem during a course of treatment with an antibiotic.

Most serious adverse drug reactions are *toxic* in nature and are directly related to the total amount of drug in the body. *Side-effects* are the most frequent adverse drug reactions and are often unavoidable at usual prescribed dosages. Some side-effects are delayed in expression and would include carcinogenicity and teratogenicity. *Secondary effects* are an indirect, but not inevitable, consequence of the pharmacologic action(s) of the drug, e.g., oral and pharyngeal candidiasis occurring in a small percentage of patients with use of inhaled beclomethasone for treatment of asthma. *Drug interactions* pose a constant threat, particularly when several physicians are treating a patient, each for a separate condition.

Intolerance refers to a lowered threshold to the normal pharmacologic action(s) of the drug, e.g., tinnitus experienced by some patients with normal or even smaller doses of aspirin. While intolerance usually implies a quantitatively increased pharmacologic effect occurring among susceptible individuals, *idiosyncrasy* and *hypersensitivity* are qualitatively aberrant and inexplicable in terms of the normal pharmacology of the drug.

Idiosyncratic reactions occur in susceptible individuals who possess a genetically determined metabolic defect or enzyme deficiency, not expressed under normal conditions, that becomes clinically manifest after administration of certain drugs. The study of this interesting group of adverse drug reactions has been termed pharmacogenetics. The most familiar example is the hemolytic anemia occurring in those with a deficiency of glucose-6-phosphate dehydrogenase when they are treated with primaquine and other oxidant drugs.

Ideally, the term *allergy* or *hypersensitivity* should be restricted to those reactions in which an immunologic mechanism is present or, more often, presumed. Such a mechanism is often difficult to establish with certainty. *Pseudo-allergic reactions* have similar clinical manifestations and may share common pathogenic mechanisms, but the initiating event does not appear to involve a reaction between the drug and specific antibodies and/or sensitized T-lymphocytes. Criteria that may be helpful in distinguishing allergic from other adverse drug reactions are:

1. Allergic reactions occur in only a minority of patients receiving the drug.

2. The observed manifestations do not resemble the known pharmacologic actions of the drug.
3. Prior exposure to the drug may be tolerated without adverse effect. Allergic reactions to drugs rarely develop after less than 1 wk of continuous treatment in patients who have not received the drug previously. After sensitization, the reaction may develop rapidly upon reexposure to the drug. In general, drugs that have been used with impunity for several months or longer rarely are the culprits in producing drug allergy. This temporal relationship is often most helpful in determining which of several drugs being administered need to be considered most seriously as the cause of a suspected drug hypersensitivity reaction.
4. The reaction may conform to manifestations generally acknowledged as being allergic in nature, e.g., anaphylaxis, urticaria, serum sickness-like reactions, and bronchial asthma; often they do not. A variety of skin rashes, pulmonary reactions, drug-induced fever, hepatitis, acute interstitial nephritis, and connective tissue disorders have been attributed to drug hypersensitivity.
5. The reaction may be reproduced by administering small doses of the suspected drug or other agents possessing similar or cross-reacting chemical structures.
6. Blood and/or tissue eosinophilia may be helpful if either is present.
7. On occasion specific antibodies and/or T-lymphocytes have been identified that react with the suspected drug.
8. The reaction usually resolves itself within several days after the drug has been discontinued.

PROBLEMS IN DEFINING DRUG ALLERGY

The objective diagnosis of drug allergy continues to be a major, largely unresolved, challenge to the clinician. The following outline attempts to highlight where some of the problems are encountered.

Immunochemical considerations

- Drug as immunogens: relevant drug metabolites unknown or unavailable
- Immunologic response to drugs: may not correlate with clinical hypersensitivity
- Immunologic mechanisms vary: allergic and pseudo-allergic
- Clinical manifestations protean and usually non-specific
- Paucity of supporting in vivo and in vitro tests
- Diagnosis often based on clinical criteria

Immunochemical considerations

Drugs as immunogens. Only a few agents in current usage, e.g., insulin and foreign antisera, are

complete antigens. Most commonly used drugs are simple organic chemicals of relatively low molecular weight, usually less than 1000 daltons. It is generally accepted that for such a small molecule to become immunogenic, it must form a stable bond with a circulating or tissue macromolecule to form a complete immunogen (hapten-macromolecular complex). Many drugs are not sufficiently reactive to combine with a carrier macromolecule; in this case, it is probably a *reactive drug metabolite* that binds with a carrier macromolecule to become immunogenic. Such reactive metabolites have been identified for penicillin and tentatively identified in allergic drug reactions involving acetaminophen, practolol, and halothane. For most allergic drug reactions, the formation of reactive metabolites and their conjugation with protein can only be inferred. This requirement for metabolic processing may ultimately explain some of the enigmas of drug hypersensitivity.⁴ These include its low overall incidence, its occasional occurrence in specific organs (the nature of the metabolic pathways of an organ may predispose to local accumulation of metabolites), the predisposition of certain drugs to cause sensitization (the drug may form highly reactive metabolites), and the inability of skin testing and other immunologic testing with the unaltered drug to establish the reaction as being immunologic in nature.

In addition to reactive metabolites, *reactive drug contaminants* may occasionally be responsible for drug hypersensitivity. Aspirin anhydride, a contaminant of aspirin, can react with protein to form a stable conjugate. During infection or tissue death, altered proteins may serve as "*Schlepper*" carriers to promote hapten immunogenicity. Last, some drugs, e.g., procainamide and methyldopa, may induce immune responses to tissue nuclear components with resultant *autoimmune diseases*, such as lupus erythematosus and hemolytic anemia.

In summary, we are still painfully ignorant when it comes to the identification of drug antigens. Without relevant antigens, a meaningful immunologic assessment is not possible.

Immunologic response to drugs. Even when immunologic sensitization to a drug can be demonstrated, it may not be associated with clinical hypersensitivity to that drug. The most familiar example is the almost invariable production of IgG and IgM anti-penicilloyl antibodies in patients who have received penicillin therapy. One must not only demonstrate that there are immunologic alterations present but also a reasonably consistent relationship with the drug-induced disease. For example, antibodies against drugs causing hematologic reactions are rarely present unless associated with thrombocytopenia or hemolytic anemia.

Immunologic mechanisms. An immunologic response to any antigen may be quite diverse, and the attendant reactions quite complex. Drugs are no exception and have been associated with all of the immunologic reactions proposed by Gell and Coombs; in fact, penicillin has produced all of them. Anaphylactic and urticarial reactions caused by penicillin are type I reactions; the hemolytic anemia that occasionally follows high-dose penicillin treatment is type II; the serum sickness-like reaction, now most commonly associated with penicillin, may be type III, whereas the contact dermatitis, developing when penicillin was used topically, is an example of a type IV reaction.

In addition to immunologic mechanisms, drugs may produce reactions by nonspecific activation of immunologic effector mechanisms. The term *pseudo-allergy* has been used to describe this group of reactions. They often mimic type I reactions, but the initiating event does not involve interaction between the drug and drug-specific IgE antibodies. Certain drugs, such as narcotics, polymyxin B sulfate, and d-tubocurarine iodide may directly release pharmacologic mediators from mast cells. Iodinated contrast media may also release mediators from mast cells and basophils, although activation of the complement system may be involved. Aspirin and other nonsteroidal anti-inflammatory drugs may trigger asthma in susceptible patients through an effect on arachidonic acid metabolism.

At a practical level, it is probably best not to become overly speculative regarding a classification of drug allergy solely on the basis of immunologic mechanisms. It should be apparent that much relevant information is lacking.

Protean clinical manifestations

The clinical manifestations of allergic drug reactions are protean and not specific or unique for drug hypersensitivity. It is likely that many such reactions are not recognized and are attributed to the illness for which the drug(s) were prescribed. Similarly, symptoms attributed to a drug may be unrelated to that drug. The following is a list of clinical manifestations that have been attributed to drug allergy.

- Generalized or multisystem involvement
- Anaphylaxis or anaphylactoid reactions
- Serum sickness-like reactions
- Drug fever
- Drug-induced autoimmunity
 - Reactions simulating systemic lupus erythematosus
- Others
- Vasculitis
 - Henoch-Schönlein purpura

Reactions predominantly involving one organ system

- Dermatologic manifestations
- Respiratory or pulmonary manifestations
 - Bronchial asthma
 - Acute infiltrative reactions
- Hematologic manifestations
 - Eosinophilia
 - Drug-induced immune cytopenias
- Hepatic manifestations
 - Cholestasis
 - Hepatitis
- Renal manifestations
 - Glomerulonephritis
 - Nephrotic syndrome
 - Acute interstitial nephritis
- Reactions involving lymphoid cells
 - Lymphoma-like syndrome
- Neurologic manifestations

A brief discussion highlighting some features of these manifestations follows. There is not space available to list all the drugs implicated in these reactions. More detailed lists of implicated drugs are available in a monograph by Cluff et al.,⁸ a recent textbook by Davies,⁹ and periodic literature reviews by Meyler and Herxheimer,¹⁰ and Dukes.^{11, 12} These latter reviews are particularly useful in tracing infrequently reported reactions.

Drug-induced anaphylaxis and anaphylactoid reactions. Although these reactions are uncommon, they pose a serious problem as they often occur unexpectedly and may be lethal. Estimates of nonfatal penicillin anaphylaxis range from 0.7% to 10%; fatal anaphylactic reactions occur at a frequency of 0.002%.¹³ For most drugs other than penicillin, there are no estimates of the frequency of anaphylactic reactions. Until recently, little information was available describing hypersensitivity reactions to cancer chemotherapeutic agents.¹⁴ The polypeptide L-asparaginase is the cytotoxic agent most commonly associated with such reactions; in fact, there has been 1% mortality from anaphylaxis among all treated patients. Intravenously administered muscle relaxants and anesthetics can produce anaphylaxis and are a significant cause of morbidity during the perioperative period.¹⁵ If one surveys the literature carefully, virtually all drugs, including corticosteroids¹⁶ and cimetidine¹⁷ have been implicated in anaphylactic reactions. These infrequent case reports should not lead one to withhold essential medication. Some of these reactions have an established immunologic mechanism mediated by IgE; however, for many, such a mechanism cannot be demonstrated or may not even be present. Many of these anaphylactoid reactions may be due to the nonspecific release of vasoactive amines or some other form of activation of

nonspecific immunologic effector mechanisms. As approximately 10% of severe anaphylactic reactions are fatal, one would like to predict such in advance. This will be considered under management strategies.

Serum sickness-like reactions are most commonly associated with penicillin administration, although equine antitoxins are still used in the management of snake and spider bites, botulism, gas gangrene, diphtheria, and to prevent organ transplant rejection. The cardinal manifestations include skin eruptions, fever, joint symptoms, and lymphadenopathy. A diagnosis of this syndrome without a skin eruption must be questioned. Serum sickness is one of the few illnesses where plasma cells may occasionally be observed in the peripheral blood. This is considered to be an immune complex disease; however, clinically significant renal involvement is unusual. Altered serum complement levels have been detected in a procainazine-induced serum sickness-like reaction.¹⁸ IgE antibodies to horse serum are often present. Animal experimental data suggest that IgE-initiated mediator release may facilitate deposition of soluble immune complexes, and this may be prevented by antihistamines.¹⁹ As serum sickness often follows the initial administration of an agent, it cannot be predicted in advance by testing.

Drug fever is often associated with cutaneous and systemic drug hypersensitivity but may be the sole manifestation. It is thought that immune complexes and/or antigen-stimulated lymphocytes are responsible for the fever. A distinguishing feature is often the disparity between the recorded fever and the relative well-being of the patient. However, a septic course has been described.²⁰ Drug fever is most commonly associated with treatment of infections with the use of β -lactam antibiotics.

The most familiar example of *drug-induced autoimmunity* is drug-induced lupus erythematosus. Drugs that have the most pronounced capacity to induce antinuclear antibodies or a lupus-like syndrome include hydralazine, procainamide, and isoniazid. Procainamide-induced lupus syndrome resembles idiopathic SLE more closely than other drug-induced lupus syndromes. Many patients with drug-induced lupus fulfill American Rheumatism Association criteria for SLE, but the clinical features are often milder and more restricted with regard to systems involved. All patients have antinuclear antibodies; in fact, they may be present in a high percentage of patients taking these drugs without clinical disease. The presence of antinuclear antibodies in asymptomatic patients is not an indication to stop the drug since most will not develop clinical symptoms. The antinuclear antibodies are directed primarily against histones²¹ and may per-

sist for months or even years after discontinuing the offending drug. The presence of antibodies to ssDNA is highly specific for spontaneous SLE and is helpful in distinguishing it from drug-induced lupus. Hypocomplementemia and the presence of circulating immune complexes are rarely reported in drug-induced lupus; a feature that is consistent with the infrequency of significant renal disease. The pathogenesis of the drug-related lupus syndrome has not been fully elucidated. Although these drugs may induce antinuclear antibodies in many individuals, additional, as yet undefined, environmental, genetic, hormonal, and other immunologic factors may be required to act in concert to determine which patients will develop clinical symptoms.

In addition to drug-induced lupus, other possible examples of drug-induced autoimmune reactions include hemolytic anemia secondary to methyldopa; hemorrhagic alveolitis simulating Goodpasture's syndrome and a polymyositis-like syndrome after penicillamine; hepatitis after oxyphenisatin, methyldopa, and possibly halothane; practolol-induced Sjögren's syndrome; tubular nephropathy after methicillin sodium; and anti-factor VIII antibodies after penicillin therapy.⁴

Of the *vasculitic syndromes*, drugs are most likely to be implicated in the etiology of allergic vasculitis (hypersensitivity angiitis, leukocytoclastic vasculitis). The skin is the most common organ involved and is usually why the patient seeks treatment. The pathognomonic lesion is a palpable, sharply circumscribed area of purpura. Drugs frequently implicated include penicillin, sulfonamides, thiouracils, hydantoins, and allopurinol. Henoch-Schönlein (anaphylactoid) purpura is a type of allergic vasculitis, but drugs have rarely been incriminated. Laboratory findings are usually not helpful, although immune complex deposition has occasionally been demonstrated within blood vessel walls. The most convincing evidence for such an association is the occasional report of an exacerbation after readministration of the drug.

Dermatologic reactions are the most frequent manifestations of drug allergy. Drugs may produce almost any kind of skin eruption, although exanthematous eruptions are the most common. Virtually any drug may produce an eruption of this type; in fact, it is probably easier to list those drugs that have not been associated with this eruption.²² Most drug eruptions are of mild or moderate severity; on occasion they may be severe, e.g., exfoliative dermatitis, the Stevens Johnson syndrome, and toxic epidermal necrolysis. With the possible exception of the fixed drug eruption (often caused by phenolphthalein), the appearance of the eruption usually is not characteristic

enough to implicate a drug as the most likely etiology. Any skin eruption appearing in a patient receiving drugs should be considered for a possible drug reaction.

The mechanism for most of these skin rashes is unknown. For exanthematous eruptions, immune complexes (particularly with IgM) and cell-mediated sensitivity have been suggested. Although some drug-induced urticaria and angioedema are mediated by IgE, this mechanism is not present in many cases. Contact dermatitis is produced by medications applied topically and is an example of drug-induced, T-lymphocyte-mediated hypersensitivity. After topical sensitization, the dermatitis may be elicited by subsequent topical administration or systemic administration of the same or immunochemically related substance. Once sensitized to ethylenediamine topically, a patient may develop a severe exfoliative erythroderm after systemic administration of aminophylline (a theophylline ethylenediamine).²³ Although the fixed drug eruption appears to be specific for drug hypersensitivity, there has been no convincing demonstration of an immunologic mechanism. For other drug eruptions, an immunologic mechanism remains speculative.

A more detailed discussion of drug-induced skin eruption is not possible in the space permitted; for such information the reader is directed elsewhere.^{3, 5, 6}

Drug-induced pulmonary manifestations are being recognized with increasing frequency.^{24, 25} Asthma is the most common drug-induced respiratory manifestation; aspirin the most common etiologic agent. The prevalence among asthmatic subjects based on history is 2% to 6%; it is 8% to 34% on the basis of oral challenge. Among asthmatic subjects with nasal polyps and sinusitis, aspirin sensitivity detected by oral challenge is 30% to 40%. The definitive diagnosis of current aspirin sensitivity is on the basis of cautious oral challenge.²⁶ Such a challenge not only identifies aspirin-sensitive patients with negative histories, but also identifies 25% to 35% of patients with positive histories of aspirin-induced bronchospasm who are no longer sensitive. Aspirin challenge is potentially hazardous and should be performed by experienced personnel. Currently, the most attractive hypothesis to explain aspirin-induced asthma is blockade of the cyclooxygenase pathway of arachidonic acid metabolism thereby permitting increased production of products of the lipoxygenase pathway, notably leukotrienes (SRS-A) that are potent bronchoconstrictors.²⁷ Patients with aspirin sensitivity may develop bronchospasm with other nonsteroidal anti-inflammatory agents. In a small percentage of patients, tartrazine (Food, Drug,

and Cosmetic no. 5 yellow azo dye), a color additive used in foods and drugs, has produced bronchospasm. Alarming hypersensitivity to intravenous hydrocortisone is occasionally observed in aspirin-sensitive patients.²⁸

Most reported metabisulfite reactions have occurred among asthmatic subjects. The postulated mechanism is generation of sulfur dioxide from the sulfites that irritate receptors in the airways. Some medications—isoetharine, metaproterenol inhalant solution, and epinephrine 1:1000—contain bisulfites as preservatives and may produce reactions in some asthmatic subjects.²⁹ Continued observation will ultimately establish whether a significant role will eventually be assigned to metabisulfite sensitivity.

Acute, drug-induced, infiltrative diseases in the lung are probably immunologic in mechanism. Although a number of drugs have been associated with pulmonary infiltrates with eosinophilia, nitrofurantoin is one of the most common causes of drug-induced pulmonary disease. Peripheral eosinophilia is not usually as impressive as the pulmonary infiltrates with eosinophilia syndrome. With the exception of drug-induced lupus, nitrofurantoin appears to be the only agent producing an acute drug-induced pleural effusion. A positive lymphocyte transformation test has been demonstrated in patients with clinical sensitivity, and nitrofurantoin has induced lymphocytes in vitro to become cytotoxic to human alveolar cells.³⁰ Withdrawal of the drug usually results in resolution of the disorder within 48 hr. Chronic interstitial pneumonitis and/or fibrosis occasionally develops after 6 mo or more of treatment and may be partially reversible with steroids.

Drug-induced, chronic fibrotic reactions are probably nonimmunologic in nature and are primarily associated with antineoplastic agents, e.g., busulfan, cyclophosphamide, bleomycin, chlorambucil, nitrosoureas, and mitomycin. Unlike the chronic nitrofurantoin reaction, fever is usually present. Methysergide, in addition to producing retroperitoneal fibrosis, may cause pulmonary and/or pleural fibrosis. It is the only drug that causes a chronic pleural effusion.

Drug-induced hematologic reactions are of major importance because of the potential for a fatal outcome. Many instances of drug-induced thrombocytopenia and hemolytic have been unequivocally demonstrated by in vitro methods to be mediated by antigen-antibody interactions. There is less certainty regarding drug-induced agranulocytosis, and evidence for such a mechanism in aplastic anemia is largely circumstantial. These reactions usually appear alone without other organ involvement. These reactions are reviewed extensively elsewhere.³¹

On occasion, eosinophilia may be present as the sole manifestation of drug hypersensitivity.³² Drugs that may be associated with eosinophilia in the absence of clinical disease include gold salts, allopurinol, aminosalicylic acid, ampicillin, tricyclic antidepressants, capreomycin sulfate, carbamazepine, digitalis, phenytoin, sulfonamides, vancomycin, and streptomycin. The presence of eosinophilia may give early warning of hypersensitivity reactions that could be more severe. However, most would agree that eosinophilia alone is not sufficient reason to discontinue treatment. In fact, digitalis regularly produces eosinophilia; yet hypersensitivity reactions to this drug are rare.

Drug-induced "hypersensitivity" hepatic reactions are suspected when hepatic injury is associated with fever, skin rash, and eosinophilia; a variable sensitization period of 1 to 4 wk; prompt exacerbation of hepatic dysfunction after readministration of small doses of the drug; eosinophil-rich inflammatory infiltration or granuloma in the liver; inability to demonstrate dose-related hepatic damage in animal studies; and absence of hepatitis-associated antigen. The demonstration of hepatocyte-specific antibodies or sensitized lymphocytes is usually lacking; hence an allergic basis remains largely unproved.

Intrahepatic cholestasis is the most common reaction and must be differentiated from other forms of obstructive jaundice. It is most commonly associated with the use of phenothiazines, occasionally with erythromycin estolate (not other erythromycin salts), chlorpropamide, thiouracils, methimazole, troleanomycin, and nitrofurantoin. The prognosis is excellent, and recovery is generally complete after the drug is discontinued.

Hepatocellular damage resembles acute viral hepatitis. This reaction is more serious with a less favorable prognosis. The most commonly incriminated drugs were the hydrazine monoamine oxidase inhibitors; the newer tricyclic antidepressants are less likely to induce hepatic damage. Less commonly incriminated agents include aminosalicylic acid, hydantoins, isoniazid, methyl dopa, sulfonamides, and halothane. Halothane-induced hepatitis does meet some of the criteria suggesting hypersensitivity, but it has rarely been possible to produce convincing evidence of *in vitro* sensitization in typical cases. Unexplained postoperative fever is a constant feature of liver damage after halothane anesthesia. Although an immunologic mechanism may be present in a few cases of isoniazid-induced liver injury, it is more likely caused by a toxic metabolite acetylhydrazine.³³

Drug-induced renal manifestations, notably glomerulonephritis, nephrotic syndrome, and acute in-

terstitial nephritis, occasionally have been ascribed to drug hypersensitivity. Glomerulonephritis is a prominent feature of experimental serum sickness and SLE but is rarely of clinical significance in drug-induced serum sickness-like reactions and lupus erythematosus. The nephrotic syndrome induced by drugs occurs primarily from immunologic processes that result in membranous glomerulonephritis. The syndrome has been associated with heavy metals (especially gold), penicillamine, anticonvulsants (mephenytoin [Mesantoin; Sandoz Pharmaceuticals, Albuquerque, N.M.] trimethadione, paramethadione), and captopril.

Acute interstitial nephritis caused by drug hypersensitivity may account for up to 8% of all cases of acute renal failure.³⁴ This disorder has been most frequently associated with penicillins, particularly methicillin sodium. The classic features include fever, maculopapular skin rash, blood eosinophilia, hematuria, moderate proteinuria, leukocyturia (often with eosinophils in the urinary sediment), and rapidly progressive renal failure. The nonsteroidal anti-inflammatory drugs may produce similar features but often are associated with heavy proteinuria and nephrotic syndrome. Both humoral and cellular mechanisms have been incriminated in the renal damage, namely, the presence of circulating antitubular basement membrane antibodies, linear deposits of the penicilloyl hapten, IgG, IgM, and/or C3 along the tubular basement membrane, predominant mononuclear cell infiltrate, positive lymphocyte transformation test, positive intradermal skin test, and the presence of suppressor T cells of the Ia type.³⁵

Reactions involving lymphoid cells, although rare, have been associated with prolonged treatment with anticonvulsants, notably phenytoin. The most common reaction is a pseudolymphoma, which usually resolves after withdrawal of the drug. However, not all patients recover, and some develop Hodgkin's disease or a malignant lymphoma. Angioimmunoblastic lymphadenopathy, characterized by hyperglobulinemia and lymphadenopathy, is often associated with phenytoin and penicillin. The pathogenesis of these anticonvulsant syndromes is unknown. Phenytoin administration has been associated with the following aberrant immunologic functions: decreased mean IgA, transient hypogammaglobulinemia, increased IgE levels, decreased lymphocyte counts, decreased delayed skin test responsiveness, decreased lymphocyte response to mitogens, and excessive suppressor T-lymphocyte activity. This cell-mediated immunosuppression may lead to an increase in lymphoreticular abnormalities.

An allergic mechanism for *drug-induced neuro-*

logic manifestations is unusual. Post-vaccinal encephalomyelitis does resemble experimental allergic encephalomyelitis in animals.

Paucity of supporting in vivo and in vitro tests

The identification of the drug responsible for a suspected hypersensitivity reaction still depends largely on circumstantial evidence and the clinical skills of the attending physician. With few exceptions, conventional methods to diagnose allergic disorders are either unavailable or not applicable for determining a drug etiology. The single most important factor in diagnosis is an awareness by the physician that an unexplained symptom or sign may be related to a drug that the patient is receiving. Since essentially none of the clinical manifestations are unique or specific for drug hypersensitivity, it is essential for the physician to be aware of the propensity of an agent to provoke a reaction and to consider this very treatable condition along with other diagnostic possibilities. The history should establish temporal eligibility of the suspected agent. Unless previously sensitized, there should be an interval between initiation of drug treatment and the subsequent reaction. This is rarely less than 1 wk for most drugs, and reactions generally appear within a month or so after initiation of therapy. Withdrawal of the suspected drug with prompt resolution of the reaction is suggestive, but such results may be true for any adverse reaction regardless of mechanism. These criteria are not absolutely reliable but often provide the correct diagnosis. Direct challenge of the patient with a test dose of the drug is the only absolute method to establish an etiologic relationship, but this is potentially hazardous and usually not recommended in most clinical situations.

There is an urgent need for safe and reliable tests to confirm drug allergy and detect susceptible patients before drug administration. The lack of knowledge regarding the immunochemistry of most drugs seriously hampers the development of meaningful tests. Furthermore, where tests are available, they may only indicate an immunologic response to a drug, but there may be no correlation with clinical manifestations. Clinically useful in vivo and in vitro tests may be summarized as follows:

I. Skin tests

A. Immediate (wheal and flare) prick or intracutaneous tests

1. Reliable for high-molecular-weight compounds (complete antigens): xenogenic antisera, hormones, vaccines, enzymes (chymopapain, streptokinase)
2. Generally unreliable for low-molecular-weight

compounds (haptens): penicillin is an exception; rarely others

B. Delayed (tuberculin-type) tests

1. Little correlation with clinical picture; occasional exceptions

C. Patch or photopatch tests

1. Useful for drug-induced contact dermatitis and photoallergic reactions
2. Rarely positive in drug-induced purpura and drug-induced morbilliform eruptions

II. In vitro tests

A. IgE-mediated reactions

1. RAST test: usefulness limited by lack of relevant metabolites
2. Total IgE: suggestive in nonatopic patients

B. IgG- and IgM-mediated reactions

1. Hematologic reactions: tests available are generally useful
2. Passive hemagglutination: often little correlation with clinical picture
3. Demonstration of drug-induced immune complexes: investigational, but promising

C. Cell-mediated reactions

1. Lymphocyte reactivity in tissue culture: usefulness variously interpreted
 - a. Lymphocyte transformation test
 - b. Lymphokine production

The demonstration of drug-specific IgE antibodies is usually accepted as evidence that an individual may be at significant risk for anaphylaxis if the drug is administered. For high-molecular-weight drugs, positive immediate wheal-and-flare skin tests are useful to screen for potential anaphylactic reactors. For the more commonly used lower-molecular-weight drugs, with the exception of penicillin, the significance of positive skin tests is uncertain. The RAST test has been validated mainly for the detection of benzylpenicilloyl-specific IgE antibodies and correlates with skin testing with use of the benzylpenicilloyl-polylysine conjugate. Recently, specific-IgE antibodies against antigenic determinants on sodium aurothiomalate have been detected in patients receiving gold therapy for rheumatoid arthritis.³⁶ Although an elevated IgE does not establish an allergic drug reaction, its presence, in the absence of atopy, is suggestive.

With the exception of drug-induced, immune thrombocytopenia, hemolytic anemia, agranulocytosis, and possibly some penicillin-induced exanthematous eruptions, there is often little correlation with the presence of drug-specific IgG- and IgM-antibodies and the occurrence of an allergic drug reaction. Most patients who have received penicillin have demonstrable hemagglutinating antibodies. The study of drug-induced immune complexes will undoubtedly improve with the current ability to measure circulating immune complexes in human sera.

Cell-mediated reactions may be present in some patients with drug hypersensitivity. Delayed (tuberculin-type) skin test reactions have been observed infrequently in drug allergy and generally do not correlate with clinical reactivity. On the other hand, patch testing is valuable in drug-induced contact dermatitis, even if the eruption was provoked by systemic administration of the drug. In photoallergic reactions, the patch test may become positive only after exposure to an erythemal dose of ultraviolet light. Lymphocyte reactivity in vitro has become one of the more commonly performed experimental tests for the diagnosis of drug allergy. There is considerable disagreement as to the value of this procedure; however, one should not ignore reports from reliable laboratories indicating the association of positive tests with manifestations of drug allergy.³⁷

MANAGEMENT STRATEGIES

Considering the obstacles encountered in the diagnosis and prediction of drug hypersensitivity—lack of relevant information regarding the immunochemistry of drug allergens, protean and nonspecific clinical manifestations, and few supporting in vivo and in vitro tests—allergists have developed practical *strategies* to cope with these clinical *problems*. It is appropriate that those who are experienced in dealing with hypersensitivity phenomena become actively involved with this dilemma. As a result of such, many patients are now able to receive appropriate therapy, diagnostic evaluations, and necessary prophylaxis. For others, it has been possible to remove the incorrect label "allergic to a particular agent." The following outline of the strategies provides an overview of these approaches.

- I. Prevention or avoidance
 - A. Considerations of drug usage
 - B. Evaluate clinical necessity for treatment
 - C. Select less sensitizing agents if available
 - D. History of prior adverse reaction to the drug
 1. Use clinically effective alternate drugs
 - E. Screening of patients before treatment
 1. Skin testing: mandatory for some drugs
 - a. Immunization materials
 - b. ?Penicillin, ?insulin, ?enzymes
 2. In vitro tests: generally not applicable
 - F. Method of administration
 1. Oral route preferable
 2. Avoid intermittent treatment courses
 - G. Follow-up after a reaction
- II. Administration of drugs to patients at increased risk or with a history of a prior reaction
 - A. Administer allergy suppressants simultaneously
 1. Pretreatment

- a. Contrast media
 2. Concurrent treatment to permit continued therapy
- B. Cautious administration of the drug
 1. Test dosing (incremental challenge)
 - a. Local anesthetics
 - b. Others
 2. Desensitization
 - a. β -lactam antibiotics
 - b. Insulin
 - c. Immunization materials
 3. "Desensitization" (clinical tolerance)
 - a. Aspirin
 - b. Others

Prevention or avoidance

Considerations of drug use. The simplest way to reduce or prevent drug reactions is to prescribe medication only when clinically necessary. Of a group of 30 penicillin anaphylactic deaths, only 12 subjects had a clear indication for treatment.³⁸ Also, the inappropriate use of drugs may sensitize an individual to an agent that may be necessary in the future. Obviously, drugs with a reputation for producing allergic reactions should be avoided if possible. Certain modifications in available therapy have provided less sensitizing preparations, e.g., the substitution of human for equine tetanus and rabies antisera, the use of synthetic polypeptides to replace ACTH and posterior pituitary hormones, the availability of purified insulins and human (recombinant DNH) insulin, and the development of vaccines free of egg protein.

Assessment of drug history. In a report of fatal penicillin anaphylaxis, approximately one third of patients or their relatives could have provided information about a previous allergic reaction to penicillin had that information been solicited.³⁸ Although overdiagnosis may be a problem, it is prudent to accept what the patient believes or has been advised without the need for further documentation. Fortunately, there are usually equally effective, nontoxic, noncross-reacting drugs available.³⁹

Screening tests. Skin testing is mandatory for all patients who are about to receive foreign antisera. A prick or scratch test with the use of antiserum diluted 1:10 with normal saline and a saline control is performed. If the test is negative, perform an intradermal skin test with the use of 0.02 ml of a 1:100 dilution of serum (a 1:1000 dilution if a history of a prior reaction or presence of atopic symptoms to horse dander) and a saline control. A positive test requires reconsideration of the need for treatment, and desensitization if it is necessary. Skin testing with egg-containing viral vaccines (influenza, rubeola, mumps, yellow fever) is a reliable method to screen out potentially

allergic reactors from patients reported to be allergic to egg.⁴⁰ A prick test is performed with a 1:10 dilution of the vaccine in normal saline and a normal saline control. If the test is negative, an intradermal skin test by use of 0.02 ml of a 1:100 dilution is performed with a saline control. If the test is negative, it is likely that the patient will tolerate the vaccine.

The value of penicillin skin tests to predict individuals at increased risk of developing immediate and accelerated allergic reactions after penicillin administration has been repeatedly confirmed.⁴¹ Testing with both benzyl PPL and BPG should detect 90% to 95% of potential anaphylactic reactors. This would approach 100% if the benzylpenicillin MDM were available.⁴² Although skin testing with reagents prepared from other semisynthetic penicillins and cephalosporins will increase the number of patients with positive skin tests,⁴³ it appears that PPL, BP, and MDM reagents detect most clinically significant allergic reactivity to all penicillins and probably cephalosporins.⁴⁴ Currently, penicillin skin testing is performed only when penicillin is necessary in a patient with a history suggesting penicillin allergy.

A case might be made for routine skin testing with insulin before resuming this agent after a lapse in treatment. However, approximately 40% of patients with no clinical allergic problems have skin test reactivity to the insulin used for treatment.⁴⁵ Currently, the role of skin testing before the use of chymopapain and streptokinase is being assessed. Skin testing with most other drugs is unreliable.

At the present time none of the *in vitro* tests for assessment of drug allergy qualify as screening procedures. However, an eventual role may be assigned to the RAST test for detection of drug-specific IgE antibodies.

Method of administration. When there is a choice, the oral route is preferable as it is least apt to sensitize the patient, and allergic reactions are less frequent and generally less severe. Intermittent or unduly prolonged exposure to a drug clearly increases the potential for sensitization. An important factor when repeated courses of therapy are administered may be timing. With penicillin as an example, the risk of a reaction appears to be greater during the first few months after a preceding course of treatment.

Follow-up after a reaction. The responsibility to a patient who has sustained an allergic drug reaction does not end with discontinuation of the drug and treatment of the reaction. The patient or responsible persons must be informed of the reaction and advised how to avoid future exposure to the suspected agent.

All medical records must display the patient's drug sensitivities in a conspicuous location. The patient should carry a card or wear an identification tag or bracelet designating the drugs to be avoided.

Administration of drugs to patients at increased risk or with a history of a previous reaction

Simultaneous administration of allergy suppressants. Although patients with a previous anaphylactoid reaction to RCM may tolerate a subsequent study with no adverse effect, such individuals are at increased risk (20% to 35%) of a repeat reaction.⁴⁶ Since (1) no method is available to identify those who will react again, (2) repeat RCM studies may be essential, and (3) there are no suitable alternative agents, pretreatment regimens have been recommended. Pretreatment with prednisone and diphenhydramine reduces the reaction rate to 9%, and repeat reactions are usually mild. The addition of ephedrine reduces the reaction rate to 4.1%.⁴⁷ Although this approach is primarily useful in reducing the risk of anaphylactoid reactions after intravascular RCM administration, it should be used even if the repeat study is nonvascular, e.g., retrograde pyelography, myelograms, and arthrograms.

On occasion, when a reaction occurs during a treatment course and no alternatives are acceptable or available, the use of medication to suppress the reaction may permit continued use of the drug. Corticosteroids have been used to suppress drug-induced fever and rash (not hepatitis) during antituberculous therapy.⁴⁸ With the diminishing use of aminosalicic acid, this approach is rarely a consideration. In general, concomitant use of allergy suppressants should be reserved for mild reactions, and the decision should be left to those experienced in managing hypersensitivity.

Cautious administration of the drug. True local anesthetic allergy (except contact dermatitis) is extremely rare; however, patients commonly report adverse reactions to these agents. As *in vivo* and *in vitro* tests are unavailable, *test dosing* has been used to establish whether the patient may safely receive the drug. The principle is to administer sufficiently small doses initially and to increase the dose by safe increments over a matter of hours or days. During the past 15 to 20 yr, various physicians have used local anesthetic incremental challenge as described elsewhere.^{49, 50} There have been no problems in establishing a safe local anesthetic. The success of this approach is undoubtedly related to the rarity of true allergic reactions to local anesthetics, and one might

argue that it is not worth the bother. However, it does serve to allay the anxiety of patients, referring dentists, and physicians.

For most other drugs test dosing or incremental challenge may be the only way to rule out allergy when treatment is necessary. The route of administration should be that used for treatment. The starting dose is arbitrarily determined, taking into account the severity of the previous reaction, the experience of the clinician, and possible risk to the patient. If the previous reaction was severe, the initial dose should be 1/100,000 or less of the expected therapeutic dose. Subsequent doses are increased tenfold at appropriate intervals until the desired dose is achieved.

Desensitization implies an abolition of sensitivity to an antigen. This approach has been used to permit treatment with β -lactam antibiotics among patients with positive skin tests to PPL, BP, and MDM, among diabetics with systemic insulin allergy, and among patients with positive skin tests to immunization materials. After successful desensitization, skin tests frequently become negative.

Penicillin desensitization may be necessary when there are no suitable alternatives. Skin testing will help evaluate the level of sensitivity and provide some indication of an appropriate starting dose. The dose is then increased at frequent intervals while monitoring for the development of allergic reactions. As most physicians have rarely been called upon to consider such a procedure, there is no standard regimen of dosing or route of administration agreed on by all. Desensitization has been successfully accomplished by use of the subcutaneous, intramuscular, intravenous, and oral routes of administration. The subcutaneous route has had more proponents and does permit placement of tourniquet proximal to the injection site should a reaction occur.⁵¹ The intravenous route is preferred by some who feel that it is quicker and allows absolute control over the rate and concentration of the drug being administered.³ Any untoward reaction will be detected promptly and rapidly treated. As oral administration of β -lactam antibiotics appears to be safer, it has been recommended that this route be selected for initiation of desensitization.⁵² After successful desensitization, approximately 30% of patients will experience mild, transient allergic manifestations that usually subside even though penicillin is continued. Only one fatality has been reported during penicillin desensitization.⁵³ On rare occasions after successful penicillin desensitization, long-term clinical tolerance to oral penicillin may be desirable, e.g., among individuals who must handle penicillin⁵⁴ and patients allergic to penicillin who require intermittent

penicillin therapy.⁵⁵ Proposed hypotheses to explain penicillin desensitization include absorption of circulating IgE antibodies, induction of "blocking" IgG antibodies, depletion of mediator stores, hapten inhibition by circulating, monovalent conjugates, and antigen-specific desensitization of tissue mast cells.⁵⁶

Systemic allergic reactions to insulin are rare. Most commonly the patient will have a history of interruption of insulin therapy. After such a reaction and assuming insulin therapy is necessary, insulin should not be discontinued. The next dose should be reduced to one third and slowly increased by 2 to 5 units per treatment. If there has been a lapse in treatment, desensitization may be attempted by use of the least antigenic (usually pork) insulin.⁵⁷ Successful desensitization is initially associated with a decline in both specific-IgE, insulin-binding levels and skin test reactivity. Later, increased production of IgG anti-insulin antibodies may also afford protection.

Where there is no alternative to the use of equine antisera and skin tests are positive, desensitization has been successfully accomplished. There are several protocols recommended as there were for penicillin desensitization. The package insert may describe a schedule that can be followed. A conservative schedule begins with the subcutaneous administration of 0.1 ml of a 1:1000 dilution in an extremity. The dose is doubled every 15 min until reaching 1.0 ml of undiluted antiserum, after which larger volumes may be given intramuscularly. At times rapid delivery of antiserum may be required.⁵⁸ Here, it is recommended that intravenous infusions be established in both arms, one to deliver the antiserum and the other to treat complications. Premedicate with 50 to 100 mg of diphenhydramine hydrochloride intravenously, followed by a slow infusion of the antiserum. If there is no reaction after 10 to 20 min, the infusion rate may be increased. If a reaction occurs, the infusion is stopped, and epinephrine is administered. After the reaction has been controlled, the slow infusion is resumed. After successful desensitization, it is likely the physician and patient will be faced with the development of serum sickness 1 or 2 wk later.

Attempts to desensitize patients with positive skin tests is not without risk and should be carried out in a setting where trained personnel and resuscitation equipment are immediately available.

The term *desensitization* has been used to describe the development of clinical tolerance to some drugs, notably aspirin, that previously had produced a reaction. Many patients who are aspirin sensitive can obtain an adequate analgesic response by use of acetaminophen, propoxyphene, and other salicylates.

However, these salicylates may be ineffective in treating rheumatoid arthritis; aspirin "desensitization" may be considered here.⁵⁹ The process is an extension of an aspirin challenge and appears to take advantage of a refractory period after a reaction. However, the mechanism of this is not presently understood. The tolerance achieved to aspirin is extended to the other nonsteroidal anti-inflammatory agents as well. Once accomplished this state of clinical tolerance must be maintained by daily drug use. If aspirin therapy is discontinued, this refractory state lasts only 2 to 5 days. The therapeutic potential of this phenomenon for aspirin-induced rhinosinusitis and asthma needs clarification. To date there are no reports of aspirin "desensitization" among patients whose problem is aspirin-induced urticaria.

Approximately 2% of patients develop what is presumed to be a hypersensitivity reaction (fever, rash) to sulfasalazine. As this is an important drug in the treatment of inflammatory bowel disease, a program of "desensitization" has been recommended.⁶⁰ This approach is ineffective for nonallergic toxicity (headache, nausea, vomiting, abdominal pain) and should not be considered for patients who have had severe reactions, e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, agranulocytosis, or fibrosing alveolitis.

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