Introduction

Reactions to medications are an extremely common problem. In a general ambulatory practice, the likelihood of medication-related problems is about 5%. At least 20% of hospitalized patients experience an adverse drug reaction. The most common organ in which such reactions are apparent is the skin. About 0.1% of hospitalized patients will have a serious, potentially fatal cutaneous reaction.

While patients and physicians speak of allergic reactions and drug allergies, the immunology of drug eruptions is complex and poorly understood. All the basic types of immunologic reactions as outlined by Gell and Coombs can be seen. In addition, many medications have physiologic or toxic reactions which are dose-related. If the dose required for the adverse reaction far exceeds the usual dose, then the change is viewed as an adverse event. When the threshold for a reaction is close to the therapeutic level, as with many chemotherapy agents, then the reaction is accepted as a pharmacologic effect. Some medicines are capable of degranulating mast cells, for example aspirin and codeine, to produce a pseudoallergic reaction. Other medications cause problems in patients who lack a specific enzyme or other factor. For example, some patients slowly or poorly inactivate isoniazid. Biologic modifiers such as interferons are finding increasing usage. They cause reactions which are an exaggeration of their normal biologic role. Another variation, which is not discussed further in this chapter, is the complications of immunosuppression including viral infections and tumors. Finally, sometimes a reaction is very rare, occurs at low dosage, perhaps on the first exposure or without any evidence for immunologic changes; then one speaks of an idiosyncratic reaction. No matter what type of reaction is involved, once the offending agent is identified and stopped, improvement is usually prompt.

Drug reactions can resemble or even reproduce many of the diseases discussed throughout this text. In order to avoid repetition, we have discussed...
lichen planus-like (Chap. 14), bullous (Chap. 15), lupus erythematosus-like (Chap. 18) and acneiform (Chap. 28) reactions elsewhere and only mention them here.

The history is the key to intelligently evaluating patients with possible drug eruptions. First, one must be sure that the list of medications is complete. Patients tend to forget over-the-counter medications and even more often, products they have been taking for many years. In general, they are correct in assuming that a diuretic they have used for 10 years is not a likely cause of their rash, but sometimes it happens. One should be particularly suspicious of drugs taken in recent days, but there are cautions. If an allergic reaction is involved, then either prior exposure or a cross-reaction is required. Delayed reactions, such as serum sickness, occur 7–10 days after exposure, as the body mounts a response, as to an injection of horse-derived immunoglobulin. Idiosyncratic reactions can occur almost instantly, as can life-threatening anaphylactic reactions through an inadvertent rechallenge. Other medications, such as ampicillin, are notorious for causing late reactions. Finally, the medication may enter the body by unusual routes. Iodine toxicity has been described from usage of large amounts of Iodoform gauze to pack a wound. One must often repeat the history several times to get all the pertinent facts.

Cofactors may be involved. Considering ampicillin once again, the use of the antibiotic in a patient with infectious mononucleosis is very likely to cause a purpuric eruption. Erythema nodosum drug eruptions are much more common in women, suggesting a hormonal influence. The patient's HLA type may also play a role, as for example in drug-induced lupus erythematosus. Sunlight is another trigger; many drug reactions are either photoallergic or phototoxic.

Drug reactions are another great imitator. They can produce a wide spectrum of clinical pictures, ranging from lichen planus (gold salts) to pityriasis rosea (gold salts) to lupus erythematosus (hydralazine, for example). Some drug reactions occur in only one or two areas, and then mysteriously reoccur in these same sites on reexposure. Such a fixed drug reaction is commonly seen with tetracycline, phenolphthalein and phenobarbital. Nonetheless, the most common drug reaction is a diffuse macular exanthem or toxic erythema. The differential diagnostic question is usually drug reaction or viral exanthem. Sometimes, pruritus is the first or even only sign of a drug reaction. However, pruritus in the absence of any clinical lesions such as a macular exanthem or urticaria is uncommon, especially if cholestasis and other drug-induced liver malfunction is excluded. In other cases, paresthesias may be a clue, such as with isoniazid, griseofulvin or thalidomide.

To approach patients with potential drug eruptions, one needs a very current and handy source of information about the likelihood of different types of drug reactions with various medications. We recommend Bruinsma W, A Guide to Drug Eruptions as listed in general references.

**Etiology and Pathogenesis**

Even though cutaneous drug reactions cover a wide morphologic range and involve many different mechanisms, some immunologic and some toxic, we will try to discuss them simultaneously considering both the clinical appearance and the probable underlying disease mechanism. Table 10.1 summarizes most of these reactions.

**Allergic Reactions**

Allergic exanthems comprise the vast majority of all drug reactions. They develop when a medication is administered to which the patient has previously been exposed and against which he is capable of reacting. Two factors should be considered at this step. Medications usually are not a pure product containing just the active ingredient, but also have a vehicle consisting of allegedly inert ingredients. A patient may be allergic to a constituent of the vehicle, such as a dye or preservative. In addition, cross-reactions between chemically related pharmacologic agents occur. Both of these scenarios should be considered when a patient reacts to an agent to which he denies exposure, but the usual explanation is an inaccurate drug history.

Most drugs are relatively small molecules which function as incomplete antigens or haptenes. They or their metabolites are bound in the body to various proteins, thus forming antigens which are recognized by the host as foreign triggering an immune response. The hapten determinants of most medications have not been determined. They are best identified for penicillin and some of the sulfonamides. The chemical structure of a product plays a considerable role in its antigenic or aller-