0031-6997/82/3401-0085$02.00/0
PHARMACOLOGICAL REVIEWS
Vol. 34, No. 1
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Printed in U.S.A.

PHARMACOLOGICAL REVIEWS

Allergic Reactions in Man

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General Mechanism of Allergic Drug Reactions

IT HAS long been recognized that proteins, glycoproteins, lipopolysaccharides and polysaccharides are effective inducers of immune responses (85). More recently, it has been found that other macromolecules such as nucleic acids and even relatively small molecular weight polypeptides have the capability of inducing an immune response either spontaneously or after immunization, although special efforts such as repeated administration of them in substantial quantities in an immunologic adjuvant or conjugation to a protein may be needed to promote a response. Some of the important variables effecting the immunogenicity of a macromolecule include degree of antigenic foreignness, structural complexity, molecular size, degree of polymerization, overall charge, and rate of biodegradability or elimination. Genetic factors also exert a significant influence, particularly when the immunogen closely resembles an endogenous antigen in the host or is relatively simple structurally. While the immune system is capable of producing antibodies to a wide variety of small molecular weight organic chemicals of pharmacologic value, allergic symptoms to these agents are much less common than they are to proteins, particularly the whole serum preparations that were used originally for passive immunization (76, 78, 82). It is generally believed that a small molecular weight organic chemical is not immunogenic unless it forms a stable bond with a macromolecule, usually a protein or glycoprotein. The necessary stability can be provided by covalent, coordination and in rare instances multiple salt linkages, summating along a long polymer whereas the reversible ionic and hydrophobic interactions most drugs undergo with albumin and other serum proteins apparently are ineffective (57, 74, 79, 90). This was suggested originally by Landsteiner (57) and confirmed and extended by Eisen and his colleagues (88). The term "hapten" was used to describe such substances which were not immunogenic to themselves but became immunogenic in the presence of a carrier macromolecule. Penicillin allergy is the most carefully studied and best understood of the allergic human drug reactions. Based on the classic studies of Landsteiner and Eisen, it was anticipated that drugs would be effective immunogens only if they formed stable bonds with proteins or other endogenous macromolecules. This concept was directly verified for human penicillin allergy in a large survey of individuals with penicillin allergy by our group, which included myself, Herman Eisen, Milton Kern, Alain de Weck, and Jack Shapiro (87, 89). Allergic skin reactivity was present frequently to the penicilloyl group, a breakdown product of penicillin capable of existing in covalent linkage with proteins introduced by the direct reaction of penicillin with protein amino groups or through a penicillenic acid intermediate (75, 86, 89). It was also shown that antibodies present in the serum of individuals receiving penicillin were not directed toward penicillin itself but to various breakdown products of penicillin that can combine with proteins, particularly the penicilloyl group (122). Levine and his colleagues independently drew similar conclusions (59, 61). The formation of these breakdown products and their reactions with proteins can be explained by the unusual chemical reactivity of the penicillin molecule itself and some of its metabolites.

While other drugs presumably conjugate to macromolecules to produce allergic manifestations, very few have direct protein reactivity and it is necessary to assume that reactive metabolites are formed in vivo (78). In the attachment of penicilloyl groups to proteins, the β-lactam ring of the parent penicillin is opened and its carbonyl moiety forms an amide bond with amino groups primarily on lysyl residues on the protein (fig. 1). There are two possible mechanisms for formation of protein-bound penicilloyl groups: 1) by direct reaction of penicillin with amino groups, or, 2) by initial rearrangement to penicillenic acid, a highly reactive acid anhydride. Penicillenic acid reacts very rapidly with protein amino groups (fig. 1) although other reactions also are possible including the formation of penicillenate mixed disufides (78). When penicilloyl groups are produced by the penicillenate rearrangement a mixture of penicilloyl diastereoisomers is formed, whereas in the direct aminolysis reaction the D-α-configuration of the original penicillin molecule is retained. Initially the penicillenate rearrangement was thought to be the principal pathway by which protein-bound penicilloyl was formed in vivo; this raised the possibility that poorly allergic penicillins that did not undergo this rearrangement readily but were therapeutically effective might be identified. However, subsequent studies indicated that the direct conjugation reaction is of at least equal importance (7, 75, 77, 110, 111, 131). Most of the antibodies present in the serum of individuals with penicillin allergy were directed toward ther D-α-penicilloyl group and acid stable penicillins that formed little or no penicillenate spontaneously were apparently as immunogenic as benzylpenicillin itself in animals.

The pattern of potential allergic reactivity in penicillin allergy is actually quite complex in that penicillin, in

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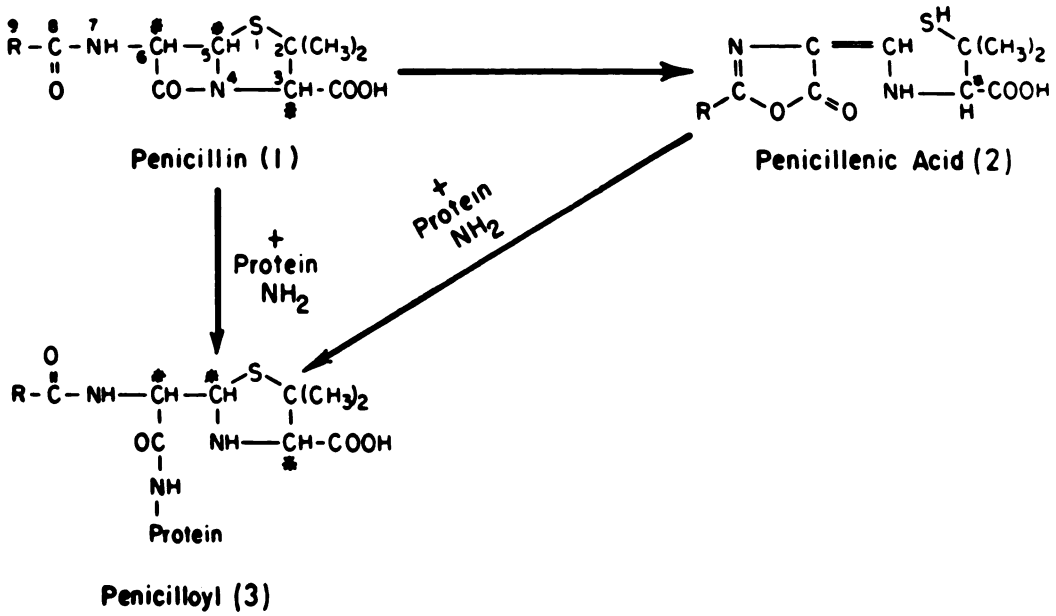

FIG. 1. Alternative pathways for the formation of protein-bound penicilloyl groups in human penicillin allergy. The asterisk indicates asymmetric carbons. The formation of penicilloyl groups through penicillenic acid leads to a mixture of penicilloyl diastereoisomers. Whereas when penicilloyl is formed directly from penicillin the Dα-configuration of the parent penicillin is retained.

addition to being reactive with proteins itself, gives rise to a variety of breakdown products with protein reactivity in addition to penicillenic acid, including penicillamine and penicilloic acid. Virtually everyone who is treated with penicillin develops an immune response to the penicilloyl group, as determined by hemagglutinin testing (75, 122) but, in addition, antibodies are sometimes demonstrable to penicillenate (or its oxidation products), penicillamine, penicilloate, penamaldoyl, penicilloaldehyde, and polymers of 6-aminopenicillanic acid (23, 61, 89, 122) or other poorly characterized penicillin determinates suggested by different patterns of allergic reactivity in different individuals (21, 23, 61, 89, 112, 122). All of the determinants that have been conclusively identified have the capability of forming covalent bonds with proteins.

The most effective and practical method of detecting the form of penicillin allergy likely to be associated with anaphylaxis is by immediate skin testing although solid phase immunoassays for IgE antibodies are also useful, at least for penicilloyl specific antibodies. Some of the penicillin haptens crossreact immunologically with one another. Others, like the penicillenate molecule, appear to represent largely or entirely distinct antigenic determinants. Interesting, individuals who have an allergic response to one penicillin hapten frequently have reactivity to other penicillin determinants as well, for reasons that are not altogether clear. Routine skin testing is usually carried out with a combination of test materials including penicilloyl-polylysine, penicillin, and in some instances penicilloic acid. Penicilloyl-polylysine is a preformed multivalent conjugate of penicilloyl attached to a relatively small molecular weight homopolymer of the amino acid, lysine. It was used originally by our group to minimize the danger of sensitization that would have been incurred if penicilloyl proteins had been used for testing (75, 87, 89, 91). Reactivity to penicilloyl-polylysine is present in about 75% or more of individuals with recently documented penicillin allergy. Testing is also carried out with penicillin and penicilloic acid, which together detect nearly all of the remaining individuals with penicillin allergy who do not react to penicilloyl-polylysine alone.

In contrast to immediate skin testing or measurements of IgE antibodies in vitro, serologic tests for IgG or IgM antibodies are of little or no value in the diagnosis of penicillin allergy, since antibody responses to the drug are frequent in individuals who have not had allergic symptoms. The absence of allergic responses in many of these individuals indicates that the right types of antibodies were not present or conditions were not otherwise favorable for the appearance of allergic manifestations (84). Among the contributing factors are a requirement for the formation of multivalent conjugates in the elicitation as well as in the induction of allergic reactivity and the ability of unconjugated drug or nonparticipating antibodies (IgG antibodies in IgE-mediated reactions) to competitively inhibit the allergic response.

Antibodies to structurally complex haptens such as the benzylpenicilloyl group may be present in any of the five immunoglobulin classes and vary in their overall affinity and degree of adaption to different portions of the hapten molecule. Heterogeneity of this sort has also been observed with model haptenic determinants such as the 2,4-dinitrophenyl group in experimental animals. All penicillins contain the 6-aminopenicillanic acid nucleus and are

therefore potentially crossreactive immunologically. Benzylpenicilloyl-polylysine and 2,6-dimethoxybenzylpenicilloyl-polylysine (the penicilloyl polylysines derived from penicillin G and from methacillin (staphcillin), respectively) are almost equivalent as elicitors of cutaneous allergic responses in some individuals with benzylpenicillin allergy, but show little or no crossreactivity in others (90, 125). Thus the extent of adaptation of the antibody to the 6-aminopenicillanic nucleus and the R group at the 6-amino position varies considerably from one individual to another. Judging from studies in inbred animals such variations are at least in part genetically mediated. Since the biologic effectiveness of an antibody in vivo is dependent on its binding affinity for antigen, these differences in antibody affinity may strongly influence the development of an allergic response.

Most drugs do not have direct protein reactivity, and it is necessary to assume that a reactive metabolite is formed in vivo. A requirement for metabolic processing and conjugation to a macromolecule can explain a number of otherwise puzzling features of drug allergy including the frequent localization of clinical manifestations to a single organ or cellular system. However, direct verification in man that metabolites or spontaneous breakdown products of drugs are involved in the initiation of drug allergy is limited. Tentative or suggestive identification of active metabolites in drug allergy has been made in reactions to aminonucleoside antibiotics, acetaminophen, mesantoin, phenylbutazone, phenacetin, halothane, and amidopyrine (30, 65, 82, 84, 96). For most drug allergies the formation of the presumed reactive intermediates and their conjugation with protein can only be inferred. Identification of the presumed protein-reactive metabolites formed in vivo may present major problems because of the many different metabolites form from drugs, and the possibility that the reactive metabolite might be a quantitatively minor product or a sufficiently labile chemical that isolation and identification are difficult (77, 81). For these and other reasons, the determination of possible reactive intermediates in drug allergy is a challenging problem that has rarely been pursued to a successful conclusion. The approach most likely to provide real dividends in drug allergy should begin with a thorough consideration of the chemical properties of the drug, its minor as well as major metabolites, and any contaminants that might be introduced during its manufacture. Information on metabolites formed in man, if available, is of particular value. Possible reactive intermediates are then synthesized either chemically or enzymatically and studied for their reactivity with functional groups on macromolecules. Hapten macromolecular conjugates and reactive intermediates are then injected in sufficient quantities to immunize animals, a variety of immunologic detection systems are used for evaluation, and the specificities of any immune responses are examined in detail. At this point, human beings who have had adverse reactions to the drug can be studied with some degree of confidence that suitable and sensitive assay systems are being employed. Even this approach has its limitations because of the importance of genetic and environmental influences on drug metabolism and immune responsiveness and the very real possibility that the most effective multiple antigenic determinants might differ from one animal species to another or even one human being to another.

In the absence of extensive preliminary studies to identify possible antigenic determinants in drug allergy, a variety of screening procedures may be attempted (85): 1) A variety of assay systems are available for the detection of serum antibodies. However, many serologic assay systems such as hemagglutination require that the candidate haptens be rendered multivalent by attachment to soluble or insoluble macromolecular carriers before a positive response can be expected. Serum antibodies involved in hematologic reactions to drugs are sometimes detected by using the patients serum, the drug, and the cell involved in the reaction in combination (see below). Seeing whether radiolabeled drug is bound specifically by immunoglobulins in the serum of individuals with drug reactions has occasionally been helpful in the apparent substantiation of allergy (105, 113). However, success with this approach requires that the drug have considerable structural similarity to the actual immunogen which may or may not be the case. Also a haptenic marker of reasonably high specific activity is needed, as are rigorous controls to exclude nonspecific binding to other serum proteins. 2) Occasionally a drug may elicit an immediate hypersensitivity response during cutaneous testing in vivo although unless appropriate controls are performed in normal subjects the results are difficult to interpret. 3) Frequently a delayed hypersensitivity response is produced but again the appropriate controls are needed. Moreover, the possibility must be considered that delayed hypersensitivity responses may be entirely negative in face of a vigorous humoral immune response. 4) Drugs sometimes stimulate lymphocyte proliferation or lymphokine release with peripheral blood lymphocytes in vitro (64). These responses are of considerable interest in that they suggest that reactive metabolites are being produced in situ in the cell culture leading to the formation of an effective antigen (81). Indeed the possibility must be seriously considered that the major site of reactive metabolite formation is in the lymphoid system rather than the liver, even though the liver is the major drug-metabolizing organ. Regardless of the screening procedure that is used a negative result is hard to interpret and in the long run elucidation of antigen structure through a detailed analysis of the chemical properties of the drug, its mode of organic synthesis or biosynthesis and the nature and immunogenicity of its metabolites is a much better approach (79).

Even when an immune response to a drug is demonstrated the possibility that it might be an ancillary manifestation rather than actual cause of the tissue damage

must be seriously considered (76, 80). It is necessary to show not only that there are immunologic alterations but also that there is a reasonably consistent relationship between the altered immunologic reactivity and the drug-induced disease. In addition, since the immune process is dynamic and changes with time after sensitization, it cannot be assumed that testing will always be successful, particularly when there has been a long time interval since the reaction. False negative results may also be obtained when active symptoms of hypersensitivity are still present, particularly if the reaction is of the serum sickness type. This is presumably because most or all of the circulating antibody is already complexed to antigen in sufficient antigen excess that the further addition of antigen does not lead to the fixation of complement.

As far as the evaluation of new drugs for immunogenicity in animals is concerned, it seems to me that conventional immunologic screening procedures should be retained. However, I also feel that drugs should be evaluated for protein reactivity in vitro before and during treatment with drug-metabolizing enzymes. This should permit the drugs with the greatest immunogenic potential to be identified and perhaps eliminated at any early stage if they do not possess unique therapeutic advantages. Obviously screening procedures in animals may be inadequate to detect unusual types of reactions that might be prone to occur in man, although, as our understanding increases of the mechanism of certain reactions, such as drug-induced lupus, the most appropriate animal models may become easier to identify.

Genetic and Environmental Influences on Drug Allergy

While drug allergies are not linearly related to drug dose, in general, higher drug levels are associated with an increased risk of allergy (80, 82, 84). This is particularly evident in systemic lupus erythematosus (SLE) induced by hydralazine or procainamide where the rate of metabolism of the drug as well as the dose and duration of drug therapy are an important influence. As was demonstrated initially for hydralazine toxicity it is mainly the half of the population with a low level of hepatic acetyl transferase activity (and therefore higher drug levels) that is susceptible to clinical toxicity (93). The importance of drug levels is also illustrated by penicillin-induced hemolytic anemia where high sustained levels of the drug are needed to produce this particular form of allergic response. For drugs taken in high doses over sustained periods of time, such as penicillin, one might question whether high antigen dose tolerance would be induced. This has been suspected during long term treatment with penicillin for serious blood stream infections (60, 79) but the data are not completely convincing. Any congenital or acquired disease or inherited enzyme abnormality which alters the rate of absorption, metabolism, excretion, binding of a drug may affect the likelihood of an allergic drug reaction. In addition, drugs taken concomitantly which induce or compete for the cytochrome P-450 drug-metabolizing system in the liver may exert an influence either through changes in the overall rate of drug metabolism or possibly because the metabolites themselves are needed to form immunogenic drug conjugates. For drugs taken over long periods of time the most susceptible individuals often develop allergic reactions relatively early in the initial course of therapy and in the remainder the risk of an allergic reaction is considerably diminished. Nonetheless since an allergic reaction to a drug may occur for the first time after many previous courses of therapy, or in the late stages of a prolonged single course of treatment, any underlying disease which must be repeatedly or continuously treated obviously increases the risk of an allergic reaction. A critical factor when repeated treatments are given may be the timing of the subsequent courses of therapy. While allergy may persist for many years if the results in penicillin allergy are any indication the risk is normally greater during the first few months after a preceding course of treatment than at later times. Underlying chronic connective tissue diseases such as SLE or Sjogren's syndrome have been reported to considerably increase the risk of allergic drug reactions. Since multiple autoantibodies and circulating immune complexes are present in both diseases one might speculate that the immune system is already compromised, increasing its susceptibility to further immunologic insult. On the other hand, there is overlap in the clinical manifestations of drug allergy with these autoimmune diseases and further documentation is needed. Individuals with hyperuricemia, infectious mononucleosis, and lymphocytic leukemia have an extraordinary incidence of maculopapular rashes during treatment with ampicillin (16) but the role of allergy in these rashes is open to considerable doubt. Allergy to respiratory antigens in the environment is associated with increased serum levels of various IgE antibodies and affected individuals might be expected to have a greater overall incidence of IgE-mediated drug reactions. Some studies do in fact suggest that cutaneous skin reactivity to penicillin antigens is more frequent in allergic individuals (106) although other studies do not support this [reviewed by Parker (84)].

The route of therapy and nature of the drug preparation undoubtedly exert an influence on drug allergy. Anaphylaxis is much less common with oral than with parenterally administered drugs (117) although elicitation by oral exposure certainly does occur. The frequency of other types of allergic reactions may also be somewhat decreased to oral drug preparations although the data available are rather limited. With penicillin, for example, there is generally a lower incidence of allergic reactions with oral, than with intramuscular preparations. However, it is hard to know whether this is due to differences in the purity, or chemical types of penicillins given by the two routes, to differences in blood levels, or even to differences in types of diseases being treated. In guinea

pigs the oral administration of contact skin sensitizers such as picryl chloride induced partial immunologic tolerance to later attempts at cutaneous sensitization (17) and it is conceivable that a similar process may occur during oral treatment in man (84). Vehicles administered with drugs to delay absorption have sometimes acted as immunologic adjuvants and promoted the development of allergy (80). With some drugs such as the antihistamines and penicillin, topical administration on the skin is particularly likely to sensitize. One would suspect that drugs that cross the placenta might produce partial immunologic tolerance in the fetus but the available data are too limited to permit firm conclusions.

Under special circumstances an underlying genetic defect may apparently protect against an allergic drug reaction. This appears to be the case in the Bernard-Soulier syndrome (56) where a surface macromolecule normally present on platelets is absent and the cells are no longer susceptible to damage by serum antibodies from patients with quinine- or quinidine-induced thrombocytopenia (56). While this condition is very rare it does illustrate the potential critical role of normal cell surface macromolecules in antibody or cell-mediated cytotoxic responses involving drugs.

Based on the known role of the major histocompatibility antigen complex in immune responsiveness one would predict that different HLA types would be correlated with an increased or decreased risk of drug allergy. There is a limited amount of experimental data to support this possibility. There is one study in guinea pigs that indicates that the ability to undergo cellular and humoral immune responses to hydralazine is markedly different in two highly inbred strains (32). Since these same strains show impressive differences in their ability to respond to polypeptide and protein antigens (50, 66), it seems likely that innate differences in immune responsiveness per se are involved rather than quantitative or qualitative differences in drug metabolite formation. In an extensive study of humans with rheumatoid arthritis treated with gold or penicillamine, the susceptibility to drug-induced nephropathy was markedly affected by their HLA DR type. With both drugs individuals with the HLA DR3 phenotype have a markedly increased risk of developing nephropathy. The relative risk of proteinuria during treatment with aurothiomalate was 32 times higher in patients who are HLA DRW3 positive than in HLA DRW3 negative patient group. No significant associations were seen between any HLA antigens and cutaneous or hematologic complications. Hughes has observed recently that the HLA DR4 phenotype markedly increases the risk of hydralazine-induced lupus through an effect independent of the rate of acetylation (47).

Pathogenesis of Allergic Tissue Damage

Anaphylactic sensitivity to drugs, like anaphylactic sensitivity to macromolecular antigens is largely or entirely mediated by IgE antibodies. IgE antibodies sensitize by attaching to the surface of basophils and mast cells in a reversible reaction involving high-affinity receptors [reviewed by Sullivan and Kulczycki (119)]. Once the cells are sensitized antigens can trigger them to release their histamine and other allergic mediators such as slow reacting substance (SRS). Secretion is initiated when granule membranes fuse with the plasma membrane opening a channel to the outside of the cell. At this point preformed or newly formed mediators are released into the medium and produce changes in vascular permeability and smooth muscle contraction. SRS, a potent mediator of hypersensitivity produced by mast cells, has been characterized recently by our laboratory (49) as a product of arachidonate metabolism through the lipoxygenase pathway. The cell surface receptor for IgE is a glycoprotein with a molecular weight of about 50,000 which reacts with IgE with an association constant of about 10^{10} liters/mole. The attachment takes place through the Fc portion of the IgE molecule. We have recently obtained highly purified active IgE receptor from a rat basophilic cell line by affinity chromatography and are attempting to determine the structural basis for its interaction with IgE (55).

While the mechanism by which mast cells are stimulated by antigen is not completely clear it is apparent that IgE antibody molecules on the cell surface must be crosslinked by antigen for a reaction to be initiated (120). This requirement for crosslinking explains why univalent penicillin haptens can inhibit allergic responses in penicillin allergy (87, 89).

Two of the earliest intracellular responses during mediator release from rat mast cells are increased phosphorylation of the IgE receptor (45) and a rise in cAMP (120). In view of the established role of protein phosphorylation in the control of enzymatic and transport processes it is tempting to speculate that the increase in receptor phosphorylation is cAMP related and is part of the stimulus for secretion although both postulates remain to be demonstrated directly. In addition the receptor contains a 30,000 molecular weight protein associated with it that probably resides on the cytoplasmic side of the plasma membrane and may be involved in the transmission of the extracellular signal into the cell interior. The stimulated cells also generate hydroxylated fatty acids, some of which are capable of promoting secretion (118).

Serum sickness like anaphylaxis is an antibody-mediated reaction. The antibodies involved probably are largely of the IgG class, as judged primarily by studies of immune complex disease in experimental animals, and to a lesser extent by studies in human drug and foreign protein reactions. IgE antibodies may play an indirect role by leading to the release of histamine and other mediators of immediated hypersensitivity that apparently promote the deposition of immune complexes in blood vessel walls. Some of the small molecular weight antigens that produce serum sickness also produce ana-

phylaxis; this suggests the existence of direct protein reactivity or rapid metabolic conversion to antigenic products. Penicillin, for example, conjugates readily to serum proteins such as albumin in vivo during penicillin therapy, apparently without markedly affecting their metabolic half-life (84). Under these circumstances hapten substituted proteins are available in the circulation at the time antibody begins to be secreted. Multivalence of the initiating antigen is required in serum sickness reactions, just as it is in anaphylactic reactions. Tissue damage occurs when multiply substituted serum protein molecules form aggregates with antibody in moderate antigen excess (84). This leads to the fixation of complement. The aggregates then deposit in blood vessel walls including the glomeruli and attract leukocytes which release lysosomal enzymes and chemotactic factors creating a local inflammatory response. In contrast to serum sickness and anaphylaxis, Arthus reactions are very rarely produced by drugs, probably because neither the antigen nor the antibody concentration is high enough to produce the very intense local inflammatory response that characterizes this lesion. Many allergic drug reactions are probably due primarily to cellular immune reactions. This is certainly true of contact and other forms of eczematous dermatitis produced by drugs and very probably for some systemic drug reactions characterized primarily by fever. In addition, cellular immunity is almost certainly involved in some of the organ directed drug reactions described below, particularly those in which mononuclear cells are prominently represented in the inflammatory response.

In addition to anaphylaxis, serum sickness, and febrile reactions due to generalized cellular hypersensitivity reactions, all of which are systemic allergic drug reactions and characteristically affect multiple organ systems simultaneously, immunologic reactions to drugs may result in damage to individual organs or tissues. Some of these reactions simply represent the localized expression of systemic allergy as in a localized urticarial response that is IgE mediated, but in which not enough antigen is present systemically to produce a generalized response. However, others apparently represent a truly selective form of allergic tissue damage. Reactions of this type are much more frequent with small molecular weight therapeutic agents than they are with macromolecular products. Commonly affected target sites include the liver, kidneys, formed elements of the blood, lungs, heart, muscle, skin, and nervous system (80). Several possible mechanisms for organ direct immune tissue damage in this situation appear possible: 1) The drug may react chemically with the target, introducing haptenic groups on the cell surface and rendering it susceptible to antibody or cell-mediated cytotoxicity. One straightforward example of such a mechanism is penicillin-induced hemolytic anemia; another probable example is quinidine- or quinine-induced thrombocytopenia, where the two drugs apparently interact reversibly with a receptor present on the platelet surface. The basis for localized tissue damages in visceral organs such as the liver is less clear. One possibility is that an enzymatic reaction leading to conjugation of an otherwise unreactive drug to protein is primarily localized in that tissue. This could result in a higher concentration of antigen in that tissue than elsewhere, making it the most likely target in a hypersensitivity response. Sensitization of the tissue would be particularly likely to occur if the metabolite became conjugated to the cell surface, since antibodies and sensitized lymphocytes have immediate access to antigen at this location. In addition to providing a possible basis for localized organ damage in drug allergy, a requirement for metabolic processing and conjugation of a drug with a macromolecule can explain the generally low incidence of drug allergy and its marked variation in frequency depending on the drug. 2) As a second possible explanation for selective cell damage, antigen-antibody complexes may be formed in the fluid phase, react with complement, and secondarily localize on the cell surface, either nonselectively or through Fc or complement receptors. Under these circumstances the cell may be damaged as an innocent bystander. Alternatively soluble products of immune activation produced by lymphocytes, mast cells, monocytes, or polymorphonuclear leukocytes may damage nearby cells and tissues. Obviously reactions of this type are likely to be less intense and selective than reactions where the localization is hapten directed. 3) Chemical or toxic reactions of drugs with cells may increase the immunogenicity of organ specific macromolecules or otherwise increase the accessibility of these macromolecules to the immune system promoting an organ directed autoimmune response. Alternatively the hapten might fortuitously crossreact immunologically with a cellular antigen or interfere with normal homeostatic mechanisms involved in the control of autoimmunity with the same end result.

One way in which a drug might promote the immunogenicity of a normally poorly immunogenic macromolecule such as DNA would be by a reversal of the normal relationship between the immunologic carrier and the hapten. If both hapten protein and hapten DNA conjugates were formed, the more immunogenic protein conjugates would be better able to initiate an immune response (82). As antibodies to the hapten developed, the hapten might then initiate antibody formation to DNA. Unfortunately, while this mechanism is attractive, there is no really good information on the extent to which drugs that induce anti-DNA antibodies conjugate to DNA under normal conditions of pharmacologic use.

Clinical Features of Drug Allergy

Allergic drug reactions are represented by a vast array of clinical syndromes some of which are difficult to distinguish from other forms of human disease. Many have an uncertain mechanism and must be classified as possibly or probably allergic rather than definitely al-

lergic. Subsequent sections will discuss some of the most representative or interesting and perplexing reactions without attempting to be fully comprehensive.

Anaphylaxis

Systemic anaphylaxis is an acute life-threatening allergic reaction characterized by hypotension, bronchospasm, angioedema, urticaria, diffuse erythema, pruritus, pharyngeal or epiglottal edema, cardiac arrhythmias, nausea and vomiting, dyspnea, uterine and intestinal cramping, and hyperperistalsis and it occurs alone or in various combinations (80). Symptoms usually develop within seconds to minutes, reaching a maximum within 5 to 20 minutes. Occasionally, if a repository preparation has been given, the delay is considerably longer. The reaction occurs during the initiation of a new course of treatment with a previously used drug. Approximately 10% of overt anaphylactic reactions are fatal. Death, when it occurs, is usually due to hypotension, laryngeal edema, cardiac arrest, or bronchospasm (84). Anaphylactic symptoms are most frequently produced by parenteral injections, but in highly sensitive persons, oral, percutaneous, vaginal, or even respiratory exposure may produce this response.

Penicillin and structurally related drugs are probably still the most common causes of drug-induced anaphylaxis. At one time it was estimated that there were approximately 500 deaths per year in this country (73), but at the present time the figure is probably lower. There is a long list of other drugs that have been reported to cause anaphylaxis (80). While some of them undoubtedly do, most of them probably act through other mechanisms (see below). The infrequency of drug-induced anaphylaxis is almost certainly due to the relatively low immunogenicity of most nonmacromolecular drugs as well as the requirement that a drug must create a multivalent or conjugate with a soluble macromolecule or cell to elicit an anaphylactic response.

Serum Sickness

Serum sickness is a systemic allergic reaction produced by circulating antigen-antibody complexes characterized by fever, urticarial or maculopapular rash, lymphadenopathy, edema, arthralgia or arthritis, nephritis, neuropathy, and vasculitis. The term was originally applied to foreign serum reactions, but drugs are now the most frequent cause, producing an apparently identical clinical syndrome. In the initial exposure to the causative agent, clinical manifestations normally develop one to three weeks after the initiation of therapy; this reflects the time required for primary sensitization. After a previous sensitizing exposure, accelerated serum sickness may occur within one to two days. Symptoms usually last 10 days or less after the drug is withdrawn, but occasionally a reaction persists for several weeks. Low molecular weight drugs that produce serum sickness include the penicillins, sulfonamides, thiouracils, hydantoins, *p*-aminosalicylic acid, phenylbutazone, thiazides, and streptomycin (4, 68, 77, 123). Nirvanol (5,5-phenylethylhydantoin), a drug used in the past as a sedative and hypnotic, was associated with an exceptionally high incidence of clinical manifestations strongly suggestive of drug allergy, particularly drug fever and serum sickness (15). This substance is formed when mesantoin is demethylated and probably is an important intermediate in allergic reactions to mesantoin. Phenytoin also commonly produces serum sickness, sometimes in the form of a pseudomononucleosis syndrome similar to that of *p*-aminosalicylic acid hypersensitivity.

Hematologic Reactions

Immunologically mediated destruction of erythrocytes, leukocytes, and platelets must be distinguished from direct cytotoxic damage that results in diminished cell synthesis, distribution, or life span (84). Many of the latter reactions involve toxic or idiosyncratic suppression of hemopoietic stem cells in bone marrow although accelerated destruction due to untoward effects on cellular metabolism may also occur. Problems in interpretation are particularly prone to arise with inherited abnormalities of metabolism in which otherwise latent enzymatic defects create undue susceptibility to certain drugs. For example, individuals with congenital glucose-6-phosphate dehydrogenase deficiency develop acute hemolytic anemia during the administration of analgesics, such as aspirin, sulfonamides, antimalarials, and several other agents. Taking reactions of this general nature into account as well as the extent to which cytotoxic drugs that affect formed elements of the blood are now used in the chemotherapy of malignancy and autoimmune disease, there are many more cases of drug-induced thrombocytopenia, anemia, and granulocytopenia due to cytotoxicity than to immunologic reactions.

Thrombocytopenia

The most common proved or strongly suspected causes of immunologically mediated thrombocytopenia are quinine, quinidine, digitoxin, gold, meprobamate, chlorothiazide, rifampin, stibophen, and the sulfonamides (95). In the past allyl-isopropyl-acetylcarbamide was a leading cause (1), particularly in the United Kingdom, and the initial studies elucidating the mechanism of the thrombocytopenia involved this drug. However, with restrictions in use this drug is no longer an important cause. At present, quinidine and quinine probably are the most frequent precipitating agents, at least in the United States. Bleeding and petechial hemorrhages in the skin, related directly to the fall in circulating platelet levels, are the most important symptoms, although rash, fever, arthralgia, and other manifestations of allergy can occur. Bleeding is usually not seen until the platelet count falls to below 50,000. However, bleeding occurs occasionally at higher platelet counts. It has been suggested that a capillary abnormality may exist in this situation due to

loss of a sustaining effect of platelets on endothelial cells or immunologic crossreactivity between these cells and platelets in the presence of the drug (2). While the initial clinical manifestations referable to thrombocytopenia usually develop during treatment, they may be delayed for a week or considerably longer if gold is the inciting agent. In sensitized persons who are challenged with the drug, the blood platelet count usually falls within minutes to a few hours after drug readministration; this strongly suggests peripheral destruction of platelets. Manifestations of bleeding may be preceded by fever, chills, and other constitutional symptoms in this situation and support a role for allergy in the response (1). Examination of the bone marrow usually reveals that the megakaryocytes are normal or elevated; this suggests that platelet formation is not decreased. A marked diminution in megakaryocytes in the early phases of a reaction is usually considered to be indicative of a toxic rather than immunologic reaction. However, decreased platelet synthesis and release may also occur to a limited extent in immunologically mediated thrombocytopenia, particularly when the reaction is prolonged. Discontinuation of the drug ordinarily results in a return of the platelet count to normal within several weeks and sometimes within a few days (69). Blood or platelet transfusions or glucocorticoid administration is usually not necessary but may be helpful, as an interim measure, if bleeding is a problem or the platelet count is below 10,000/mM^3 in the blood.

The immunologic nature of the reaction has been demonstrated both by passive transfer and in vitro studies primarily in thrombocytopenia produced by apronalide, quinine, and quinidine (1, 2, 114). The sera and Ig fractions of affected patients contain antibodies that, in the presence of the drug, produce platelet lysis or agglutination, depending on the antibodies and whether complement is present. Not surprisingly, the antibody can also be detected by changes in platelet function such as altered platelet release reactions, diminished serotonin uptake or delayed clot retraction (1). In all of these assay systems, both the drug and the antibody must be present for a reaction to occur; this indicates that the specificity of the antibody is directed either toward the drug or a drug-platelet complex rather than the platelet per se. Most of the antibodies that have been characterized are members of the IgG class. The response is highly specific in that although quinidine and quinine are closely related structurally, the immune reactivity is limited to one or the other drug, but not both.

In other apparently immune drug-induced thrombocytopenias, in vitro assays for antibodies may sometimes fail probably because a metabolite of the drug is recognized rather than the drug itself. For example, based on in vitro studies, a sulfate-containing metabolite of acetaminophen isolated from the urine has been suspected to be responsible for sensitization in a patient with thrombocytopenia induced by this drug (30). A metabolite of a drug has also been implicated in a case of *p*-aminosalicylic acid-induced thrombocytopenia (31).

This basis for the cooperative interaction between drug (or drug metabolite), antibody, and platelet which leads to platelet damage has been the subject of much speculation. In both quinidine and apronalide sensitivity the cells become susceptible to injury by a reversible reaction of the drug with platelets (24). Quinidine has been shown to affect the susceptibility of platelets to nonspecific aggregation. Moreover, quinidine and quinine can sensitize normal platelets but not platelets from individuals with the Bernard-Soulier syndrome, an inherited disorder characterized by prolonged bleeding time, moderate thrombocytopenia, reduced platelet adherence to endothelial surfaces, and giant circulating platelets (56). The simplest interpretation is that these abnormal platelets apparently lack a surface constituent that is present on normal platelets and is critical for binding of these two drugs to the cell surface. It can be assumed that normal individuals undergo a similar reaction between platelets and drug in vivo sensitizing their cells to antibody and rendering them susceptible either to complement-mediated lysis or phagocytosis by the reticuloendothelial system. While the bond is weak, complex formation between the platelet and the drug may be responsible for the initial immunization by the drug as well as for the immune platelet destruction.

There is no useful animal model for drug-induced immune thrombocytopenia. Antibodies have been prepared in animals to apronalide by conjugating it in diazo linkage to protein (18). However, administration of the drug or even the immunizing hapten-protein conjugate did not result in thrombocytopenia. Nor did the antibody react with human or rabbit platelets in the presence or absence of the drug.

Agranulocytosis

The subject of immunologically induced agranulocytosis has been reviewed recently (84). Proved or suspected immunologically mediated granulocytopenia has been produced by amidopyrine, phenylbutazone, oxyphenbutazone, the sulfonamides, phenothiazines, gold, the thiouracils, antihistamines, anticonvulsants, indomethacin, arsenicals, antidepressants, chloramphenicol, tolbutamide, barbiturates, dipyrone, *p*-aminosalicylic acid, semisynthetic penicillins, and cephalothin (95). Formerly, amidopyrine was the commonest cause of drug-induced agranulocytosis but with decreased use of this drug, because of this potentially fatal complication, the phenothiazines and semisynthetic penicillins are probably now the most frequent cause of this condition, at least in the United States (128). The estimated incidence of agranulocytosis in association with a single course of amidopyrine therapy is about 1%. For propylthiouracil and methimazole the incidence may be a little higher (44, 70, 97). Leukopenia is a complication of chlorpromazine

(and related drug) therapy occurring in about 1 in 10,000 treated individuals (44, 83, 94, 97).

As a rule, the agranulocytosis develops between the second and eighth week of drug therapy, but rarely may not occur until after a year or more of continuous therapy. The dominant clinical manifestations are usually those of infection due to the markedly decreased granulocyte count with associated ineffective host resistance. However, skin rash, fever, and other noninfectious symptoms may be present. Initial symptoms are usually those of severe oropharyngitis with severe edema and ulceration. Not infrequently the initial clinical manifestations are in the anogenital area, which may create difficulty in making the diagnosis. Symptoms usually do not appear until the polymorphonuclear count in the peripheral blood drops to below 800 to 1000 mm^3. In severe cases there may be a reduction in the number of monocytes and lymphocytes but ordinarily these blood elements are unaffected. Bone marrow studies usually reveal a marked diminution in mature granulocytes with a shift to the left, but in severe cases there may be an apparent loss of granulocytic stem cells. Withdrawal of the drug is usually followed by rapid recovery (within one to two weeks) although the disease still has at least 5% to 10% mortality and recovery may require many weeks to months. Management primarily involves withdrawal of the drug, the use of antibiotics, and other supportive measures. Leukocyte transfusions are potentially of value as a temporary measure if suitable facilities are available and transfusions have not been given previously. Androgens and somatotrophin are probably of no value.

The granulocytopenia appears to involve both peripheral destruction of leukocytes and a maturational arrest at the level of bone marrow stem cells. In individuals who have recovered from the reaction and been rechallenged the leukopenia may redevelop rapidly, with changes occurring as early as a few minutes, indicating peripheral destruction of leukocytes (94). This has been most frequently observed with amidopyrine or phenylbutazone induced agranulocytosis. In this situation as little as a few milligrams of the responsible drugs may produce a severe exacerbation of the leukopenia, and if an ordinary therapeutic dose is used fever, chills, arthralgia, and even shock may occur (84). These symptoms may be due to acute leukocyte lysis and the systemic release of leukocytic pyrogens and lysosomal enzymes. However, even in amidopyrine induced agranulocytosis leukocyte precursors in the bone marrow may be decreased suggesting that decreased leukocyte formation is probably contributing to the leukopenia, at least in some individuals (70).

The involvement of serum antibodies in at least some of these reactions is evident from successful passive transfer experiments in which the passive administration of blood, serum, or plasma and drug to another human being or experimental animal has resulted in rapid leukopenia (84). This was originally shown by Moeschlin and Wagner (71), who found that 300 ml of blood from a patient who had had amidopyrine agranulocytosis and had received a further dose of the drug three hours previously, produced acute agranulocytosis in two normal recipients. Subsequent passive transfer studies have yielded variable but sometimes successful results, as have attempts to demonstrate antileukocyte antibodies in vitro by techniques such as leukocyte agglutination. Unfortunately, the usefulness of these assays in vitro for diagnostic purposes is limited since they are difficult to perform and agglutinating activity may not be observed unless the drug has been given within hours to a few days before the blood sample is taken (97). This may involve a requirement for metabolic processing of the drug before it can react with the antibody. Unfortunately, because of the seriousness of the reaction deliberate readministration of the drug for diagnostic purposes is rarely if ever justified. The greatest success in identifying a serum antibody in vitro has been in the study by Weitzman et al. (128) who demonstrated an antineutrophil antibody in the sera of 16 neutropenic patients by using an opsonic assay. The largest number were taking semisynthetic penicillins and in these reactions opsonic activity was only demonstrable when the drug was present, suggesting that penicillin was participating as a hapten. In two other patients receiving antithyroid medications complement was required for opsonic activity. In one it appeared that a true autoantibody to the neutrophil had developed. Serum effects on leukocyte metabolism in the presence of the drug have also been described (8). It was postulated by the authors that the serum contained an antibody or drug antibody complex that was toxic to the leukocytes. Drug and serum effects on granulocyte colony formation in vitro have been reported in a patient with amidopyrine-induced agranulocytosis; this raises the possibility of a direct effect on granulocyte maturation (6). Cellular immune responses were observed in vitro with propylthiouracil and methimazole in five of six patients studied two months to 10 years after these reactions (126).

In contrast to amidopyrine, drugs such as phenothiazine, sulfonamides, and thiouracil often fail to produce acute manifestations when the drug is readministered and the agranulocytosis tends to develop somewhat later in the course of therapy. In addition, anemia and thrombocytopenia are frequently present and the prognosis for complete recovery is not as good. These features suggest that the major site of damage is in the bone marrow. Unfortunately, as with the other immunologically induced blood dyscrasias produced by drugs, attempts to develop a convincing animal model have met with limited success at best (84). Animals immunized with protein conjugates of diazotized 4-amino antipyrine (a metabolic derivative of amidopyrine) did develop a leukopenia when rechallenged with the immunizing conjugate, but the response was transient and mild and the unconjugated drug itself had no effect on the leukocyte count (43). Since leukopenia can occur transiently during any

antigen-antibody reaction, whereas drug-induced agranulocytosis in man is much more severe and prolonged, it is apparent that the effects in animals do not mimic the human disease.

Hemolytic Anemia

A variety of pharmacologic agents has been reported to produce an immune hemolytic anemia, particularly penicillin and α-methyldopa. Other agents include dipyrone, *p*-aminosalicylic acid, stibophen, quinine, quinidine, and phenacetin (77, 84, 95, 123). α-Methyldopa produces its effect on red cells by inducing an autoantibody and will be discussed in the section on drug-induced autoimmune disease. Penicillin-induced hemolytic anemia is an example of an immunodestructive response in which the drug participates as a hapten. It is an occasional complication in individuals receiving prolonged high-dose penicillin therapy (94, 124). For hemolytic anemia induced by benzyl penicillin the dose of penicillin is almost always at least 10,000,000 units/day given over a period of several weeks or more. At sustained high penicillin blood levels the red cells become substituted with penicillin haptens. In about 3% of individuals enough antihapten antibody is produced to give a positive antiglobulin (Coombs') reaction on the red cells. Occasionally complement components can also be demonstrated, but as a rule the evidence for complement activation is minimal. If enough of the right kind of antihapten antibody is present, there is accelerated red cell destruction. If the bone marrow cannot compensate, anemia develops. However, the anemia is usually mild and clinical improvement is rapid after the termination of drug therapy since newly synthesized erythrocytes have not reacted with penicillin and, therefore, survive normally. The causative role of penicillin in the hemolytic process has been demonstrated conclusively in several cases by showing that readministration of the drug after recovery caused reappearance of hemolysis.

The red cell destruction is produced by a classical antibody-hapten mechanism. The serum of affected individuals contains antibodies which react with normal red blood cells sensitized with penicillin. The sensitization involves the formation of stable bonds between penicillin breakdown products, particularly the penicilloyl group and the red cell surface (122). Virtually everyone receiving penicillin makes some antipenicillin antibodies but amount or type of antibody may not be appropriate to produce red cell destruction or the red cells may not contain enough hapten to serve as an immunologic target.

A positive antiglobulin reaction occurs in a high percentage of individuals receiving cephalothin, but apparently involves a nonimmunologic reaction in which the cephalothin reacts with serum proteins (including immunoglobulin, complement, or fibrinogen) that become nonspecifically absorbed to the red cell surface. Very few patients treated with cephalothin have developed significant anemia. As far as the other drugs that may produce an immune hemolytic anemia are concerned, there are a few well-studied individual cases supporting specific mechanisms but the available data are limited. Some of these reactions have been described as involving an "innocent bystander" mechanism in which the red cells are damaged nonselectively by circulating immune complexes and perhaps by secondary binding to complement receptors on the red cells that have taken up complement but the documentation for this mechanism is very limited.

Drug-Induced Autoimmunity

Examples or possible examples of drug-induced autoimmunity include SLE induced by hydralazine, procainamide, and isoniazid; hemolytic anemia by α-methyldopa; polymyositis and hemorrhagic alveolitis by penicillamine, hepatitis by oxyphenisatin, venocuran, and halothane: scleroderma by vinyl chloride; Sjogren's syndrome by practolol; tubular nephropathy by penicillin; antifactor VIII antibodies by penicillin (29, 53, 84, 121).

A clinical syndrome resembling SLE has been observed during treatment with hydralazine (93), procainamide (27, 104, 121), isoniazid, oral contraceptive pills, griseofulvin, methyldopa, tetracycline, thiouracil, penicillamine, antimalarials, practolol, and anticonvulsant agents (3, 11). Clinical manifestations include polyarthritis, polyserositis, fever, lymphadenopathy, dermatitis, leukopenia, and hyperglobulinemia. A common feature of drug-induced lupus is that the drugs involved had been used over at least a six- to eight-week period before symptoms appeared. As a rule the symptoms and laboratory manifestations subside slowly over a period of at least several months after the drug is withdrawn. The sera of patients with this syndrome contain antibodies to single stranded DNA and not infrequently LE cell producing antibodies also are present (3). Antinuclear antibodies may also be present in the absence of overt clinical symptoms. Procainamide has the highest propensity for causing drug-induced lupus. More than two-thirds of patients taking procainamide in sizeable doses over a several-month period develop antinuclear antibodies (10). About 10% of patients with hypertension receiving hydralazine in moderate to large doses over a period of at least several months develop clinical symptoms of a lupus-like syndrome, but a higher percentage develop serologic abnormalities. Antinuclear antibodies have been demonstrated in up to 20% of patients receiving isoniazid therapy for active tuberculosis but overt clinical manifestations are unusual. The other drugs produce lupus-like syndromes much less frequently. For hydralazine, the frequency of serologic abnormalities and symptoms is strongly correlated with the amount of drug administered and individuals who metabolize the drug slowly (slow acetylators) are particularly at risk.

Most or all of the responsible drugs appear to produce a lupus-like syndrome de novo rather than activating

latent SLE (84). 1) As already noted the majority of persons receiving sustained procainamide therapy in substantial dosage develop antinuclear antibodies. In addition, in a prospective study of patients going on procainamide therapy most of the individuals developing antinuclear antibodies during treatment had had negative serologic reactions for these antibodies originally (10). 2) In general, clinical patterns differ in drug-induced and spontaneous SLE in that involvement of male patients is relatively frequent and leukopenia, anemia, nervous system, cutaneous, and renal involvement are less frequent (42, 46). 3) Serum complement levels in drug-induced SLE are normal in contrast to spontaneously occurring, clinically active SLE (123). 4) The specificity of the anti-DNA antibodies differs in that antibodies reactive with native (double stranded) DNA are much more frequent in SLE than in drug-induced lupus. Moreover, the specificity of the antibodies in drug-induced SLE may show considerable selectivity. In hydralazine-induced lupus, for example, the antibodies are primarily directed toward histones, which is very unusual in spontaneous SLE.

α-Methyldopa produces an autoimmune hemolytic anemia in which the antibodies are directed toward native antigens on the red cell surface and the drug is clearly not required as a hapten in the reaction (130). Clinically significant hemolysis develops in something under 1% of individuals receiving the drug in substantial dosage over a period of at least several months. However, red cell bound antibodies (as indicated by direct Coombs' antiglobulin reactivity) is demonstrable in as many as 10% to 15% of treated individuals (130); this indicates that antibody formation is relatively frequent. α-Methyldopa induced hemolytic anemia is more common in Caucasians than in blacks, Orientals, and Indians, suggesting the importance of genetic factors. Evidence of immunoglobulin binding to red cells is almost always delayed for at least several months after the start of treatment. This delay is not shortened when a patient with a previous positive reaction that has subsided is restarted on the drug. In addition to α-methyldopa, mefanamic acid (which is unrelated structurally to α-methyldopa) has been reported to cause autoimmune anemia involving autoantigens on the red cell whereas L-dopa (a structurally related drug) causes a positive antiglobulin reaction but very rarely produces overt hemolysis.

The antibodies involved in α-methyldopa induced autoimmune hemolytic anemia are IgG immunoglobulins predominantly in the IgG_1 subclass. They have specificity for ordinary Rh determinants present in many individuals and unlike penicillin-induced hemolytic anemia there is no requirement that the drug be present in order for a reaction to occur. In hemolytic anemia associated with α-methyldopa administration, an antibody eluted from the patient's red cells when clinical manifestations of hemolysis were at a maximum was stored and later was shown to bind to the patient's own red cells, well after recovery when the antiglobulin test was negative. Thus, a true autoantibody was present with reactivity for autologous red blood cells synthesized when no drug was available. After cessation of α-methyldopa therapy, clinical improvement usually occurs slowly over a matter of months and positive antiglobulin reactivity may persist for at least several years. The major difference from the anti-Rh antibody in spontaneously occurring autoimmune hemolytic anemia is its lower affinity and greater heterogeneity of specificity and structure (5). The lower affinity may explain why individuals who receive the drug frequently have a positive direct Coombs' test, but fail to develop anemia. There is a good correlation between the incidence of a positive antiglobulin reaction and the dose of the drug administered.

Another possible relationship between a drug and an autoimmune process is the hemorrhagic alveolitis simulating Goodpasture's syndrome, seen in association with penicillamine therapy. Polymyositis has also been described in individuals with rheumatoid arthritis treated with penicillamine and while rheumatoid arthritis itself may cause muscle inflammation, remission and exacerbation of muscle manifestations occurred in association with withdrawal and reinstitution of the drug (19).

A clinical syndrome related to but distinct from drug-induced SLE has been produced by venocuran, which is a mixture of pharmacologically active substances used in the treatment of venous disease in Europe. Affected individuals developed symptoms very similar to those in drug-induced lupus, including arthralgia, pleuritis, fever, myalgia, and pericarditis, but the serum contained primarily antimitochondrial instead of antinuclear antibodies.

Another very interesting reaction to a drug simulating a spontaneously occurring connective tissue disorder has been seen in response to practolol, which was used at one time therapeutically as a selective β-blocking agent. The affected individuals developed eye manifestations similar to those in Sjogren's syndrome, a common autoimmune disorder affecting the eyes, joints, and exocrine glands, (33). Practolol and other β-blocking agents also produce a lupus-like syndrome.

Penicillin produces a tubular nephropathy in which both humoral and cellular immune mechanisms have been postulated. It appears possible that penicillin-induced nephropathy may initiate the development of autoimmunity to renal tubular antigens in this situation. The serum of one patient with nephropathy occurring during penicillin therapy contained antibodies reactive with tubular epithelial basement membrane in a normal kidney that had not been exposed to penicillin (12). The presence of the antitubular basement antibodies suggests a drug-induced autoimmune reaction in which renal tubular cells exposed to high concentrations of penicillin became chemically altered; this results in the interruption of immunologic tolerance (80).

An inhibitor of coagulation factor VIII which may or may not produce bleeding manifestations has been de-

scribed in association with penicillin therapy (53). The inhibitor appears to be an antibody with specificity either for factor VIII alone or for both factor VIII and penicillin. In one study penicillin was reported to block the antifactor VIII activity of the immunoglobulin, and a resin containing bound penicillin removed it entirely. One possible explanation is that an antipenicillin antibody is present which has fortuitous crossreactivity for an area on the factor VIII molecule which is critical in its procoagulant activity (84).

Induction of antibodies and sensitized lymphocytes with specificity for a cell surface lipoprotein autoantigen in hepatocytes has been suggested as a possible disease mechanism in oxyphenisatin and α-methyldopa induced chronic active hepatitis, where the disease progresses after the drug is withdrawn (29). Some evidence is available to indicate that an autoimmune reaction to this antigen may contribute to the acute liver damage in halothane-induced hepatitis.

Some possible, but not necessarily mutually exclusive mechanisms for drug-induced autoimmunity have recently been presented (85): 1) direct substitution of the hapten on a protein or other macromolecule altering it immunologically and breaking immunologic tolerance; 2) a direct effect of the drug on normal immune control mechanisms, such as a direct toxic or pharmacologic action interfering with normal suppressor T cell function or blocking of the reticuloendothelial system leading to ineffective immune complex disposal; 3) an immune response to the drug with a fortuitous crossreaction between the haptenic determinant of a drug and a normal tissue antigen; 4) a superimposition of an immunologic response to a drug on a preexisting subliminal autoimmune process leading to overload of normal control mechanisms; 5) denaturation or redistribution of a normal tissue constituent due to drug binding or drug induced cytotoxicity; 6) activation of a latent viral or other infection due to nonspecific immunosupression or a direct metabolic action of a drug; 7) an action of the drug as a direct polyclonal mitogen or some other form of immunologic adjuvant.

As discussed above, the possibility that drug-induced SLE is due to unmasking of latent classical SLE by the drug now seems largely excluded by prospective studies, the different spectra of organ involvement and certain differences in the specificities of the autoantibodies formed in the drug-induced and spontaneous forms of the disease (84). One situation in which a drug appears to be acting by affecting normal immune control mechanisms is the enhanced immunologic activity associated with cytoxan and therapeutic radiation. While such treatments can suppress autoimmune processes, under the right circumstances they may also enhance them, as has been clearly shown in the inbred mouse models for SLE. This enhancement by cyclophosphamide is probably due to a direct cytotoxic effect on suppressor T cells. Interestingly IgE responses appear to be particularly susceptible to control by suppressor T cells and, while documentation in man is limited, in animals cyclophosphamide has been shown to produce very marked increases in IgE antibody formation. Exacerbations of SLE reported in association with estrogen therapy (usually in the form of contraceptive drug combinations) are presumably due to a direct hormonal action, perhaps at the level of immune B cells or T cells since sex hormones profoundly affect the course of SLE in animal models for the disease. In regard to the lupus-like syndromes associated with β-adrenergic blocking agent therapy, it should be noted that T cells contain receptors for catecholamines and are altered functionally by adrenergic agonists and antagonists. One of the drugs that produces a lupus-like syndrome in man, procainamide, recently has been reported to directly stimulate B cells in vitro. Since polyclonal mitogens for B cells such as lipopolysaccharide can stimulate autoantibody formation in vivo in genetically predisposed mice this observation is of interest although convincing evidence that procainamide can function as a polyclonal mitogen in vivo is not yet available.

A number of the drugs that produce lupus-like syndromes are nitrogen-containing compounds with one or two benzene rings which are susceptible to oxidation (82, 84). Antibodies formed in response to these drugs might fortuitously crossreact with one or more of the bases in DNA. Indeed Hess, and Litwin, and associates (132) have artificially conjugated hydralazine and a hydralazine metabolite to serum albumin and induced antibodies in rabbits that reacted with DNA as well as with haptens. Moreover, patients with hydralazine-induced lupus have antibodies that react with diazotized hydralazine coupled to red cells and their lymphocytes undergo very weak but possibly significant responses to the free drug, suggesting that an immune response to the hydralazine may have occurred (42). Moreover, direct evidence is emerging that hydralazine and procainamide give rise to reactive metabolites in vitro when the appropriate hepatic enzyme systems are present (85). In addition, procainamide can be induced photochemically to react with DNA increasing its antigenicity (9). If reactive metabolites of procainamide and hydralazine interacted to differing extents with different macromolecules in the nucleus this would explain the distinctive antinuclear reactivities seen with the two drugs which differ from one another and from spontaneous SLE. While a nonselective interruption of immunologic tolerance still has to be considered, I find this possibility to be considerably less attractive, at least for most of the drugs that produce lupus-like syndromes.

The mechanism of the formation of the autoantibodies in α-methyldopa-induced hemolytic anemia is unclear (84). While there is no convincing evidence that the drug is acting as a hapten, it might be denaturing the red cell surface making the Rh antigens more immunogenic; α-methyldopa is subject to autooxidation giving it potential

reactivity with protein and it can even be used as a substitute amino acid in a protein. A pharmacologic effect on the immune system of affecting normal mechanisms of tolerance also has to be considered. In this connection it is of interest that antinuclear antibodies and rheumatoid factor activity are not infrequently demonstrable in patients with a positive Coombs' test while taking α-methyldopa. However, such antibodies are often not demonstrable in other patients with α-methyldopa-induced anemia or with mefenamic-acid-induced hemolytic anemia making the significance of this finding unclear. Certainly the spectrum of autoantibodies is considerably less impressive than it is in spontaneously occurring SLE.

Organ-Directed Drug Reactions Suspected to Be Allergic

The role of allergy in drug-induced inflammation of the liver, kidney, lungs, and blood vessels is not well delineated. Many of the reactions in the liver appear to involve some form of direct toxicity, as suggested by a higher overall reaction frequency, rapid induction of symptoms in the absence of known previous exposure, a reasonably consistent dose dependency in different individuals, an inability to demonstrate marked fluctuations in sensitivity in serial studies of the same individuals, and an absence of pathologic features which suggest an allergic response. Moreover, some of the offending agents produce direct toxic effects on liver cells in vitro indicating that a straightforward mechanism exists for the production of tissue damage that does not require the participation of the immune system (78, 80). On the other hand, some of these reactions have features which strongly suggest an immune mechanism. Drug-induced hepatitis will be used for purposes of discussion since drug reactions involving the liver are common and medically important. Moreover, they illustrate some of the problems in interpretation for all forms of organ directed drug toxicity where allergy is suspected as a possible mechanism.

The first drug to receive widespread attention as a possible cause of allergic hepatitis was thorazine (chlorpromazine). Jaundice has been reported to occur in 1% to 3% of all patients receiving chlorpromazine (135). The clinical picture is that of a cholestatic jaundice closely simulating primary biliary cirrhosis and extrahepatic biliary obstruction (133). Clinical or laboratory evidence of marked hepatocellular damage is rare, but mixed hepatocanicular picture is not infrequent (135). Other phenothiazines and chlordiazepoxide produce a similar clinical syndrome. Generally there is a latent period of one to four weeks after beginning treatment before the onset of jaundice. If jaundice does not occur within the first few weeks of phenothiazine treatment, it is unlikely to occur later although there are rare exceptions. As far as extrahepatic manifestations suggestive of allergy are concerned, rash or leukopenia is present in only about 5% of patients but eosinophilia is present in about two-thirds (48). Liver biopsy is very helpful in the differential diagnosis. The typical pathologic change is that of cholestatic hepatitis, frequently with eosinophilic and lymphocyte infiltration in the peripheral areas. In approximately 50% of patients readministration of small doses of the drug results in prompt recurrence of jaundice, other manifestations of hepatic dysfunction or both. Hyposensitization has been possible in a few individuals, usually by cautious readministration after a period of drug withdrawal. However, further use of these drugs when a reaction is known or strongly suspected is justified only rarely. In the absence of further drug therapy the prognosis for complete recovery is very good—one-third of patients recover completely within four weeks, another third in four to eight weeks (135). The remainder require at least several months to return to normal. Occasionally there is a prolonged course with clinical, histologic, and biochemical features typical of primary biliary cirrhosis.

More recently the fulminating hepatitis induced by halothane has been strongly suspected to have an allergic etiology and has received particular attention. Halothane (2-broma-2-chloro-1,1,1 trifluoroethane), was introduced into clinical pharmacologic use as a general anesthetic in 1956 and had since gained more or less general acceptance as the agent of choice for generalized anesthesia. The clinical picture of the hepatitis is primarily that of acute hepatocellular dysfunction, developing a few days to several weeks after generalized halothane anesthesia. Halothane-induced hepatitis typically occurs in an individual who has been exposed previously to the same agent. In a recent study, 24 of the 26 patients with hepatitis had received halothane more than once and 18 had it twice within a four-week period (72). Multiple exposures to halothane within the same four-week period appear to be particularly hazardous, although even here the risk of jaundice is probably no greater than 1 to 3 per 6000 patients. When jaundice occurs after halothane use, the prognosis is serious. In a review by Little in 1968 (62) the mortality rate was calculated to be 35% in the 400 patients who had developed this complication. If recovery occurs, however, it is almost always complete. In nonfatal cases there is diffuse hepatocellular injury resembling the pathologic picture found in acute viral hepatitis. In fatal cases there is likely to be widespread necrosis which may be particularly marked in the centrizonal areas, and resembles the lesion of acute carbon tetrachloride poisoning.

The possible role of allergy in halothane hepatitis has been much discussed (127). Apart from the frequent history of multiple exposures to halothane in affected individuals, perhaps the most striking indication that allergy may be involved is the description of an anesthesiologist who developed jaundice repeatedly after administering anesthesia with halothane. Also, jaundice occurring after halothane use is sometimes accompanied by eosinophilia. Fever is usually a premonitory manifesta-

tion of the liver dysfunction, often appearing four to six days postoperatively, followed by jaundice within the next several days. After multiple recent exposures to halothane the fever may recur within several hours. The accelerated appearance of fever in a situation where a prior sensitization may have occurred is certainly consistent with an allergic reaction. On the other hand, some of the suggestive features present in the hepatitis induced by phenothiazine are absent.

The hepatitis induced by anticonvulsants, aminosalicylates, sulfonamides, and α-methyldopa is similar to that produced by the phenothiazines and to a less extent to halothane reactions in that there is frequently one or more features that suggest allergic inflammation including fever, skin rash, eosinophilia, leukopenia, infiltration of the liver with eosinophiles, lymphocytes or plasmacytes, lymphodenopathy, and recrudescence or appearance for the first time of symptoms on reexposure to low doses of the drug (82, 84, 115, 116, 134). Moreover, the onset of hepatitis is typically delayed and some individuals who have previously failed to tolerate the drug can tolerate it in full dosage later. Other individuals taking equal or even much greater quantities of these drugs may show no evidence of hepatic damage, whereas some may develop a recrudescence of symptoms when challenged with very small quantities of drug. Finally, a number of these drugs are recognized as causing allergic reactions outside the liver thus increasing the possibility that hepatic inflammation might occur on a similar basis. Manifestations suggestive of allergy may also be present in hepatic reactions to phenylbutazone, zoxazolamine, nitrofurantoins, iproniazid, indomethacin, isoniazid, chlorpropamide, and erythromycin estolate (82, 84, 134).

Despite certain pathologic, clinical, and epidemiologic features suggestive of allergy in these reactions, the only definitive way of proving that the reaction to a drug is immunologic is to demonstrate that there is altered immunologic reactivity (85). In view of the importance of the liver microsomal cytochrome P-450 system in the overall oxidative metabolism of drugs (100), one might suspect that the formation of reactive metabolites presumably involved in drug immunogenicity would be particularly prominent in the liver, but at present there is no real evidence directly implicating this pathway in allergic responsiveness either within or outside the liver (82). Even under circumstances in which large quantities of active metabolites are known to be formed in the liver and to produce direct hepatotoxicity, as in acute acetaminophen poisoning, there is no evidence for an associated immune response. However, admittedly this possibility may not have been subjected to careful analysis. It is perhaps more significant that no real evidence implicating an allergic mechanism in thorazine-induced jaundice has been forthcoming even though this form of liver disease has been presumed to be a major model for drug-induced allergic hepatitis for many years.

Attempts to directly substantiate that an immune mechanism exists in halothane-induced hepatitis have been more suggestive, but as yet have to be considered as inconclusive. Paronetto and Popper (92) reported that positive lymphocyte transformation responses could be obtained with halothane in 10 of 15 subjects with suspected halothane hepatitis. However, with rare exceptions subsequent similar studies have been negative or unconvincing (127). On the other hand Price et al. (98) and Davis et al. (20) have reported that a high percentage of patients show a modest but significant lymphokine response [production of a factor that inhibits leukocyte migration (LIF)] when their lymphocytes are stimulated by halothane. Moreover, Eddleston and his colleagues have observed that positive responses can sometimes be obtained by administering the drug to rabbits, allowing time (usually 12 hours) for the drug to be metabolized in the liver, obtaining crude liver homogenates, and using these preparations to stimulate lymphokine production by lymphocytes from patients with halothane hepatitis (29). Moreover, the serum of these individuals appeared to contain antibodies which reacted with the liver cells of halothane treated animals. However, not all individuals with halothane-induced liver damage showed evidence of altered immune reactivity and alterations were sometimes absent when the patient was first examined even though liver damage was already present and later immunologic analysis was positive (25). Mathieu et al. (65) have reported that trifluoroacetate, a metabolite of fluroxene and halothane, can be conjugated to serum proteins and animal liver cells and used to induce delayed hypersensitivity in guinea pigs; this suggests that a specific metabolite might be responsible for the induction of an immune response to halothane. Taking the results of these various studies together, it appears that an immune response can occur in association with halothane hepatitis. However, it remains to be demonstrated that allergy plays a major role in the initial tissue destruction occurring in this organ.

Reactions Involving Lymphoid Cells

Phenytoin- or mephenytoin-induced serum sickness may be associated with or superseded by prolonged and marked lymphadenopathy, occasionally simulating malignant lymphoma (107). Less frequently other drugs such as sulfonamides, propylthiouracil, *p*-aminosalicylic acid, and procainamide may produce this response (84). This syndrome may also occur in the absence of an overt serum sickness episode. As a rule clinical manifestations improve considerably or subside completely within a few weeks after the drug is withdrawn. In rare instances patients with hydantoin-induced lymphadenopathy have gone on to develop progressive manifestations of invasive lymphoid disease with classic manifestations of Hodgkin's disease or other form of lymphoma at autopsy. Whether this represents the de novo development of lymphoma related to drug use due to an unusually intense immunologic stimulus without effective negative

feedback, failure of immune surveillance, or a chance association with spontaneously developing lymphomas is not clear (116). Certainly these antiepileptic agents are commonly used drugs and this particular complication is rare. Nonetheless, it is of interest that sustained phenytoin therapy may be associated with decreased production of immunoglobulins, particularly IgA, as indicated by decreased serum levels, so it is possible that the drug is sufficiently potent as an immunosuppressive agent to interfere with normal immunologic surveillance. In a study by Grob and Herold (40, 41) decreased IgA levels were present in 5 of 20 patients who had received prolonged treatment with phenytoin in substantial dosage. Only one of these individuals had lymphadenopathy. Decreased complement levels were also frequent in this study, as were negative reactions to delayed skin antigens. Prolonged administration of phenytoin may also be associated with altered peripheral blood lymphocyte numbers and spontaneous incorporation of tritiated thymidine into these cells in vitro, suggesting that activation may be occurring in vivo (63). Direct effects of phenytoin in vitro on normal lymphocyte responses to mitogens also have been described. Whether these effects explain the depression of IgA levels and alterations in delayed cutaneous sensitivity seen in vivo remains to be established. The drug concentrations required for in vitro effects are high and other mechanisms need to be considered.

A clinical syndrome possibly related to drug-induced lymphadenopathy is immunoblastic lymphadenopathy, a frequently fatal, quasi-neoplastic condition characterized clinically by hyperglobulinemia and lymphadenopathy (38, 54, 99). The lymph nodes in this disease show marked accumulation of immunoblasts, plasma cells and lymphocytes, and extensive proliferation of small blood vessels, frequently with destruction of nodal structure (38). Extracellular deposition of an uncharacterized amorphous acidophilic periodic acid-Schiff positive material is frequently present. Less marked morphologic changes are present in the spleen, liver, and bone marrow. The disease usually occurs in patients over the age of 50, beginning suddenly, frequently in association with therapy with drugs such as penicillin or phenytoin or after a recent acute infection. Other manifestations may include fever, hepatosplenomegaly, Coombs' positive hemolytic anemia, leukocytosis, and thrombocytopenia. Frequently, the clinical course is rapidly downhill with more than half of the patients dying within two years (99). The hypergammaglobulinemia is usually of the polyclonal type with increases in the serum concentration of several immunoglobulin classes. Dysgammaglobulinemia may also occur and monoclonal bands are occassionally present. Autoantibodies of various types may be demonstrable in the serum. Marked increases in the percentage of B-lymphocytes, some of which have a plasmacytoid appearance, may be demonstrable in the peripheral blood. Altered responsiveness of peripheral blood B cells to lipopolysaccharide, a nonspecific B cell mitogen (39), may be demonstrable (54).

The nature of the disease, taken together with the ability of both drugs and acute infections to precipitate it, suggests that the initiating event may be an antigenic stimulus that is not handled appropriately by the immune system presumably because normal mechanisms for the control of lymphoid proliferation fail. This may lead not only to encroachment by the proliferating lymphocytes on surrounding tissue but also to the release of lymphokines that alter the response of otherwise unaffected lymphocytes and act directly on small blood vessels to induce their proliferation.

Acute Systemic Drug Reactions Simulating Allergy

Many acute life-threatening systemic reactions to drugs or diagnostic agents have an uncertain etiology (85). Although systemic anaphylaxis is simulated clinically and is difficult to exclude, most of these reactions are probably nonallergic in etiology. Some may be due to the nonspecific release of vasoactive amines or some other form of activation of nonspecific immunologic effector mechanisms, although pharmacologic hypersensitivity or allergy also must be considered. Iodinated radioopaque dyes which cause severe reactions in about 1 in 1000 examinations release histamine nonspecifically by a direct effect on mast cells or basophils, although high concentrations are required (34, 102). Moreover, it has been reported in dogs that contrast media produce an elevation in plasma histamine in veins draining organs with a high histamine content (58) and that histamine levels may be increased in peripheral blood and may occur during examination with contrast media (13). Since the contrast dye solutions used clinically are markedly hypertonic the possible importance of osmotic effects in these responses have been repeatedly considered (34, 102). This is an attractive possibility since hypertonic solutions of sucrose and glucose can also produce systemic reactions and stimulate histamine release in vitro (34). Another possible cause of iodinated dye reactions is activation by the alternative pathway of the complement system. This might result in the formation of histamine-releasing peptides (anaphylotoxins) or other peptides which act on small blood vessels. While a role for anaphylactic mediators in these reactions is attractive, histamine itself may not be the major mediator. Moreover, it should be kept in mind that increases in plasma histamine can occur during contrast dye infusions in the absence of any symptoms. Obviously further studies in regard to possible mechanisms are needed.

Intravenous anesthetic agents that have caused acute systemic reactions resembling anaphylaxis include althesin, thiopentone, suxamethonium, *d*-tubocurarine, propanidid, and methylhexitone (28, 35). In a recent survey of 86 episodes of hypersensitivity to i.v. anesthetic agents, althesin was responsible in 70 and thiopentone in

12; all 4 deaths were due to thiopentone (28). Althesin produced a serious reaction in about 1 in 15,000 administrations of the drug. While the incidence of reactions to these agents is apparently increasing, this may be due to increased reporting. Pentothal, a short-acting barbiturate given i.v. for brief general anesthesia also occasionally causes acute laryngeal or bronchial spasm. While the role of allergy in these reactions is uncertain, it is suggested by the frequency, reported to be as high as 90% (28), with which serious reactions followed the use of an agent which had caused a previous reaction. Most of these agents have been reported to produce acute increases in plasma levels of histamine, but the mechanism of the increase is not clear (35).

Local anesthetics may produce a variety of systemic symptoms including disorientation, urticaria, circulatory or respiratory collapse, convulsions, and coma. A role for allergy is suspected in some of these reactions but is not well-documented experimentally. Fortunately, even when a serious reaction has occurred it is ordinarily safe to substitute a structurally unrelated local anesthetic if future local anesthetic use is required (84).

Opiates produce nonspecific skin responses when injected locally, probably because they are nonspecific releasers of histamine and presumably other mediators of immediate hypersensitivity (83). In vitro studies indicate that the addition of codeine and morphine to isolated mast cells or basophils in vitro can directly stimulate histamine release (52). The role of pharmacologic mediators of hypersensitivity in systemic reactions to opiates is much more uncertain (83). Very large quantities of opiates given i.v., particularly heroin, in addicted or nonaddicted individuals may produce acute respiratory distress, as well as respiratory depression and the clinical and pathologic changes of acute pulmonary edema (26, 36, 37, 103). This has become an important cause of death in teenagers and young adults in this country, particularly in low income urban areas. Barbiturates which do not resemble heroin structurally also cause pulmonary edema when given in marked overdosage, although this is considerably less common (37). The acute pulmonary edema syndrome can also occur after oral overdosage with narcotics or nasal insufflation; this indicates that exposure via the i.v. route is not obligatory (26, 36, 37). The syndrome of respiratory depression induced by heroin and other addictive drugs is usually accompanied by stupor and malaise, thus suggesting a possible role for hypoxia in the response. However, occasionally the pulmonary edema has not become clinically overt until after the respiratory depression has subsided; this suggest that hypoxia per se may not be crucial in the response. The role for allergy in these reactions is doubtful. To my knowledge systematic attempts to demonstrate IgE antibodies to opiates by cutaneous testing have not been reported but would be complicated by the nonspecific irritancy of these drugs in the skin in any event. Although bronchospasm may be induced by opiates, particularly in a drug abuser who also has chronic bronchial asthma, the usual clinical and pathological picture in the lung following an overdose of heroin is not that of an acute allergic reaction. Moreover, circulatory collapse is not a prominent early clinical feature and it has been reported that the entire clinical syndrome can be reproduced during an initial exposure to the drug (103). It seems possible that the change in pulmonary function involves a combination of localized nonspecific histamine release in the lung resulting in increased pulmonary capillary permeability, usually in combination with central respiratory depression (83). Brashear et al. (14) have reported that i.v. injections of heroin or morphine can produce increased plasma histamine concentration in dogs.

While the acute pulmonary edema produced by heroin abuse is almost certainly not an anaphylactically mediated reaction, there is evidence to indicate that antibody formation does occur during chronic opiate use in man. Most opiate addicts studied in New Mexico (105) showed increased levels of one or several immunoglobulins in their serum. Moreover, many sera of these contained increased binding activity for radiolabeled morphine. While a subsequent study did not confirm this latter finding (120), a radioactive hapten marker of lower specificity was employed that may have reduced the sensitivity of the analysis. It is also quite possible that regional differences in the drug preparations used by addicts in the two studies might explain the variation in results. The evidence for morphine immunogenicity in man is supported by studies in experimental animals in which it has been shown that antimorphine antibodies are produced in rabbits when morphine is administered repeatedly in adjuvant (101). Transformed lymphocytes are not infrequently seen in the peripheral blood in opiate addicts, providing possible further support for an in vivo allergic drug reaction (109). Nonetheless, there is some evidence that the abnormality in lymphocyte morphology may persist after all known use of the drug has been stopped, so, it may not be related to an ongoing immunologic response as such. Indeed, evidence is emerging that opiates may exert a pharmacologic action on human peripheral blood lymphocytes, particularly T cells.

In addition to possible allergic manifestations, a major role for antimorphine antibody formation in induction of tolerance to the pharmacologic actions of narcotic agents has been suggested. While there is no doubt that antibodies can partially block or reverse the effects of opiates in experimental animals in vivo when limited amounts of opiates are given, it is very doubtful that the usual manifestations of opiate tolerance can be explained by this mechanism (83). It is unlikely that enough antibody could be produced to neutralize the very large quantities of opiates that can be tolerated in individuals who are chronically addicted. Moreover, tolerogenic effects of opiates can be demonstrated locally at the level of the responding cells in the central nervous system under conditions in which the immune system cannot be implicated.

Even though it is very doubtful that antiopiate anti-

bodies can be implicated in opiate tolerance, as reported originally in 1970 by Spector and Parker, conjugates of morphine and related agents with proteins can be used to raise antimorphine antibodies for use in radioimmunoassays and pharmacologic studies. Such antibodies have been widely used in the detection and experimental study of opiate addiction. As discussed elsewhere in this symposium, suitably chosen antibodies readily discriminate between heroin, morphine, methadone, and other drugs.

In susceptible individuals aspirin produces rhinitis, acute bronchospasm, urticaria, or, even very rarely, sudden death. A few of these reactions appear to represent IgE-mediated reactions to aspiroyl groups probably due to the presence of aspiroyl anhydrides in commercial aspirin (83). However, the vast majority probably have some other mechanism which may involve an ability of aspirin to nonspecifically release histamine and other pharmacologic mediators of immediate hypersensitivity, such as SRS. Some individuals with aspirin sensitivity have a history of vasomotor rhinitis and asthma, often present for many years before difficulties with aspirin are identified (108). Aspirin also may cause symptomatic exacerbations in individuals with urticaria, regardless of the underlying cause. As a rule, respiratory symptoms are absent when urticaria is prominent thus indicating a different site or possibly even a different mechanism of action than in aspirin sensitive asthma. When individuals with adult onset idiopathic asthma who do not have known aspirin sensitivity are challenged under controlled conditions with aspirin, approximately 10% experience an acute exacerbation of their respiratory symptoms that appear from 10 minutes up to four hours after challenge. When the challenge is repeated the response may be much less marked, suggesting the depletion of an inflammatory mediator (67).

The mechanism of these reactions is not completely clear. Organic chemicals such as tartrazine, a yellow dye used as a food and drug additive, and other nonsteroidal antiinflammatory agents (antipyrine, mefenamic acid, or idomethacin), which do not resemble aspirin structurally, also frequently cause reactions in these patients (108). Most of these agents interfere with prostaglandin biosynthesis. This suggests that sudden interference with the cyclooxygenase pathway may underlie the symptomatic exacerbations. Arachidonate metabolites with bronchodilator activity such as PGE_2 or prostacyclin may be present in increased amounts in the lung of these individuals as a compensatory mechanism for some chronic local inflammatory stimulus (83). When their synthesis is suddenly inhibited an acute symptomatic exacerbation occurs. Alternatively, these drugs may increase the formation of SRS, a potent bronchoconstrictor shown by our laboratory to be a product of the lipoxygenase pathway. Both aspirin and indomethacin consistently enhance SRS biosynthesis in model animal systems. Part of this effect is almost certainly due to their inhibitory action on the cyclooxygenase pathway, which increases the availability of free arachidonate substrate for SRS synthesis. Moreover, these agents also inhibit the long chain fatty acid peroxidase which metabolizes the immediate SRS precursor, 5-hydroperoxyeicosatetraenoic acid, providing an additional mechanism for enhanced SRS release. We have recently studied the peripheral blood leukocytes of three patients with aspirin-sensitive asthma and in two it appears to increase the release of SRS in response to the divalent cation ionophore, A23187, as well as increased formation of other lipoxygenase products (85). These results suggest the possibility that some aspirin-sensitive patients may have abnormalities of lipoxygenase metabolism, but further studies are needed.

New Approaches in Prevention and Treatment

Ordinarily, withdrawal of the causative agent and treatment, if necessary with appropriate antiallergic agents for severely symptomatic or medically important complications of drug allergy, results in the rapid control of allergic manifestations. Based on recent or earlier work other approaches to the prevention or treatment are theoretically possible including the use of univalent hapten inhibitors (22, 78, 89), antiidiotype antibodies, and tolerogenic drug-macromolecular conjugates (51). However, the everyday practicality, efficacy, and safety of these approaches in man remains to be established. For example, it has been evident for some time that univalent penicilloyl haptens can be used to prevent and treat anaphylaxis related to this hapten (22, 88, 89), but this approach will not work if the allergy is primarily directed toward other penicillin determinants and the possibility of rare reactions to the hapten itself would have to be considered (84). Many of the same comments could be made in regard to the use of antiidiotypic antibodies or tolerogens for preventive purposes. Nonetheless, it is exciting to consider that one day approaches such as these may be put to practical use.

Summary

The general features of allergic drug reactions in man have recently been reviewed by Parker (85). By definition allergic drug reactions are produced by specific immunologic processes. Allergic drug reactions must be distinguished from adverse reactions due to overdosage, normal pharmacologic action, toxic metabolite formation, idiosyncrasy, nonspecific release of pharmacologic effector molecules, or drug interactions. The clinical manifestations of drug allergy are quite protean. In addition to classical manifestations of allergy such as serum sickness, anaphylaxis, contact dermatitis or urticaria, drug allergy may produce hemolytic anemia, thrombocytopenia, granulocytopenia, hepatitis, nephritis, pneumonitis, vasculitis, or neuritis where a single organ or cell type is affected. While many drugs produce reactions with features suggestive of allergy, definitive experimental evidence either for or against an allergic mechanism is usually not available. Some of these reactions may involve allergic

mediators released or produced nonimmunologically through pharmacologic, osmotic, or toxic effects on cells involved in immune inflammation (mast cells, basophils, phagocytes, and lymphocytes) or through nonspecific activation of effector molecules in extracellular fluid such as the complement proteins. Drugs may also induce the formation of autoantibodies through mechanisms that are largely obscure, but may in some instances involve the direct participation of the drug as a hapten and in other instances occur indirectly through a pharmacologic or toxic action on the cells responsible for immune homeostasis.

REFERENCES

1. Ackroyd, J. F.: The immunological basis of purpura due to drug hypersensitivity. Proc. R. Soc. Med. **55**: 30–36, 1962.
2. Ackroyd, J. F.: Immunological mechanisms in drug hypersensitivity. *In* Clinical Aspects of Immunology, 3rd ed., ed. by P. G. N. Gell, R. R. A. Coombs, and P. J. Lackmann, Blackwell Scientific Publications, Oxford, 1975.
3. Alaracon-Segovia, D., Fishbein, E., and Bentancourt, V. M.: Antibodies to nucleoprotein and to hydrazide-altered soluble nucleoprotein in tuberculous patients receiving isoniazid. Clin. Exp. Immunol. **5**: 429–437, 1969.
4. Alexander, H. L.: Reactions with Drug Therapy. W. B. Saunders Co., Philadelphia, 1955.
5. Bakemeier, R. F., and Leddy, J. P.: Erythrocyte antibody associated with alpha-methyl-dopa: Heterogeneity of structure and specificity. Blood **32**: 1–14, 1968.
6. Barrett, A. J., Weller, E., Rozengurt, N., Longhgurst, P., and Humble, J. D.: Amidopyrine agranulocytosis: Drug inhibition of granulocyte colonies in the presence of patient's serum. Br. Med. J. **2**: 850–851, 1976.
7. Batchelor, F. R., Dewdney, J. M., and Gazzard, D.: Penicillin allergy: The formation of the penicilloyl determinants. Nature (Lond.) **206**: 362–364, 1955.
8. Bilezikian, S. B., Lalei, Y. R., and Tsan, M. F.: Immunological reactions involving leukocytes. III. Agranulocytosis induced by antithyroid drugs. Johns Hopkins Med. J. **138**: 124–129, 1976.
9. Blomgren, S. E., and Vaughan, J. H.: Immunogenicity of photooxidized DNA and of the photoproduct of DNA and procainamide hydrochloride. Arthritis Rheum. **11**: 470A, 1968.
10. Blomgren, S. E., Condemi, J. J., Bignall, M. C., and Vaughan, J. H.: Antinuclear antibody induced by procainamide. A prospective study. N. Engl. J. Med. **281**: 64–66, 1969.
11. Bole, G. G., Friedlaender, M. H., and Smith, C. K.: Rheumatic symptoms and serological abnormalities induced by oral contraceptives. Lancet **1**: 323–326, 1969.
12. Border, W. A., Lehmann, D. H., Egan, J. D., Sass, H. J., Glode, J. E., and Wilson, C. B.: Antibular basement-membrane antibodies in methicillin-associated interstitial nephritis. N. Engl. J. Med. **291**: 381–382, 1974.
13. Brasch, R. C., Rockoff, S. D., Kuhn, C., and Chraplyvy, M.: Contrast media as histamine liberators. II. Histamine release into venous plasma during intravenous urography in man. Invest. Radiol. **5**: 510–513, 1970.
14. Brashear, R. E., Kelly, M. T., and White, A. C.: Elevated plasma histaaine after heroin and morphine. J. Lab. Clin. Med. **83**: 451–457, 1974.
15. Braverman, I. M., and Levin, J.: Dilantin-induced serum sickness. Am. J. Med. **35**: 418–422, 1963.
16. Brown, G. I., and Kanwar, B. S.: Drug rashes in glandular fever. Lancet **2**: 1418, 1967.
17. Chase, M. W.: Inhibition of experimental drug allergy by prior feeding of the sensitizing agent. Proc. Soc. Exp. Biol. Med. **61**: 257–259, 1946.
18. Cronin, R.: Immunology of Allergic Drug Reactions. Ph.D. Thesis, University of Cambridge, 1965.
19. Cucher, B. G., Goldman, A. L.: D-Penicillamine-induced polymyositis in rheumatoid arthritis (letter). Ann. Intern. Med. **86**: 615–616, 1976.
20. Davis, M., Williams, R., Chakraborty, J., English, J., Marks, V., Ideo, G., and Tempini, S: Prednisone or prednisolone for the treatment of chronic active hepatitis. Br. J. Clin. Pharmacol. **5**: 501–505, 1978.
21. de Weck, A. L., and Blum, G.: Recent clinical and immunological aspects of penicillin allergy. Int. Arch Allergy Appl. Immunol. **27**: 221–256, 1965.
22. de Weck, A. L., and Girard, J. P.: Specific inhibition of allergic reactions to penicillin in man by a monovalent hapten. II. Clinical studies. Int. Arch Allergy Appl. Immunol. **42**: 798–815, 1972.
23. de Weck, A. L., Schneider, C. H., and Gutersohn, J.: The role of penicilloylated protein impurities, penicillin polymers and dimers in penicillin allergy. Int. Arch Allergy Appl. Immunol. **33**: 535–567, 1968.
24. Deykin, D., and Hellerstein, L. J.: The assessment of drug-dependent and isoimmune antiplatelet antibodies by the use of platelet aggregometry. J. Clin. Invest. **51**: 3142–3153, 1972.
25. Dienstag, J. L.: Halothane hepatitis: Allergy or idiosyncrasy. N. Engl. J. Med. **303**: 102–104, 1980.
26. Duberstein, J. L., and Kaufman, D. M.: A clinical study of an epidemic of heroin intoxication and heroin-induced pulmonary edema. Am. J. Med. **51**: 704–714, 1971.
27. Dubois, E. L.: Procainamide induction of a systemic lupus erythematosus-like syndrome. Medicine (Baltimore) **48**: 217–228, 1969.
28. Dundee, J. W.: Hypersensitivity to intravenous anaesthetic agents. Br. J. Anaesth. **48**: 57–58, 1976.
29. Eddlestone, A. L. W. F.: Immunology and the liver. *In* Clinical Immunology, ed. by C. W. Parker, vol. 2, pp. 1009–1050, W. B. Saunders, Philadelphia, 1980.
30. Eisner, E. V., and Shahidi, N. T.: Immune thrombocytopenia due to a drug metabolite. N. Engl. J. Med. **287**: 376–381, 1972.
31. Eisner, E. V., and Kasper, K.: Immune thrombocytopenia due to a drug metabolite of para-aminosalicyclic acid. Am. J. Med. **53**: 790–810, 1972.
32. Ellman, L., Inman, J., and Green, I.: Strain difference in the immune response to hydralazine in inbred guinea pigs. Clin. Exp. Immunol. **9**: 927–937, 1971.
33. Felix, R. H., Ive, F. A., and Dahl, M. G. C.: Cutaneous and ocular reactions to practolol. Br. Med. J. **4**: 321–324, 1974.
34. Findlay, S. R., Dvorak, A., Kagey-Sobotka, A., and Lichtenstein, L. M.: Hyperosmolar triggering of histamine release from human basophils. J. Clin. Invest., **67**: 1601–1613, 1981.
35. Fisher, M.: Severe histamine-mediated reactions to intravenous drugs used in anaesthesia. Anaesthesia **3**: 180–187, 1975.
36. Frand, U. I., Shim, C. S., and Williams, M. H.: Heroin induced pulmonary edema. Ann. Intern. Med. **77**: 29–35, 1072.
37. Frand, U. I., Shim, C. S., and Williams, M. H.: Methadone-induced pulmonary edema. Ann. Intern. Med. **76**: 975–979, 1972.
38. Frizzera, G., Moran, E. M., and Rappaport, H.: Angioimmunoblastic lymphadenopathy with dysproteinemia. Lancet **1**: 1070–1073, 1974.
39. Goodman, G. W., and Sultzer, B. M.: Endotoxin protein is a mitogen and polyclonal activitor of human B lymphocytes. J. Exp. Med. **149**: 713–723, 1980.
40. Grob, P. J., and Herold, G. E.: Immunological abnormalities and hydantoins. Br. Med. J. **2**: 561–563, 1972.
41. Grob, P. J., Muller-Schoop, J. W., Hacki, M. A., and Joller-Jemelka, H. I.: Drug induced pseudolupus. Lancet **2**: 144–148, 1975.
42. Hahn, B. H., Sharp, G. C., Irvin, W. S., Kantor, O. S., Garoner, C. A., Bagby, M. K., Perry, H. M., and Osterland, C. K.: Immune responses to hydralazine and nuclear antigens in hydralazine-induced lupus erythematosus. Ann. Intern. Med. **76**: 365–374, 1972.
43. Hartl, P. W.: Drug allergic agranulocytosis (Schultz's disease). Semin. Hematol. **2**: 313–337, 1965.
44. Hartl, P. W.: Drug-induced agranulocytosis. *In* Blood Disorders due to Drugs and Other Agents, ed. by R. H. Girdwood, Excerpta Medica, Amsterdam, 1973.
45. Hempstead, B. L., Kulczycki, A., Jr., and Parker, C. W.: Phosphorylation of the IgE receptor from ionophore A23187 stimulated intact rat mast cells. Biochem. Biophys. Res. Commun. **98**: 815–822, 1981.
46. Holley, H. L.: Drugs and the lupus diathesis (editorial). J. Chronic Dis. **17**: 1–4, 1964.
47. Hughes, G.: Kroc Foundation Conference on drug related systemic lupus erythematosus. Arthritis Rheum., in press, 1981.
48. Ishak, K. G., and Irey, N. S.: Hepatic injury associated with the phenothiazines clinicopathologic and follow-up study of 36 patients. Arch. Pathol. **93**: 283–304, 1972.
49. Jakschik, B. A., Falkenhein, S., and Parker, C. W.: Precursor role of arachidonic acid in slow reacting substance release from rat basophilic leukemia cells. Proc. Natl. Acad. Sci. U.S.A. **74**: 4577–4581, 1977.
50. Kantor, F. S., Ojeda, A., and Benacerraf, B.: Studies on artificial antigens. I. Antigenicity of DNP-polylysine and DNP copolymer of lysine and glutamic acid in guinea pigs. J. Exp. Med. **117**: 55–69, 1963.
51. Katz, D. H., Hamaska, T., and Benacerraf, B.: Induction of immunological tolerance in bone marrow-derived lymphocytes of the IgE antibody class. Proc. Natl. Acad. Sci. U.S.A. **70**: 2776–2780, 1973.
52. Kazimierczak, W., and Diamant, B.: Mechanism of histamine release in anaphylactic anaphylactoid reactions. Prog. Allergy **24**: 295–365, 1978.
53. Klein, K. G., Parkin, J. D., and Madaras, F.: Studies on an acquired inhibition of factor VIII induced by penicillin allergy. Clin. Exp. Immunol. **26**: 155–161, 1976.
54. Kreisler, J. M., Moreno, E., Moneo, I., Bootello, A., Bouza, A., and Martinez de Letona, J.: Immunological findings in immunoblastic lymphadenopathy. A detailed case study. Clin. Exp. Immunol. **27**: 497–501, 1977.
55. Kulczycki, A., and Parker, C. W.: The cell surface receptor for immunoglobulin E. I. The use of repetitive affinity chromatography for the purification of a mammalian receptor. J. Biol. Chem. **254**: 3187, 1979.
56. Kunicki, T. J., Johnson, M. M., and Aster, R. H.: Absence of the platelet receptor for drug dependent antibodies and the Bernard-Soulier syndrome. J. Clin. Invest. **62**: 716–719, 1978.
57. Landsteiner, K.: The Specificity of Serological Reactions, Harvard University Press, Cambridge, 1945.
58. Lasser, E. C., Walters, A., Reuter, S. R., and Lang, J.: Histamine release

by contrast media. Radiology **100**: 683–686, 1971.

59. LEVINE, B. B.: Immunochemical mechanisms involved in penicillin hypersensitivity in experimental animals and in human beings. Fed. Proc. **24**: 45–50, 1965.
60. LEVINE, B. B.: Immunochemical mechanisms of drug allergy. *In* Textbook of Immunopathology, ed. by P. A. Miescher and H. J. Muller-Eberhard, vol. 1, Grune and Stratton, New York, 1968.
61. LEVINE, B. B., REDMOND, A. P., FELLNER, M. J., VOSS, H. E., AND LEVYTSKA, V.: Penicillin allergy and the heterogeneous immune responses of man to benzylpenicillin. J. Clin. Invest. **45**: 1895–1906, 1966.
62. LITTLE, D. M.: Effects of halothane in liver function. *In* Clinical Anesthesia: Halothane, ed. by F. A. Davis, F. A. Davis Co., New York, 1968.
63. MACKINNEY, A. A., AND BOOKER, H. E.: Diphenylhydantoin effects on human lymphocytes in vitro and in vivo. Arch. Intern. Med. **129**: 988–992, 1972.
64. MATHEWS, K. P., PAN, P. M., AND WELLS, J. H.: Experience with lymphocyte transformation tests in evaluating allergy and aminosalicylic acid isoniazid and streptomycin. Int. Arch Allergy Appl. Immunol. **46**: 653–667, 1972.
65. MATHIEU, A., DEPADUA, D., MILLS, J., AND KAHAN, B.: Experimental immunity to a metabolite of halothane and fluroxene: Cutaneous delayed-type hypersensitivity. Anesthesiology **40**: 385–390, 1974.
66. MCDEVITT, H. O., AND BENACERRAF, B.: Genetic control of specific immune responses. Adv. Immunol. **11**: 31–74, 1969.
67. MCDONALD, J. R., MATHISON, D. A., AND STEVENSON, D. D.: Aspirin intolerance in asthma. J. Allergy Clin. Immunol. **50**: 198–207, 1972.
68. MEYLER, L., AND HERXHEIMER, A.: Side Effects of Drugs, vol. 7, Excerpta Medica, Amsterdam, 1972.
69. MIESCHER, P. A.: Drug-induced thrombocytopenia. Semin. Hermatol. **10**: 311, 1973.
70. MOESCHLIN, S.: Agranulocytosis due to sensitivity to drugs. *In* Sensitivity Reactions to Drugs, ed. by M. L. Rosenheim, and R. Moulton, Blackwell Scientific Publications, Oxford, 1958.
71. MOESCHLIN, S., AND WAGNER, K.: Agranulocytosis due to the occurrence of leukocyte agglutinins. Acta Haematol. (Basel) **8**: 29, 1952.
72. MOULT, P. J., AND SHERLOCK, S.: Halothane-related hepatitis. Q. J. Med. **44**: 99–114, 1975.
73. PARKER, C. W.: Penicillin allergy. Am. J. Med. **34**: 747, 1963.
74. PARKER, C. W.: The immunochemical basis for penicillin allergy. Postgrad. Med. **40**: 141, 1964.
75. PARKER, C. W.: Immunochemical mechanism in penicillin allergy. Fed. Proc. **24**: 51–54, 1965.
76. PARKER, C. W.: The biochemical basis of an allergic drug response. Ann. N.Y. Acad. Sci. **123**: 55–63, 1965.
77. PARKER, C. W.: Drug reactions. *In* Immunological Diseases, ed. by M. Samter and H. L. Alexander, Little, Brown and Co., Boston, 1965.
78. PARKER, C. W.: Allergic drug responses: Mechanisms and unsolved problems. *In* Critical Reviews in Toxicology, ed. by L. Goldberg, vol. 1, issue 3, pp. 261–281, CRC Press, Cleveland, 1972.
79. PARKER, C. W.: Practical aspects of diagnosis and treatment of patients who are hypersensitive to drugs. *In* International Encyclopedia of Pharmacology and Therapeutics, Section 75: Hypersensitivity to drugs, vol. 1, ed. by M. Samter and C. W. Parker, Pergamon Press, Oxford, 1972.
80. PARKER, C. W.: Drug allergy (review in three parts). N. Engl. J. Med. **292**: 511–514, 732–736, 957–960, 1975.
81. PARKER, C. W.: Problems in identification of responsible antigenic determinants in drug allergy. *In* Drug Design and Adverse Reactions, ed. by H. Bundgaard, P. Juul, and H. Lofod, pp. 153–160, Academic Press, New York, 1977.
82. PARKER, C. W.: Drug allergy. *In* Berger's Medicinal Chemistry, John Wiley and Sons, pp. 419–454, New York, 1979.
83. PARKER, C. W.: Major drugs acting on the central nervous system. *In* Handbook of Experimental Pharmacology, Ed. by A. de Weck, Springer-Verlag, New York, in press, 1981.
84. PARKER, C. W.: Drug allergy. *In* Clinical Immunology, pp. 1219–1260, W. B. Saunders, Philadelphia, 1980.
85. PARKER, C. W.: Hapten immunology and allergic reactions in humans. Kroc Foundation Conference on drug related systemic lupus erythematosus. Arthritis Rheum., **24**: 1024–1036, 1981.
86. PARKER, C. W., KERN, M., AND EISEN, H. N.: Skin testing with penicillin derivatives of inapparent immunogenicity. J. Lab. Clin. Med. **58**: 948–949, 1961.
87. PARKER, C. W., DE WECK, A. L., KERN, M., AND EISEN, H. N.: Preparation and some properties of penicillenic acid derivatives relevant to penicillin hypersensitivity. J. Exp. Med. **115**: 803–819, 1962.
88. PARKER, C. W., KERN, M., AND EISEN, H. N.: Polyfunctional dinitrophenyl haptens as reagents for elicitation of immediate type allergic skin responses. J. Exp. Med. **115**: 789–801, 1962.
89. PARKER, C. W., SHAPIRO, J., KERN, M., AND EISEN, H. N.: Hypersensitivity to penicillenic acid derivatives in humans with penicillin allergy. J. Exp. Med. **115**: 821–838, 1962.
90. PARKER, C. W., AND THIEL, J. A.: Studies in human penicillin allergy: A comparison of various penicilloyl-polylysines. J. Lab. Clin. Med. **62**: 482–491, 1963.
91. PARKER, C. W., THIEL, J. A., AND MITCHELL, S.: Immunogenicity of hapten-polylysine conjugates. J. Immunol. **94**: 289–294, 1965.
92. PARONETTO, F., AND POPPER, H.: Lymphocyte stimulation induced by halothane in patients with hepatitis following exposure to halothane. N. Engl. J. Med. **283**: 277–280, 1970.
93. PERRY, H. M., JR.: Late toxicity to hydralazine resembling systemic lupus erythematosus or rheumatoid arthritis. Am. J. Med. **54**: 58–72, 1973.
94. PETZ, L. D., AND FUDENBERG, H. H.: Coombs-positive hemolytic anemia caused by penicillin administration. N. Engl. J. Med. **274**: 171, 1966.
95. PETZ, L. D., AND FUDENBERG, H. H.: Immunologic mechanisms in drug-induced cytopenias. *In* Progress in Hematology, ed. by E. B. Brown, vol. 9, Grune and Stratton, New York, 1976.
96. PIRILA, V., AND PIRILA, L.: Sensitization to the neomycin group of antibodies. Acta Derm.-Venereol. **46**: 489–496, 1966.
97. PISCIOTTA, A. V.: Immune and toxic mechanisms in drug-induced agranulocytosis. Semin. Hematol. **10**: 279–284, 1973.
98. PRICE, C. D., GIBBS, A. R., AND JONES-WILLIAMS, W.: Halothane macrophage migration inhibition test in halothane hepatitis. J. Clin. Pathol., **30**: 312–316, 1977.
99. PRUZANSKI, W., SUTTON, D. M., AND PANTALONY, D.: Angioimmunoblastic lymphadenopathy: An immunochemical study. Clin. Immunol. Immunopathol. **6**: 62–76, 1976.
100. REMMER, H., AND SCHUPPEL, R.: The formation of antigenic determinants. *In* Hypersensitivity to Drugs. ed. by M. Samter, and C. W. Parker, vol. 1, pp. 67–89, Pergamon Press, Oxford, 1971.
101. RINGLE, D. A., AND HERNDON, B. L.: Immunologic effects of morphine administration in rabbits. J. Immunol. **115**: 876–883, 1975.
102. ROCKOFF, S. D., BRASCH, R., KUHN, C., AND CHRAPLYVY, M.: Contrast media as histamine liberators. I. Mast-cell histamine release in vitro by sodium salts of contrast media. Invest. Radiol. **5**: 503–509, 1970.
103. ROSENOW, E. C.: III. The spectrum of drug-induced pulmonary disease. Ann. Intern. Med. **77**: 977–991, 1972.
104. RUSSELL, A. S., AND ZIFF, M.: Natural antibodies to procaine amide. Clin. Exp. Immunol. **3**: 901–909, 1968.
105. RYAN, J. J., PARKER, C. W., AND WILLIAMS, R. C.: Clinical and experimental γ-globulin binding of morphine in heroin addicts. J. Lab. Clin. Med. **80**: 155–164, 1972.
106. RYTEL, M. W., KLIOA, F. M., ARLANDER, T. R., AND MILLER, L. F.: Detection of penicillin hypersensitivity with penicilloyl-polylysine. J. Am. Med. Assoc. **186**: 894–898, 1963.
107. SALTZSTEIN, S. L., AND ACKERMAN, L. V.: Lymphadenopathy induced by anticonvulsant drugs and mimicking clinically and pathologically malignant lymphomas. Cancer **12**: 164–182, 1959.
108. SAMTER, M., AND BEERS, R. F., JR.: Intolerance to aspirin: Clinical studies and consideration of its pathogenesis. Ann. Intern. Med. **68**: 975–983, 1968.
109. SAPIRA, J. D.: The narcotic addict as a medical patient. Am. J. Med. **45**: 555–567, 1968.
110. SCHNEIDER, C. H., AND DE WECK, A.: A new chemical aspect of penicillin allergy: The direct reaction of penicillin with ε-amino-groups. Nature (Lond.) **208**: 57–59, 1965.
111. SCHWARTZ, M. A.: Aminolysis of benzylpenicillin by aliphatic diamines. J. Pharm. Sci. **57**: 1209–1211, 1968.
112. SCHWARTZ, R. H., AND VAUGHAN, J. H.: Immunologic responsiveness of man to penicillin. J. Am. Med. Assoc. **186**: 1151–1157, 1963.
113. SHEFFER, A. L., ROCKLIN, R. E., AND GOETZL, E. J.: Immunologic components of hypersensitivity reactions to cromolyn sodium. N. Engl. J. Med. **293**: 1220–1224, 1975.
114. SHULMAN, N. R.: Immunoreactions involving platelets. I. A steric-kinetic model for formation of a complex from a human antibody, quinidine as a haptene, and platelets; and for fixation of complement by the complex. J. Exp. Med. **107**: 665–690, 1958.
115. SIMPSON, D. G., AND WALKER, J. H.: Hypersensitivity to paraminosalicyclic acid. Am. J. Med. **29**: 297–306, 1960.
116. SORRELL, T. C., FORBES, I. J., BURNESS, F. R., AND RISCHBIETH, R. H. C.: Depression of immunological function in patients treated with phenytoin sodium (sodium diphenylhydantoin). Lancet **2**: 1233–1235, 1971.
117. SPARK, R. P.: Fatal anaphylaxis due to oral penicillin. Clin. Pathol. **56**: 407–411, 1971.
118. STENSON, W. F., AND PARKER, C. W.: Augmentation of IgE-mediated release of histamine by hydroxyeicosatetraenoic acid and 12-hydroxyeicosatetraenoic acid. Biochem. Biophys. Res. Commun. **96**: 1045–1052, 1980.
119. SULLIVAN, T. J., AND KULCZYCKI, A.: Immediate hypersensitivity responses. *In* Clinical Immunology, ed. by C. W. Parker, vol. 1, pp. 115–142, W. B. Saunders, Philadelphia, 1980.
120. SULLIVAN, T. J., AND PARKER, C. W.: Pharmacological modulation of the inflammatory mediator release by rat mast cells. Am. J. Pathol. **85**: 437–463, 1976.
121. TAN, E. M.: Drug-induced autoimmune disease. Fed. Proc. **33**: 1894–1897, 1974.
122. THIEL, J. A., MITCHELL, S., AND PARKER, C. W.: The specificity of hemagglutination reactions in human and exprimental penicillin hypersensitivity. J. Allergy **35**: 399–424, 1964.
123. VANARSDEL, P. P., JR.: Adverse drug reactions. *In* Allergy: Principles and Practice, ed. by E. Middleton, Jr., C. E. Reed, and E. F. Ellis, vol. 2, The C. V. Mosby Company, St. Louis, 1978.
124. VANARSDEL, P. P., JR., AND GILLILAND, B. C.: Anemia secondary to peni-

cillin treatment: Studies on two patients with "non-allergic" serum hemagglutinins. J. Lab. Clin. Med. **65**: 277–285, 1965.

125. Van Dellen, R. G., Walsh, W. E., and Gleich, G. J.: Differing patterns of wheal and flare skin reactivity in patients allergic to the penicillins. J. Allergy **45**: 121A, 1970.
126. Wall, J., Fang, S., Ingbar, S., and Braverman, L.: Studies of lymphocyte transformation to propylthiouracil and methimazole in patients with antithyroid drug-induced agranulocytosis. Clin. Res. **25**: 516A, 1977.
127. Walton, B., Hamblin, A. Dumonde, D. C., and Simpson, R.: Absence of cellular hypersensitivity in patients with unexplained hepatitis following halothane. Anesthesiology **44**: 391–397, 1976.
128. Weitzman, S. A., Stossel, T. P., and Desmond, M.: Drug induced immunological neutropenia. Lancet **2**: 1068–1071, 1978.
129. Weksler, M. E., Cherubin, C., Kilcoyne, M., Koppel, G., and Yoel, M.: Absence of morphine-binding activity in serum from heroin addicts. Clin. Exp. Immunol. **13**: 613–617, 1973.
130. Worlledge, S. M.: Immune hemolytic anemias. Semin. Hematol. **10**: 327, 1973.
131. Yamana, T., Tsuji, A., Miyamoto, E., and Kiya, E.: Chemical aspect of penicillin allergy: imidazole-catalysed penicilloylation. J. Pharm. Pharmacol. **27**: 287–283, 1975.
132. Yamauchi, Y., Litman, A., Adams, L., Zimmer, H., and Hess, E. V: Induction of antibodies to nuclear antigens in rabbits by immunization with hydralazine-human serum albumin conjugates. J. Clin. Invest. **56**: 958–969, 1975.
133. Zelman, S.: Liver cell necrosis in chlorpromazine jaundice (allergic cholangiolitis): A serial study of twenty-six needle biopsy specimens in nine patients. Am. J. Med. **27**: 708–729, 1959.
134. Zimmerman, H. J.: Drug-induced hepatic injury. *In* International Encyclopedia of Pharmacology and Therapeutics, Section 75: Hypersensitivity to Drugs, vol. 1, ed. by M. Samter and C. W. Parker, pp. 299–365, Pergamon Press, Oxford, 1972.
135. Zimmerman, H. J.: Drug-induced hepatic injury. *In* International Encyclopedia of Pharmacology and Therapeutics. Section 75: Hypersensitivity to Drugs, vol. 1, ed. by M. Samter and C. W. Parker, Pergamon Press, Oxford, 1972.