ALLERGY AND DRUG SENSITIVITY OF SKIN[1]

By D. Joseph Demis

Department of Dermatology, Albany Medical College of Union University, Albany, New York

Adverse drug effects are currently receiving urgent attention, in part because of their apparent increase in frequency and severity. Tabulation of reactions is being undertaken by an American Registry of the Section on Adverse Reactions recently formed by the Council on Drugs of the American Medical Association (1, 2). Many compilations of drug effects exist (3–9, 24, 25) and the *Annual Review of Phamacology* (10) and others (11) have previously considered the problems of Drug Allergy and Drug Induced Diseases (12–14). Cutaneous manifestations are often prominent in drug reactions and are far and away the most frequently reported adverse reactions. This review will attempt a discussion of the types of allergic responses and drug reactions occurring in the skin and will be limited by space almost exclusively to these.

Human skin will be emphasized in this discussion for a number of reasons. The skin is thought to be the most highly evolved organ of man and is reputed to be primarily responsible for his wide habitat. Human skin is indeed different from animal skin: large areas, relatively devoid of hair, with abundant predominantly eccrine sweat glands coupled with the virtual absence of apocrine sweat glands and a vast network of thermosensitive responsive blood vessels, are among the most distinctive features not regularly shared by animal skin. The gross characteristics are obvious, as are microscopic differences in both the epidermis and corium (15). As a consequence, no reliable animal model is readily available. Although many of the commoner skin diseases occur in domestic and wild animals (16, 17), their relationship to human disease is presently uncertain. Young white pigskin is currently felt to approximate most closely human skin, yet it is a poor and sometimes capricious model.

In this review, distinction and classification of the numerous types of currently recognized drug-induced skin lesions will be undertaken. In the first sections to follow, the classic allergic responses of skin will be discussed, with a brief definition and synonymous terms based on standard reference. (18–20). Subsequently, nonallergic and allergic reactions of skin, primarily human skin, will be enumerated with a brief description of both gross and histologic features.

[1] The survey of the literature pertaining to this review was concluded in August 1968.

Drugs are usually thought to act as haptenes and thus the route of administration often influences the type of cutaneous reacion which will develop, e.g., contact dermatitis requires direct application to the skin, whereas erythema multiforme rarely follows percutaneous absorption. Limitations of space preclude a discussion of the effect of route, but interested readers are referred to existing summaries (21, 22), and Herxheimer (23) has previously outlined, in the *Annual Review of Pharmacology,* methods of applying drugs locally for study.

Allergic Responses of Skin

Arthus phenomenon.—Following the subcutaneous injection of an antigen into a rabbit previously positively sensitized with a specifically related antibody, a local inflammatory reaction appears within 6 to 8 hr. Necrosis often develops and histologically an area of hemorrhagic necrosis with capillary thrombosis, karyorrhexis, and related nonspecific inflammatory changes can be detected (26). The reaction requires vascular tissue and occurs best in rabbit skin. Antigen is not fixed to the blood vessel wall, but complement participates with a precipitating antibody (26, 27). For a discussion of the role of complement in allergic injury see (28, 29). Like anaphylaxis, the Arthus reaction can be transferred with serum and with cells (27); the chemical mediator responsible is unknown, although evidence suggests that histamine is not involved (30). The occurrence of the Arthus phenomenon in human skin is uncertain, although fragmentation of nuclei of neutrophils (karyorrhexis), a prominent finding in the arthus phenomenon, is characteristic of allergic vasculitis in human skin (31). Drugs are often implicated in allergic vasculitis (32) and the necrotic skin lesions sometimes associated may represent the Arthus phenomenon. Occasionally injections or drug ingestion may be followed by purpura and necrosis with a histologic picture and time course suggestive of the Arthus phenomenon (28, 29). Isolated reports have appeared of this reaction following many drugs, but recently coumarin congeners in particular have been associated (33, 34).

The Schwartzman phenomenon.—Hemorrhagic necrosis at the site of a preparatory injection of the skin is the hallmark of the localized Schwartzman phenomenon. Classically, it is produced in rabbits by subcutaneous injection of a bacterial filtrate followed in 24 hr by intravenous injection of the same bacterial filtrate. The hemorrhagic necrosis reaches a maximum intensity at 24 hr and is characterized by an acute inflammatory infiltrate followed by capillary and venous thrombosis (35, 36). The coagulation mechanism plays an essential role in the development of the local Schwartzman reaction, and heparin (37) or coumarin (38) can prevent the phenomenon. A specific immunologic mechanism has not been established for the local Schwartzman reaction, and in fact, immunologically unrelated substances can be used for the preparatory injection or the provoking intravenous dose (30, 35, 36, 39).

The occurrence of the Schwartzman reaction in any form in man, although long suspected, has never been fully established. Purpura fulminans (an acute, severe hemorrhagic illness of children following acute infections, especially streptococcal and meningococcal and associated with extensive infarction and necrosis of skin) is thought to illustrate best the local Schwartzman phenomenon in man. Like the Schwartzman phenomenon in rabbits, administration of heparin seems helpful (40). Injections of drugs on rare occasions are followed by necrosis reaching a maximum in one day, and are thought to represent illustrations of the local Schwartzman reaction (assuming an antigenic component) or more often the dermal Schwartzman reaction (41).

The dermal Schwartzman reaction is the term applied to the local inflammatory response elicited by injection of endotoxin into skin (35). Although many believe that this reaction represents delayed hypersensitivity, the absence of a requirement for a provoking dose, and the absence of an antigenic component in the endotoxin preparation (42), suggest another mechanism. Lysosomal activitation, particularly by endotoxin, is one suggested mechanism of injury (43) although attention (36) remains focused on the ability of endotoxin to induce clotting (44) and to interfere with reticuloendothelial phagocytic function (45). This reaction has often been implicated in pyoderma gangrenosa (25) and lepra reactions (46).

Only the rabbit is known to be susceptible to the generalized Schwartzman reaction (both injections given intravenously lead to hemorrhagic necrosis of renal and spleen cortices), but the phenomenon is strongly suspected in man (41) and several deaths following typhoid vaccine accidents have been interpreted as a generalized Schwartzman reaction (35). Some relation to the Waterhouse-Friderichsen Syndrome is also suspected (35, 41).

Passive cutaneous anaphylaxis.—Passive cutaneous anaphylaxis results from intracutaneous injection of antiserum into the skin of a normal guinea pig, followed 6 hr later by the intravenous injection of antigen. Tissue damage, with fluid transudation from blood vessels, appears to result primarily from fixation of local antibodies (47). Complement is required in this highly sensitive test, which is essentially a form of local anaphylaxis (30, 48). Attempts to use this test with passive transfer of sera between different species have been generally unsatisfactory, as results are frequently contradictory. The Prusnitz-Kustner phenomenon (18, 19, 30), in which serum of patients with atopy is injected intracutaneously, followed by intracutaneous injection of the suspected antigen in the same site in normal human skin, appears to be analogous (49), although differences, particularly in time course, are well recognized. No other clinical counterparts of passive cutaneous anaphylaxis appear to be currently recognized.

Anaphylaxis.—Following a sensitizing dose of antigen (administered parenterally or possible orally), antibodies are formed during an incubation period of varying length and the subsequent administration of the same an-

tigen (challenge or shock dose) leads to a severe and often fatal systemic reaction. Ordinarily the challenging dose is given intravenously, although any parenteral form can lead to anaphylaxis in man and oral agents are now well known (18, 19) to produce anaphylaxis. Austin (50) has recently summarized the data on systemic anaphylaxis. The primary target cell and the mediator vary from species to species. In man, where the term "anaphylactoid response" may be preferable (2), mast cells are considered to be prime targets, but the mediator released is unknown. In other species (e.g., guinea pig), histamine and kinin appear to play predominant roles. The manifestations of systemic anaphylaxis also vary with the species (see 48): in man severe respiratory distress with subsequent vascular collapse characterizes anaphylaxis; laryngeal edema often occurs as a unique and frequently fatal component (50). Patients also develop cutaneous manifestations including generalized urticaria, angioedema, and pruritus, which are usually assumed to be the result of release of mast cell histamine; however, no substantial evidence exists to support this contention and limited clinical experience with antihistamines has not been rewarding (see 51). However, at least three immunologic mechanisms capable of releasing histamine from rodent mast cells have recently been classified by Austin & Becker (52–54).

The immunologic basis of anaphylaxis has long been studied and a great deal of information exists (see 18, 19, 30). Over the years many drugs have been reported (see 51) to produce anaphylaxis with cutaneous manifestations, but few are as well understood as penicillin; unfortunately space precludes a thorough discussion. There have been a number of recent reviews of penicillin allergy (see 2, 55, 56), but to recapitulate, benzyl penicilloyl has been implicated as the major antigen (57), which in skin testing appears to have useful predictive value (58). With sensitization, abundant antibodies have been observed in rabbits and guinea pigs (55, 59), and recently in man (55, 60) hemagglutinins and reagin (58, 61) have been detected. Similar antibody detection with anaphylaxis induced by other drugs has not yet been generally achieved but such success would seem imminent.

Serum sickness.—Clinical serum sickness develops in man within 2 to 14 days after the administration (usually by injection for the first time) of a serum or drug. It is manifested by arthralgia, lymphadenopathy (sometimes associated with splenomegaly), and a large variety of skin lesions. Urticaria or macular erythema is perhaps most common, but erythema multiforme with vesicles, bullea, and even hemorrhages may occur. Often there is profound angioedema with swelling of the eyelids, hands, feet, and genitals. Lesions are prone to relapse and often are followed by desquamation. Experimental serum sickness has been extensively studied in the rabbit (62), but appears to differ from human serum sickness by the development of arthritis and glomerulonephritis, both of which are rare in man. The clinical manifestations, including the skin lesions, appear while the antigen is still circulating but before detectable circulating antibody appears. Conversely,

the manifestations disappear when the drug is eliminated despite a high titer of circulating antibody. Lesions are thought to result from deposition of soluble antigen antibody complexes from the circulation (63), again perhaps mediated by immunologic release of mast cell histamine (52–54). Complement fixation with depletion appears to occur and in both drugs and heterologous protein-indicated serum sickness, complement activity and in particular the C"3 (beta$_1$, third component of complement) component is reduced (64, 65); this can be a very helpful clinical finding. A vast number of biologics, administered parenterally to man, have in the past led to serum sickness. The drugs now most commonly implicated include sulfonamides, penicillin, barbiturates, and anticonvulsants (24, 25, 30), but with current enthusiasm for horse-antihuman lymphocyte serum for renal transplantation (66), and with other seras on the horizon, an increase in serum sickness is predictable.

Drug fever.—Drug fever (12, 18, 19, 30), in contrast to serum sickness, may occur following the readministration of a drug and is usually not per se associated with an eruption, although the clinical distinction may become semantic since many of the classical clinical reactions (e.g., erythema multiforme) are often associated with fever. Although fever can be mediated by serum antibodies (67) in rabbits or delayed hypersensitivity (68) in guinea pigs, little is known of the mechanism and mediators responsible, particularly in man (69, 70).

Nonallergic Reactions of Skin

Side effects.—Side effects can probably be best defined as pharmacologic effects other than those sought in therapy (71). Examples include straie induced by systemic steroid therapy, blanching of skin by parenteral epinephrine, or flushing from atropine. In general, cutaneous reactions are not important side effects and in view of the frequency with which the term is misused in relation to skin lesions, it might almost better be ignored.

Toxic effects.—Toxic effects usually refer to undesirable pharmacologic actions which interfere with normal physiologic function and imply excessive pharmacologic activity. As such, there are few bona fide illustrations in relation to the skin, although industrial and environmental hazards are often considered toxic effects and topically applied fats are alleged to be toxic in several species (74). However, the real problem resides with primary irritant responses (84–86) which are often considered toxic reactions in that they lead to damage to epidermal cells and connective tissue. Unlike cutaneous allergens, first exposure leads to damage in most subjects. Organic solvents, weak alkalies, and detergents gradually remove the surface lipid film and denature proteins, which leads to dry skin (asteatosis) and even ichthyosis (fish scales) in susceptible individuals, but without true allergic sensitization (see 72, 82). Similar changes can be induced by soaps, particularly those containing hexachlorophene (83); some cosmetics also carry these liabilities (73). Many other irritants are known and extensive

compilations are available (see 82). The mechanism of their effect is poorly understood as few detailed studies have been attempted. In general, a concentration threshold is required; occlusion and repeated exposure enhance the effect. Many primary irritants often act also as allergens, thus complicating patch testing procedure (see contact dermatitis).

Cumulative effects.—Cumulative effects of drugs on the skin are well documented for several drugs. Examples include pigmentation (p. 474) induced by chronic exposure to certain drugs and heavy metals, arsenic-induced keratoses (p. 473), steroid-induced changes including acne (p. 472) and striae (p. 473), hyperkeratosis induced by hypervitaminosis A, and a few others. In addition, primary irritant responses are often cumulative and may be termed cumulative insult dermatitis (87). A reversible stage with increased percutaneous absorption and a chronic stage with epidermal (and dermal) damage are recognized (87). Differentiation from allergic contact dermatitis may be virtually impossible.

Drug intolerance.—Drug intolerance, whereby unusually small doses lead to typical pharmacologic effects (5), and drug idiosyncrasy or uncharacteristic pharmacologic responses (5) are not now of real importance in the skin.

Herxheimer reaction.—Herxheimer reaction (Jarisch-Herxheimer) is usually regarded as one of the classic cutaneous reactions (75). It may be broadly defined as a treatment-induced general reaction (fever) and local reaction with exacerbation of existing lesions (76) sometimes associated with headache, sore throat, and malaise. A classic illustration is the fever and flare-up of lesions of secondary syphilis shortly after therapy. Release of toxic products as a result of destruction of organisms has been thought to be responsible. While the local Herxheimer reaction is familiar to clinicians who recall arsenical therapy, it does not seem to occur as readily with penicillin despite a greater treponemicidal effect. This has led to speculation of another mechanism, possibly involving a direct drug effect, and to occasional doubts concerning the existence of this reaction as a real phenomenon. However, recent publications (77, 78) have emphasized the usefulness of fever (general Herxheimer) following penicillin or arsenicals as a confirmatory finding in early syphilis.

Altered ecology.—Altered ecology of the skin and mucous membranes, with resultant infection or superinfection, is being reported with increasing frequency. The bacterial and fungal flora of the skin can be altered by a number of mechanisms. A long-postulated effect is Milan's biotropic mechanism (2) whereby a drug which is toxic to certain microorganisms is stimulating to others; there is, however, little objective evidence to support this concept. Lessened resistance to infection is well known occasionally to produce cutaneous infections, especially after prolonged therapy with systemic steroids or chemotherapeutic agents. Complicating factors are the altered immunology frequently associated with the underlying disease, especially lymphoma (e.g., 79, 80), and the prolonged therapy required; these often

make interpretation of individual cases difficult. Long-term antibiotic administration, particularly with broad-spectrum agents, may lead to bacterial overgrowth of nonsensitive organisms (e.g., 12, 81) but more commonly produces yeast and saprophyte overgrowth with resultant oral thrush, moniliasis of skin, and vulvovaginitis (12, 25, 81). Tetracyclines (apparently by a direct effect) may also produce clinical changes identical with monilial vulvovaginitis but without recoverable organisms.

Enzymatic interference.—Many drugs are well known to interfere with enzyme activity but surprisingly few skin lesions can presently be attributed to inhibition of cellular enzyme systems.

Releasing agents.—A vast number of drugs are now known to act as chemical liberators of stored biogenic amines and other active compounds. In skin, as elsewhere, these are direct-acting agents, not mediated by antigen or initiation of complement cascade. Mast cells occur in the skin of most species and in some of these the skin is responsive to histamine. As a consequence, histamine releasers have been considered to be of prime importance. Extensive compilations of histamine releasers are available (88, 89) and direct degranulation may result from some common drugs including opiates, atropine, and antibiotics (89) and indeed even foods such as strawberries and citrus fruits (90). Histamine release will largely mimic idiopathic urticaria (but with some differences); bradykinin will also but to a lesser extent (91), as will serotonin (92) but largely because it releases endogenous histamine. A possible role for prostaglandin has been suggested (93).

Genetically induced drug reactions.—Genetically induced drug reactions (12) may have cutaneous manifestations. Illustrations include skin pallor in the hemolytic anemia of glucose-6-phosphate dehydrogenase deficiency induced by primaquin, sulfonamides, and other drugs; barbiturate-induced porphyria; megaloblastic anemia induced by anticonvulsants. To date, cutaneous manifestations of these diseases have remained but a minor component.

Clinical Allergic (Proven or Suspected) Reactions of Skin

Clinical characteristics of allergic reactions have often been summarized: prior tolerance to the drug, severe eruptions induced by small doses, recurrences with readministration, responses unrelated to pharmacologic action and varying with individuals (94).

Atopic reactions.—Atopy with its associated asthma and hay fever, and to a lesser degree urticaria, cataracts, and other components, is beyond the scope of the present discussion (see 18, 25, 95). The *Annual Review of Pharmacology* (96) has previously considered the antibodies and immunology of atopy. The dermatitis is per se indistinguishable from eczema, both clinically and histologically (97).

There is a great body of compelling, but not conclusive, evidence that skin-sensitizing antibodies (reagins) are responsible for many of the mani-

festations (see 30). Careful immunologic studies have been undertaken in the guinea pig and mouse (98), but the dog may be the best model for this disease, in that he spontaneously develops symptoms (pollinoisis) resembling asthma, hay fever, and eczematous dermatitis (99), which appear to be pollen allergies. Atopic patients may develop reagins to any one of a number of drugs. In their mild form these may manifest themselves only as eczematous dermatitis, but occasionally administration of a drug, particularly by injection, will lead to a severe explosive reaction (atopic reaction) characterized by asthma, urticaria, nasal symptoms of hay fever, and occasionally vascular shock. The reaction can at many times mimic the anaphylactic response (18, 30).

The drugs most commonly implicated in these reactions have included particularly antibiotics (and especially penicillin), streptomycin, topical neomycin, novobiocin, sulfonamides, procaine, promethazine, meprobamate, and chlorpromazine (see 1, 2, 30). The incidence of drug reactions in atopic patients is uncertain; the older cautions concerning an increased incidence of drug reactions, especially to penicillin, may not have been well founded (100–102).

Contact dermatitis.—Acute contact dermatitis with erythema, induration, edema, and later formation of vesicles is personally familiar to most readers. The chronic eruption tends to be dry and scaly rather than edematous and vesicular. Histologically a nonspecific dermatitis with spongiosis and a prominent inflammatory infiltrate is usually seen (97). A great deal is known about the immunologic changes occurring in association with contact dermatitis (18, 19, 30, 103–105, 107). Briefly recapitulated, an antigen, usually a simple chemical from the environment, such as 3-pentadecylcatechol (poison ivy), comes in contact with the skin and forms covalent irreversible conjugates with skin proteins, particularly epidermal proteins. These protein conjugates form principally in the epidermis, and migrate down to the upper corium, where a poorly understood reaction occurs with lymphocytes and leads to local sensitization. Generalized skin sensitivity requires the participation of local lymph glands, so that early spread of sensitivity is via the lymphatics, but later sensitization is accomplished through the blood. Circulating antibodies appear generally after the ninth day. Cell transfer of contact sensitivity can be accomplished in man but with variable success, depending on the antigen. Transfer of sensitivity to 3-pentadecylcatechol is relatively easy (19, 30, 103, 105) as is transfer of sensitivity with several other chemicals used experimentally in man. A high failure rate has however been experienced by most investigators attempting passive transfers of most substances in man (106). Experimental sensitization in man can be blocked by simultaneously sensitizing with a stronger sensitizer, e.g., dinitrochlorobenzene will block paranitrosodimethylaniline (108). Immunologic unresponsiveness to simple chemical sensitizers can also be developed, usually by simply feeding the chemical to sensitized animals (109). The pioneer studies of contact sensitivity by Landsteiner & Chase (see 104, 107,

110) have been pursued (111) and an immense literature has accumulated. Contact sensitivity develops in laboratory animals, although not all animals can be sensitized (e.g., rabbits and dogs are nonresponsive) and others animals show varying degrees of sensitivity (see 16, 17); guinea pigs, pigs, chickens, and monkeys are most frequently studied although mice can be sensitized without difficulty.

From a clinical point of view, essentially any substance which is antigenic can produce contact dermatitis in man. It has often been said, without rigorous proof, that damaged skin is more easily sensitized and for this reason drugs used for topical application to wounds are reputed to have a greater liability.

Extensive discussions of the problem (see 18, 19, 30, 105) and many compilations of sensitizing drugs (24, 30, 105) and listings of the commonest sensitizers by body region are available (see 94, 105, 112).

Production of contact dermatitis requires contact with the skin; sensitive persons can eat poison ivy leaves without developing contact sensitization and classic photographs show a contact dermatitis developing on the chin in the drool areas after poison ivy ingestion. Nonabsorption from mucous membranes or aberrant distribution or even immunologic unresponsiveness (generally believed unlikely) has been suggested. On the other hand, individuals who have developed contact sensitization of the skin to drugs may develop an eczematous contact eruption following oral ingestion of the same agent or a cross sensitizer (30, 105, 113); for a recent case report see (114). Although many commonly used drugs produce eczematous contact eruptions when handled topically (e.g., streptomycin contact dermatitis of the hands of nurses) and systemic administration may reactivate a contact sensitization, to date it has generally not been possible to demonstrate circulating antibodies (penicillin is one exception). Laboratory detection of contact sensitization is, with the exception of patch testing, of little value.

In general, contact dermatitis can be suspected on the basis of the distribution, history, and often the characteristic shape and distribution of skin lesions. Frequently patch testing (105) with suspected contactants is undertaken in attempts to determine the etiology, and this is the most reliable test now available. Yet patch testing has not gained great favor because of false positive tests (nonimmunologic responses usually thought to be primary irritant reactions) and false negatives, sometimes due to absence of generalized sensitization but often occurring for reasons not presently understood. Consequently, recommendations for careful protocols have been established (see 105, 115). Despite elaborate precautions, false positive patch tests, including primary irritant reactions (82), are often difficult to distinguish. There seems to be uniform agreement that reliable positive patch tests occur (*a*) when the patch test aggravates the existing dermatitis, or (*b*) when the dermatitis recurs (as a result of renewed contact with the allergen) and the former patch test site is also involved.

Eczema.—Eczematous (contact-type) drug eruptions may be clinically and histologically (97, 113) indistinguishable from contact dermatitis, atopic dermatitis, or even primary irritant reactions in that they are characterized by erythema, pruritus, scaling, and edema, sometimes with vesicle formation. Many drugs are capable of producing eczematous eruptions (see 1, 2, 30): particular liability has been associated with penicillin, streptomycin, sulfonamides, certain broad-spectrum antibiotics, chloral hydrate, mercurials, and quinine. Clinical observations suggest that many cases result from topical sensitization followed by systemic administration of the agent or an immunologically related drug (113), yet this is often difficult to establish in a given case. An atopic mechanism may be involved in some cases, but although the mechanism is often assumed on clinical grounds to be allergic, there is presently little data allowing justified conclusions.

Drug eruptions.—The clinical morphologic entities commonly grouped as drug eruptions include erythema, urticaria, erythema multiforme, papular drug eruptions, exfoliative dermatitis, fixed drug eruptions, erythema nodosum, and persistent erythemas. Some would also include eczema. Lichenoid drug eruptions, drug purpura, and drug photosensitivities are additional illustrations. Bona fide cases of drug eruptions are, for unknown reasons, rare in childhood.

Erythema.—Drug erythema is usually acute, pruritic, macular, and widespread, involving particularly the trunk. In general, a rash is synonymous with these exanthemas (as are scarlatinaform or morbilliform eruptions). Histological changes are minimal with only slight dilation of the blood vessels of the corium and an occasional light inflammatory infiltrate (97). Virtually any drug can be responsible for an eruption of this type, and extensive tabulation has been undertaken (see 1, 2, 30) but in particular antibiotics (especially penicillin and streptomycin), sulfonamides, barbiturates, chlorothiazides, and phenothiazines are most often responsible. The immunologic basis for these eruptions is tenuous at best; evidence for allergy is primarily clinical. Some, like penicillin (2), may be allergic in nature but many others, e.g., those due to insulin (1, 30) are probably not the results of hypersensitivity phenomena. Not infrequently they represent the first administration of a drug or its known cross-sensitizer. Of all eruptions, these are probably most often misdiagnosed as drug eruptions when they result from other causes, particularly viral infections (116).

Urticaria and angioedema.—Urticaria is often regarded as closely related to erythema but with a more severe pathophysiologic vasodilation resulting in fluid transudation through blood vessels. There are a number of recognized mechanisms capable of increasing the fluid content of the skin; these include both immunologic and nonimmunologic processes. Releasing agents (p. 463), particularly those which liberate histamine, can produce wheals which rather closely, but not precisely, simulate urticaria. Much controversy exists concerning the role of histamine and other biogenic amines, particularly serotonin, bradykinin, and slow-reaction substances (89, 117,

118). In susceptible individuals, physical factors such as cold in cold urticaria, (119, 120), warmth in heat urticaria (121), and pressure in dermagraphism (89) are thought to release the chemical mediator easily (presumed to be histamine, possibly in conjunction with an unknown substance) to produce urticarial lesions. Certain diseases associated with cryoglobulins, cryofibrinogens, and cold hemolysins, fix the first components of complement and initiate complement cascade (122–126) resulting in fluid transudation. In hereditary angioneurotic edema, Landeman et al. (127) and Donaldson (128) showed that deficiency of C^1 esterase inhibitor led to angioedema. Although the esterase is biologically active (129) the exact mechanism involved is somewhat uncertain, since deficiency of inhibitor (possibly the same inhibitor) for kallikrien is also present (127).

Three immunologic mechanisms are now known to be capable of releasing histamine, at least in rodents. These include homocytotropic antibody (53), soluble antigen-antibody complexes (54, 130), and a cytotoxic complement-fixing antibody (131). Of practical importance is the observation that complement activity as clinically measured may be decreased in certain forms of urticaria and angioedema, and in particular, decreased components of complement activity have been reported in hereditary angioneurotic edema (132) and the dysprotenemias (64). Many drugs are capable of producing urticaria and angioedema; several lists of these drugs have been prepared (e.g., 7, 25, 30, 89) and commonly include penicillin, streptomycin, sulfonamides, barbiturates, salicylates, iodides, quinidine, phenylbutazone, mercurials, and arsenicals. Unfortunately, most drug-induced urticaria cannot yet be detected in the laboratory.

Erythema multiforme.—Precise definition of this term is somewhat difficult because of variations in clinical usage. The classical, mild, clinical picture of slightly elevated erythematous rings on palms and soles (iris lesions) is as familiar to clinicians as is the severe form, described originally in children by Stevens & Johnson, with widespread multiforme and vesicular lesions of the skin and mucous membranes in association with severe systemic illness (25, 133, 134). Between these two classic, well-accepted extremes a vast number of cutaneous eruptions have been inserted under the term erythema multiforme (135); at present there are no reliable or accepted criteria for further diagnostic differentiation (136). Severe erythema multiforme is regularly associated with fever, pulmonary lesions, and renal manifestations (137) and less commonly with gastrointestinal and cardiac abnormalities. Histologically (97), striking but nonspecific changes are seen involving primarily the blood vessels with edema, inflammatory infiltrate, and in severe cases subepidermal vesicles and ultimately purpura.

An apparently new entity, toxic epidermal necrolysis, is sometimes viewed as a severe, often fatal variant of erythema multiforme and may also be associated with drugs (25, 138). A vast and seemingly endless number of causes are recognized, including primarily viral (e.g., see 116) and bacterial infections, malignancy, and drugs. Many lists of drugs inducing

erythema multiforme have been compiled (1, 7, 9, 24, 25, 137, 138). In general, antibiotics (particularly penicillin) and short-acting sulfonamides (138) are most commonly implicated; phenolphthalein, phenothiazines, barbiturates, chlorpropamide, and the thiazides are also known to carry a great liability. Although some reports mitigate against an allergic basis (apparent absence of induction period and high incidence of reactions), clinical suspicion is strong (30, 135) that an allergic mechanism is involved. There is presently available little objective documentation, although recent studies by Levine & Fellner (138) have been interpreted as constituting immunologic proof of an allergic mechanism (11). Erythema multiforme is often regarded as a more severe variant of the basic pathophysiologic processes which produce erythema and urticaria (q.v.) and for this reason some of the immunologic studies cited above may be directly applicable.

In general, erythema multiforme follows ingestion or parenteral administration of a drug, although cases following topical application (135) and an outbreak preparation of a volatile chemical (139) have occurred.

Papular drug eruptions are considered by many to represent erythema multiforme. This ill-defined term is commonly used clinically to describe a heterogenous group of eruptions characterized by pruritic, small, elevated lesions (papules) generally involving the trunk and usually widespread in distribution. Histologically, the lesions reveal only nonspecific dermatitis (97). Essentially, the same group of drugs has been implicated as for erythema multiforme, which is one of the lines of evidence suggesting a close association.

Vesiculobullous.—Vesiculobullous drug eruptions are usually thought to represent severe variants of erythema multiforme associated with prominent fluid transudation leading to subepidermal vesicles. The diagnosis of erythema multiforme is usually made in the presence of other findings (see above) but patients who develop prominent blisters on a relatively nonerythematous base without constitutional symptoms are apt to be categorized as having a vesiculobullous drug eruption (1, 2, 25, 134). The histopathologic changes are virtually identical with erythema multiforme.

The drugs most commonly listed include rather a different group from those resulting in classic erythema multiforme, and this is one reason for the clinical distinction (1, 2, 7, 9, 30). Halogens and especially bromides and iodides, as well as heavy metals including mercury and arsenic, are most commonly implicated. Salicylates are often implicated (2), but substantial documentation of the role of salicylates is lacking. With very few exceptions (97, 140), little is known about the mechanism of formation of vesicles in the skin.

Erythema nodosum.—Erythema nodosum is one of the classic clinical reactions of the skin. It is characterized by red, elevated, tender (often painful) nodules usually of the leg (particularly the shins), which appear in crops and last a few days. Mild constitutional symptoms including low grade fever, malaise, and muscle and joint pain are often associated. Histo-

logically, the changes are primarily in the subcutaneous layer with a perivascular infiltrate and evidence of blood vessel involvement often including medium-sized veins (97). Many causes of erythema nodosum appear to be well established and include primarily infectious diseases and especially streptococcosis, although a number of drugs have been implicated (7, 9, 24, 25, 134, 144) including oral contraceptives (145).

Most regularly associated with erythema nodosum are sulfone preparations when used in the treatment of lepromatous leprosy, and indeed since the advent of sulfones there has been a substantial increase in erythema nodosum in lepromatous leprosy (46). Erythema nodosum in relation to infectious disease is usually thought to result from hypersensitivity of the skin vessels to the organism or its products (239) but a number of reports have appeared implicating other drugs when there was no clear evidence of underlying infection (24, 30, 134). The most commonly listed drugs include halogens (especially iodides and bromides), sulfonamides, penicillin, and antipyrine.

As with many of these eruptions, evidence of allergy is almost exclusively clinical and many reports attest to recurrence with readministration and apparent cross-sensitivity, yet the immunologic basis of erythema nodosum is obscure and in fact there appears to be no real understanding of the mechanism involved. It has long been thought that erythema nodosum was closely akin to erythema multiforme, but this view seems to be gradually losing ground.

Exfoliation.—Exfoliative erythroderma, which is sometimes drug-induced, is characterized by extensive (usually universal) scaling, pruritus, and erythema commonly associated with diffuse loss of hair. Histologically, a subacute or chronic dermatitis is usually observed (97). Many causes, including particularly skin disease, lymphomas, and drugs, are well recognized. A number of drugs have been associated (1, 2, 25, 30) and frequently include gold compounds, arsenicals, mercurials, antibiotics (particularly penicillin), sulfonamides, and phenothiazines.

The mechanism of drug-induced exfoliation is unknown, but an allergic basis is perhaps less frequently suspected here than with many of the other common drug eruptions. Exfoliative dermatitis resulting from psoriasis has been shown to be associated with markedly increased turnover time and metabolic activity of the cells of the epidermis (141, 142); a similar release of the biochemical brake (chalone) on metabolism of epidermal cells and the rate of keratinization (142, 143) presumably is responsible for exfoliation from other causes. Direct data on this point should be shortly forthcoming. Chalone has been shown to be extractable from epidermis and other tissues; the epidermal chalone is tissue-specific (240), exhibits a diurnal cycle (241) and can be accelerated and decelerated by epinephrine (242).

Persistent erythemas.—This rather vague group of rare dermatoses is characterized by persistent or recurrent reddening (toxic erythema) of the skin (146). Few if any other changes are regularly present and these erup-

tions are poorly understood, perhaps because so few cases are recognized or reported (134). The redness is usually localized, recurrent, and asymptomatic. The most common causes are thought to be related to infectious processes and insect bites (9, 25, 134), although the classic example is usually erythema persistans produced by phenolphthalein. Almost nothing is known of the mechanisms involved, and the group seems rather closely related to fixed drug eruptions (25, 146).

Fixed drug eruptions.—These lesions are usually circumscribed and persist or recur persistently at exactly the same site for a matter of years. Edema often forms, with occasional resultant blisters but otherwise they are usually asymptomatic or mildly pruritic. Residual hyperpigmentation often develops. Many drugs (1, 2, 7, 9, 25, 30, 147, 148) are well known to produce fixed eruptions; the most common causes are phenolphthalein, antipyrine, tetracyclines, sulfonamides, barbiturates, phenylbutazone, quinidine, and gold. Patch testing is generally to no avail, although Jillson (see 149) asserts that patch tests in the exact site may sometimes be positive. The mechanism is usually assumed to be allergic, but few studies (150) have ever been undertaken and little information, other than clinical observation, exists.

Lichenoid eruptions.—Lichen planus is a chronic, pruritic eruption of unknown etiology characterized by violaceous flat-topped angulated papules distributed primarily over the wrists and ankles. The histologic picture is characteristic with hyperkeratosis, acanthosis, basal cell destruction, and atypical infiltrate (97). A limited number of drugs can reproduce in large measure the histologic and clinical appearance. Most commonly lichenoid drug eruptions occur following the oral ingestion of antimalarials, especially quinacrine and chloroquine. The thiazide diuretics have also been linked to lichenoid and lichen planus-like eruptions (7, 9, 30), as has quinidine. Some heavy metals, including particularly gold, have been reported to produce similar changes (2). No valid explanations have yet been established for the mechanism of lichenoid eruptions.

In addition, lichenoid eruptions may occur as (or after) contact dermatitis, usually on the thumbs of individuals who come in contact with color-developing solutions containing substituted paraphenylenediamine (177). Patch tests, when positive, may go on to typical lichenoid patterns (177).

Purpura.—Thrombocytopenic purpura may be related to many drugs including quinidine, quinine, Sedormid, chlorothiazide, and sulfonamides, and in some an allergic basis seems well established (151). A complement-requiring serum factor induced by Sedormid, causing lysis of platelets, has been demonstrated (152). Quinidine forms an antibody complex and induces platelet lysis by complement fixation in the platelet membrane (153), and a similar process may mediate stibophen (154) and digitoxin (155) hemolysis. Adsorption of platelets by immune complexes of drug and antibody seems to be the most likely pathogenic mechanism.

Nonthrombocytopenic purpura may be associated with any severe drug

eruption, and has particularly been associated with erythema multiforme (and depending on definition, urticaria and vesiculobullous eruptions). The term purpuric drug eruption is often applied and in these instances any drug capable of producing the primary eruption can lead to purpura. In addition, purpura without other skin lesions has been associated with a number of drugs (see 7, 9, 151) including especially antibiotics, steroids, and barbiturates.

A particularly severe purpuric eruption, regularly associated with large sloughs, has been associated with bishydroxycoumarin and other coumarins. In a recent review Nalbandian (33) discussed 87 cases, largely literature citations, resulting from coumarin congeners. Purpura with necrosis following these drugs may not be a rare side effect, for Verhagen (156) was able to accumulate 13 patients in Holland in one year, and new reports continue to appear (34). The drug is believed to have a toxic effect on small blood vessels, particularly at the capillary loop in the corium, perhaps at the precapillary arteriol. Rupture occurs which leads to petechiae and ecchymoses followed by stasis in larger vessels with thrombosis and ultimately necrosis of the skin. This leukocytoclastic response is quite similar histologically to the typical Arthus phenomenon (p. 458) and has been interpreted as a manifestation of the Arthus phenomenon in man (33).

Photosensitivity.—Certain drugs produce eruptions only after exposure to light, usually sunlight (ultraviolet action spectrum 2800 to 4300 A°). The resultant eruption is limited to light-exposed areas, even those receiving only small amounts of light, but generally involves the face, neck (V area), arms, backs of the hands, and legs (in women), although odd unilateral distributions may occur, e.g., limited to the left when driving an automobile. The reactions are comparable to a sunburn but may commonly be clinically and histologically eczematous, urticarial, vesicular, or lichenoid (97). Two mechanisms are known to exist (157). Phototoxic, which is nonimmunologic, occurs on the first exposure when adequate light and concentration of the drug are present. An exaggerated sunburn followed by hyperpigmentation is the usual response, but vesicles may occur. Photoallergy, in contrast, is a form of delayed allergic hypersensitivity and produces clinical and histologic changes comparable to allergic contact dermatitis. Distinguishing between phototoxic and photoallergic reactions may be difficult and in any particular case may require detailed clinical investigation (158–160). In general, smaller amounts of a drug are required to produce a photoallergic reaction which occurs in but a small fraction of the population, in contrast to phototoxic reactions which occur in almost every individual; photoallergic reactions require an incubation period, show cross-reactivity, exhibit flare-ups at unexposed sites, and can be passively transferred.

A number of listings of drugs causing photosensitivity are available (see 7, 9, 157, 160). Among the best known topically applied phototoxic substances are furocoumarins (psoralens) found in plants (161), and these

provide classic reports of blisters occurring in agricultural workers, especially carrot processers and celery pickers (162). These eruptions (phytophotodermatitis) require skin contact with the furocoumarin and subsequent exposure to sunlight. Whether ingestion can lead to photodermatitis is as yet not established. Certain perfumes, containing psoralen (and particularly 5-methoxypsoralen, oil of bergamot) have produced photodermatitis, so-called berloque dermatitis (163, 164); some meadow grasses also contain these psoralens and produce similar lesions. Another common topical phototoxic substance is coal tar (and derivatives), which may lead to an occupational dermatosis in workers exposed to tars and sunlight (165).

Photosensitizers are more likely to be photoallergic. In recent years the commoner causes have been related to new additives to soap and especially the antiseptics tribromosalicylanilide and tetrachlorosalicylanilide (160, 174–176) which provide the basis for advertisements of deodorant activity. Other related salicyl anilides (e.g., dibromosalicylanilide) have also caused allergic dermatitis (159, 166). Bithionol, formerly used extensively in toiletries and skin creams, is also a photoallergin (167).

A number of systemically administered drugs also produce photosensitization (160, 168). It has been estimated that 40 per cent of patients receiving demethylchlortetracycline will develop photosensitivity if given large enough quantities of both drug and sunlight. Other tetracyclines do not seem to share this liability. Sulfanilamide (171) can cause both phototoxic and photoallergic reactions; surprisingly, other sulfonamide compounds apparently are not photosensitizers (157). Phenothiazine and some derivatives, including promethazine (169, 179), may lead to photosensitivity. Cross-photosensitivity between promethazine and chlorpromazine has been reported (170). A number of other drugs, however, can cause photoallergic and cross-photosensitivity reactions: these include chlorpropamide, tolbutamide, chlorothiazide, hydrochlorothiazide, and quinethazone (172, 173).

Other Clinical Reactions of Skin (Some Possibly Allergic)

Acneform eruptions.—Certain drugs are able to produce lesions which resemble but are not identical with acne vulgaris. Histologically they are characterized by hyperplasia of sebaceous glands with an inflammatory infiltrate but generally without true comedone formation (25). These eruptions occur only infrequently and in response to a rather small number of drugs. Steroid hormones and especially ACTH are best known and produce the characteristic clinical picture of steroid acne. Halogens and particularly bromides produce acneform lesions which may also be associated with the formation of granulomas or tumors of the skin (2, 9, 25, 30, 178). A number of other drugs have occasionally been implicated (178) but the mechanism by which any drug stimulates sebaceous gland hyperplasia is unknown.

Topical application of oils or tars, particularly insoluble industrial cutting oils, is well known to lead to a distinctive acneform eruption (chloracne), generally of the extremities, which is commonly regarded as an occupational dermatosis (72). The mechanism responsible is uncertain, but a

relation to the high chlorine content of these oils has often been proposed.

Pustular eruptions, sometimes acneform, often follow bromides, iodides, and chloral hydrate (7, 24), although ulcerations may occur, especially with halogens, arsenic, and quinine (25).

Necrosis of skin may follow these eruptions, granulomas, extensive purpura (p. 470) and other processes associated with ischemia.

Granulomatous lesions of the skin.—Granulomatous lesions of the skin, generally characterized by firm, elevated, sometimes pruritic nodules and plaques with the typical histologic characteristics of a granuloma (97), can result from a number of drugs and from many other causes (25, 97). These lesions are a fairly regular finding, however, with only a small number of drugs, including primarily halogens and especially bromides and iodides but usually bromine-containing sedatives. Exogenous foreign body reactions to beryllium, coral, paraffin, calcium, and other heavy metals and salts are well known to produce granulomas under both clinical and experimental conditions (97). Topical application of zirconium has been particularly well studied and allergic hypersensitivity leading to a sarcoid-type granuloma results: nonallergic granulomas are induced only by colloidal suspensions (179).

Acanthosis Nigricans.—This distinctive, rare eruption of the neck, axillae and groin has long been related to malignancy, endocrine abnormalities, and other hamartomas (25, 134, 243). The observation that large doses of nicotinic acid (3 g daily) can induce acanthosis nigricans (244) (at least in hyperlipemic subjects) was quite surprising and suggests that this drug alters metabolism in a manner analogous to the changes induced by the known associated diseases.

Atrophy.—Atrophy may follow destruction of the corium by a lesion of any type, and atrophic striae occur following profound weight changes. In addition, steroids administered systemically may produce striae with or without other manifestations of Cushing's syndrome. Comparable local striae result from topical application (with maceration) of fluorinated steroids. The mechanism of this steroid effect on collagen is not understood although Houck (180) has reported loss of skin collagen and activation of enzymes including an apparently steroid-induced collagenolytic enzyme.

Tumors.—Chronic administration of certain drugs can lead to formation of both benign and malignant tumors. Arsenic (Fowler's Solution) in small doses may be followed by keratoses of palms and soles, some of which become malignant (usually squamous cell carcinoma), or superficial basal cell carcinomas may develop on the trunk (25, 134, 97). Benign tumors may also follow bromide or iodide ingestion (9, 24, 25). Lymphadenopathy can follow hydantoin and other drugs (7, 9) and a syndrome resembling malignant lymphoma with hepatosplenomegaly and exfoliation has followed dilantin and hydantoins (9, 181). Isoniazid and para-aminosalicylic acid may also produce similar lymphoma-like syndromes (7).

Drug-induced diseases have previously been covered in the *Annual Review* (12). In general, cutaneous manifestations of drug-induced diseases

are of some importance in initially establishing a diagnosis, particularly of a collagen disease (and especially of periarteritis nodosa or systemic lupus erythematosis), as a consequence of drugs. But otherwise the cutaneous manifestations seem of lesser import, and eruptions to date have fallen into established clinical patterns.

Pigmentary changes.—A number of drugs are capable of producing hyperpigmentation of human skin. Several mechanisms are involved.

Metallic drugs are diffusely stored in the phagocytes of the corium and change the color of the skin and mucous membranes as a result of optical changes in refraction and scattering of light. The hyperpigmentation varies from a gray to a blue-black and is usually generalized. Most commonly it results from lead, silver, mercury, gold, arsenic, and bismuth (184, 185).

Chlorpromazine given in high doses (300 to 500 mg per day) for a long time (3 to 5 years) often leads to a curious slate-gray hyperpigmentation resembling a suntan. Greiner (186) reported 70 cases among several thousand patients treated with large doses. With few exceptions all of the patients developing hyperpigmentation were females, an observation thought to suggest female hormonal dysfunction in the pathogenesis. The pigment, which appears to be melanin (187, 188), is deposited primarily around the face and neck, thorax, and hands. A similar pigment was found in the reticuloendothelial system and in the parenchymous organs (189). The pigment is distributed where phenothiazine metabolites tend to accumulate (190) but phenothiazine is known to have a reversible affinity (191) for melanin (192). To date, only chlorpromazine has been administered in sufficiently high doses, but it is reasonable to assume that other phenothiazines can cause a similar pigment abnormality.

Trophic hormones, particularly MSH and ACTH, regularly lead to pigment dispersal and consequent darkening of frog skin (182) but show only weak activity in man (183), primarily as a result of melanin deposition.

Antimalarials are well known to alter pigmentation. Quinacrine deposited in the skin or mucous membranes results in the well-known yellowing (192, 193) which fades from 2 to 6 months after discontinuation. Quinacrine also leads to bluish-gray deposits, particularly in the oral mucous membranes, which are thought to result from melanin, hemosiderin, lipofuscin, and a complex of the drug (194, 195). Reversible "pseudo-ochronosis" results on rare occasions from deposition of quinacrine in the cartilage of the nose, ears, trachea, conjunctiva, and in the nail beds where it gives a bright yellow-green fluorescence (196, 197). Whitening of the hair of the scalp, eyebrows, eyelashes, pubic, and axillary areas (198) occurs occasionally; blondes are most often affected, apparently as a result of interference with formation of phenomelanin rather than melanin itself, since the drug has no demonstrable effect on tyrosinase (199), although quinacrine is known to have an affinity for tissues high in melanin (200).

The alkylating agent busulfan, when administered chronically, produces mild hyperpigmentation of the covered areas of the body in 5 to 10 per cent

of patients given a total dose of several grams (201). The pigment represents increased deposition of melanin and is reversed by cessation of therapy.

Other drugs capable of occasionally producing hyperpigmentation are reviewed by Moller (202). Oral contraceptives (203, 204) frequently produce melasma (chloasma, pigmented mask of pregnancy).

Tetracyclines, taken up and stored almost indefinitely as part of the hydroxyapetite molecule of teeth and bones, lead to a brownish-gray discoloration which fluoresces bright yellow (205–207). Administration in the pre- and neonatal periods stains only the deciduous teeth (208) but when given between ages 2 months and 7 years, stains the permanent teeth and may be associated with hypoplasia of tooth enamel (209).

Conversely, the interesting suggestion that pigmentation regulates vitamin-D biosynthesis (210) presently finds little clinical application.

No drug given systemically, regularly produces hypopigmentation of human skin, although melatonin (211) will lighten frog skin. Topical application of a number of rubber antioxidants (in particular monobenzyl ether of hydroquinone) is well known frequently to produce leukoderma (25, 72) through inhibition of melanin formation by tyrosinase. Recently, depigmentation of the eyelids (leukoderma) has been noted following ophthalmologic application of eserine (physostigmine) (245) and the antibiotic, guanofuracin.

Sweat abnormalities.—Very little information exists concerning the effects of systemic therapy on eccrine sweat glands (212, 213). Although diapedesis with many drugs having cardiovascular and autonomic actions is common (214), there appears to be no recent documentation of drug-induced hyperhidrosis.

Conversely, diminution in sweating or even anhydrosis from systemically administered agents has only rarely been reported. Following the second world war, atabrine-induced atrophy of sweat glands was described (212, 215). This apparently irreversible degeneration of the sweat glands and ducts seemed to be a consequence of a lichenoid dermatitis, induced by atabrine. Hypervitaminoisis A has also been reported to induce anhidrosis, as have vitamin deficiencies (212).

A number of topically applied agents decrease sweating by one of several mechanisms (216). Formaldehyde appears to have a selective effect on the secretory epithelium of the eccrine gland; aluminum salts damage eccrine and apocrine glands (212).

Antidiuretic hormones and other pituitary hormones do not appear to influence sweating (217).

Alterations of hair.—Diffuse, patchy, or total loss of hair, particularly of the scalp hair, following administration of certain drugs is not uncommon and several mechanisms seem to be involved. Antimetabolites, including cytoxan, folic acid antagonists, mercaptopurines and most chemotherapeutic agents are capable of producing diffuse alopecia which is usually re-

versible. Hair growth is known to be associated with a high mitotic index in the germinative layer of the matrix (142, 218), and inhibition of these mitotic processes results in alopecia, although the selectivity of the mechanism is poorly understood.

Triparanol (MER 29), which blocks cholesterol synthesis at desmosterol, also produces diffuse alopecia (219) in addition to dry scaly skin, presumably as a result of its ability to inhibit cholesterol synthesis by epidermal cells. Inhibition of cholesterol synthesis, by other mechanisms, is a common effect of many newer tranquilizing agents including some butyrophenone derivatives (220), and alopecia with asteatosis has been observed with several of these agents also. Thus effective inhibition of cholesterol synthesis seems to produce alopecia, although the mechanism is not presently understood.

Anticoagulants, and in particular heparin, have occasionally been reported to produce a patchy alopecia (1, 30), and certain metals, especially thallium (from accidental ingestion of rat poison), have produced a patchy alopecia (25); in neither case is the mechanism understood.

Although over the years a number of drugs, particularly anticonvulsants (tridone) and heparin, have been thought to produce hypertrichosis, critical review has failed to substantiate this impression (221). Recently diazoxide, used in the treatment of hypoglycemia, has been found to produce increased lanugo hair growth, particularly in children (222, 223); the effect is reversible and a reasonable dose-response curve for the hair growth can be achieved (224).

Detection of Drug Eruptions

With a few exceptions, such as penicillin (see anaphylaxis) and drug-induced thrombocytopenic purura (see purpura), the laboratory diagnosis of a drug eruption is unsatisfactory. Evidence of an allergic mechanism is rarely demonstrable, presumably because drugs act as haptenes rather than complete antigens. Measurement of complement may aid (see urticaria), patch tests are occasionally helpful (see contact dermatitis), skin tests may be ambiguous or even dangerous (225–227), eosinophilia is often suggestive though nonspecific (228), basopenia is variable (229, 230), and the basophil degranulation test (231–234) remains to be established (235–237). The clinical maximum that, for absolute proof, the eruption must clear when the drug is stopped and reappear with readministration on three occasions, finds few patients interested enough in the etiology of their eruption to be willing knowingly to undertake this trail which is not recommended in good clinical practice and may be hazardous (133). Few eruptions are subjected to absolute proof or documentation (100). Undoubtedly drug eruptions are grossly overdiagnosed and overreported.

Consequences of a Drug Eruption

Certain drug eruptions (in particular acute severe erythema multi-

forme) are well established as sometimes being associated with fever, pulmonary and renal changes, and other lesions (25, 134), and may be fatal (e.g., see 133, 238). Other eruptions which recur for years with reexposure to the offending drug (e.g., fixed drug eruption to phenolphthalien) appear to have no systemic liability, and some reactions, such as hyperpigmentation, appear to be completely reversible by withdrawing the drug even after administration for several years. Rarely, a drug eruption will lead to permanent damage to the skin, as in the unusual lichenoid (atabrine) damage to eccrine sweat glands (q.v.). There are few data which bear on the question of the consequences, particularly to parenchymatous organs, of an extensive or chronic prolonged drug eruption, not associated with fever or constitutional symptoms; examples would be an extensive erythema, papular eruptions, eczematous lesions, or vesicular eruptions. It is commonly stated that failure to stop the offending drug when an eruption occurs will lead to parenchymal damage, especially renal and hepatic. Yet phthisiologists when forced to continue antituberculous therapy in the face of drug eruptions of this type (without constitutional symptoms) have found few serious consequences, although systemic steroids were often administered. We have never seen a patient develop severe sequelae following these eruptions, nor does there appear to be an unequivocal case report in the literature. Explanation of this apparent selectivity of the skin remains shrouded.

ACKNOWLEDGEMENTS

The author is grateful to Mrs. S. Martin and Misses E. Galakatos and C. Rovelli for assistance in the literature search and in preparation of the manuscript.

LITERATURE CITED

1. Baer, R. L., Harris, H., *J. Am. Med. Assoc.*, **202,** 710–13 (1967)
2. Fellner, M. J., Baer, R. L., *Med. Clin. N. Am.*, **49,** 709–24 (1965)
3. Meyler, L., Ed., *Side Effects of Drugs* 4th ed. (Excerpta Med. Found. The Hague, 1963)
4. Friend, D. G., Hoskins, R. G., *Med. Clin. N. Am.*, **44,** 1381–92 (1960)
5. Rosenheim, M. L., in *Sensitivity Reactions to Drugs*, 1–5 (Thomas, Springfield, Ill., 1958)
6. Friend, D. G., *Clin. Pharmacol. Therap.*, **5,** 257–62 (1964)
7. Baer, R. L., *Ann. N. Y. Acad. Sci.*, **123,** 354–65 (1965)
8. Beam, L. R., *Southern Med. J.*, **61,** 142–45 (1968)
9. Coleman, W. P., *Med. Clin. N. Am.*, **51,** 1073–88 (1967)
10. Sampter, M., Berryman, G., *Ann. Rev. Pharmacol.*, **4,** 265–80 (1964)
11. Levine, G. B., *Ann. Rev. Med.*, **17,** 23–38 (1966)
12. Modell, W., *Ann. Rev. Pharmacol.*, **5,** 285–304 (1965)
13. Moser, R. H., Ed., *Diseases of Medical Progress,* 2nd ed. (Thomas, Springfield, Ill., 1964)
14. Meyler, L., Peck, H. M., Eds., *Drug-Induced Diseases* (Thomas, Springfield, Ill., 1964)
15. Montagna, W., *The Structure and Function of Skin* (Academic Press, 1962)
16. Kral, F., Schwartzman, R. M., *Veterinary and Comparative Dermatology* (Lippincott, Philadelphia, 1964)
17. Schwartzman, R. B., Orkin, M., *Comparative Study of Skin Diseases of Dog and Man* (Thomas, Springfield, Ill., 1962)
18. Sheldon, J. M., Lovell, R. G.,

Mathews, K. P., *A Manual of Clinical Allergy* 2nd ed. (Saunders, Philadelphia, 1967)
19. Calnan, C. D., *Clinical Aspects of Immunology* (F. A. Davis, Philadelphia, 1963)
20. Kabat, E. A., Mayer, M. M., *Experiment Immunochemistry* (Thomas, Springfield, Ill., 1961)
21. Rothman, S.: *Physiology and Biochemistry of the Skin* (Univ. of Chicago Press, 1954)
22. Lorincz, A. L., Stoughton, R. B., *Physiol. Rev.*, **38,** 481–502 (1958)
23. Herxheimer, A., *Ann. Rev. Pharmacol.*, **1,** 351–68 (1961)
24. Alexander, H. L., *Reactions with Drug Therapy* (Saunders, Philadelphia, 1955)
25. Andrews, G. C., Domonkos, A. N., *Diseases of the Skin* (Saunders, Philadelphia, 1963)
26. Benacerraf, B., Kabat, E. A., *J. Immunol.*, **64,** 1–19 (1950)
27. Cochrane, C., in *The Inflammatory Process,* 613–48 (Academic Press, New York, 1965)
28. Goldberg, B., *Immunopathol., Intern. Symp., 3rd, La Jolla, Calif.,* 300–10 (1963)
29. Osler, A. G., *Advan. Immunol.*, **1,** 132–210 (1961)
30. Criep, L., *Dermatologic Allergy* (Saunders, Philadelphia, 1967)
31. Ruiter, M., Brandsma, C. H., *Dermatologica,* **97,** 265–78 (1948)
32. Winkelman, R., Ditto, W., *Medicine,* **43,** 59–89 (1964)
33. Nalbandian, R. M., Mader, I. J., Barrett, J. L., Pearce, J. F., Rupp, E. C., *J. Am. Med. Assoc.*, **192,** 603–8 (1965)
34. Dalley, D., Kelleher, P. R., *New Zealand Med. J.*, **65,** 535–38 (1966)
35. Hjort, P. F., Rapaport, S. I., *Ann. Rev. Med.*, **16,** 135–68 (1965)
36. Lee, C., Stetson, C., in *The Inflammatory Process,* 791–818 (Academic Press, New York, 1965)
37. Good, R. A., Thomas, L., *J. Exptl. Med.*, **97,** 871–88 (1953)
38. Spanoudis, S., Eichbaum, F., Rosenfeld, G., *J. Immunol.*, **75,** 167–70 (1955)
39. Zweifach, B. W., Janoff, A., *Ann. Rev. Med.*, **16,** 201–20 (1965)
40. Little, J. R., *J Am. Med. Assoc.*, **169,** 36–40 (1959)
41. Margaretten, W., *Rev. Can. Biol.*, **25,** 69–80 (1966)
42. Netter, E., Ribi, E., *Proc. Soc. Exptl. Biol. Med.*, **112,** 269–72 (1963)
43. Auzins, I., Rowley, D., *Australian J. Exptl. Biol. Med. Sci.*, **40,** 283–91 (1962)
44. McKay, D., Shapiro, S., Shanberge. J., *J. Exptl. Med.*, **107,** 369–76 (1958)
45. Lee, L., in *Bacterial Endotoxins,* 684–57 (Rutgers Univ. Press, 1964)
46. Cochrane, R. G., Davey, T. F., *Leprosy in Therapy and Practice* (Williams & Wilkins, Baltimore, 1964)
47. Biozzi, G., Halpern, B. N., Benacerraf, B., *Acta. Allerg. Suppl. III,* 184–92 (1953)
48. Austin, F., in *The Inflammatory Process,* 587–612 (Academic Press, New York, 1965)
49. Ovary, Z., Benacerraf, B., Bloch, K. J., *J. Exptl. Med.*, **117,** 965–84 (1963)
50. James, L. P., Jr., Austen, K. F., *New Engl. J. Med.*, **270,** 597–603 (1964)
51. Thompson, J. S., *Ann. Internal Med.*, **69,** 361–80 (1968)
52. Austen, K. F., Bloch, K. J., Baker. A. R., Arnason, B. G., *Proc. Soc. Exptl. Biol. Med.*, **120,** 542–46 (1965)
53. Becker, E. L., Austen, K. F., *J. Exptl. Med.*, **124,** 379–95 (1966)
54. Austen, K. F. Becker, E. L., *J. Exptl. Med.*, **124,** 397–416 (1966)
55. Levine, B. B., *Intern. Congr. Allergol., 5th, Madrid* (1964)
56. Parker, C. W., *Am. J. Med.*, **34,** 747–63 (1963)
57. Brandriss, M. W., Smith, J. W., Steinman, H. G., *J. Immunol.*, **94,** 696–704 (1965)
58. Budd, M. A., Parker, C. W., Norden, C. W., *J. Am. Med. Assoc.*, **190,** 203–5 (1964)
59. DeWeck, A. L., Intern. Arch. *Allergy Appl. Immunol.*, **21,** 23–31 (1962)
60. Levine, B. B., Fellner, M. J., *J. Allergy,* **36,** 198–205 (1965)
61. Levine, B. B., Price, V. H., *Immunology,* **7,** 542–56 (1964)
62. McCloskey, R. T., in *The Inflammatory Process,* 649–83 (Academic Press, New York, 1965)
63. McCloskey, R. T., Benacerraf, B., Potter, J. L., Miller, F., *J. Exptl. Med.*, **111,** 181–94 (1960)

64. Ahserson, G. L., *Australasian Ann. Med.*, **9,** 57–63 (1960)
65. Lundh, B. *Acta Univ. Lund., II,* **27,** 1–63 (1965)
66. Kashiwagi, N., Brantigan, C. O., Brettschneider, L., Growth, C. G., Starzl, T. E., *Ann. Internal Med.*, **68,** 275–86 (1968)
67. Grey, H. M., Briggs, W., Farr, R. S., *J. Clin. Invest.*, **40,** 703–06 (1961)
68. Uhr, J. W., Brandriss, M. W., *J. Exptl. Med.*, **108,** 905–24 (1958)
69. Atkins, E., *Physiol. Rev.*, **40,** 580–646 (1960)
70. Cluff, L. E., Johnson, J. E., *Progr. Allergy,* **8,** 149–94 (1964)
71. Modell, W., *Clin. Pharmacol. Therap.*, **5,** 265–72 (1964)
72. Schwartz, L., Tulipan, L., Birmingham, D. J., in *Occupational Diseases of the Skin,* 325–35 (Lea & Febiger, Philadelphia, 1957)
73. Burnett, C. M., Feinberg, H., Opdyke, D.C., *Drug and Cosmetic Industry,* **101,** 40–53 (1967)
74. Woods, W. D., McCune, E. L., O'Dell, B. L., *Proc. Soc. Exptl. Biol.,* **125,** 124–27 (1967)
75. Farmer, T. W., *J. Am. Med. Assoc.*, **138,** 480–91 (1948)
76. Sheldon, W. H., Heyman, A., *Am. J. Syphilis,* **33,** 213–24 (1949)
77. Knudsen, E. A., Aastrup, B., *Brit. J. Venereal Diseases,* **41,** 177–80 (1965)
78. Putkonen, T., Salo, O. P., Mustakallio, K. K., *Brit. J. Venereal Diseases,* **42,** 181–84 (1966)
79. Smith, R. T., *New Engl. J. Med.*, **278,** 1207–14, 1268–75, 1326–31 (1968)
80. Good, R. A., Finstad, J., Miescher, P. M., Smith, R. T., *Immunologic Deficiency Disorders in Man* Natl. Found. Press., New York, 1968)
81. Weinstein, L., Dalton, A. C., *New Engl. J. Med.*, **279,** 467–72 524–31, 580–87 (1968)
82. Fregert, S., Hjort, N., in *Textbook of Dermatology,* 246–50, 1874–1907 (Blackwell, Oxford, 1968)
83. Suskind, R. R., *J. Am. Med. Assoc.*, **163,** 943–46 (1957)
84. Malkinson, F. D., *Arch. Environ. Health,* **11,** 548–51 (1965)
85. Klingman, A. M., *J. Invest. Dermatol.*, **49,** 78–94 (1967)
86. Suskind, R. R., Meister, M. M., Scheen, S. R., Rebello, D. J. A., *Arch. Dermatol.*, **88,** 117–34 (1963)
87. Rostenberg, A., *Arch. Dermatol.*, **75,** 547–54 (1957)
88. Paton, W. D. M., *Pharmacol. Rev.*, **9,** 269–328 (1957)
89. Beall, G. N., *Medicine,* **43,** 131–51 (1964)
90. Winkelman, R. K., *Proc. Mayo Clin.*, **32,** 329–34 (1957)
91. Demis, D. J., Zimmer, J. G., Verhonick, P. J., Catalano, P. M., *J. Invest. Dermatol.*, **39,** 419–29 (1962)
92. Demis, D. J., Davis, M. J., Lawler, J. C., *J. Invest. Dermatol.*, **34,** 43–50 (1960)
93. von Euler, U. S., Eliasson, R., *Prostaglandins* (Academic Press. New York, 1967)
94. Baer, R. L., Witten, V. H., *Year Book of Dermatology,* 9–37 (Year Book Publishers, Chicago, 1960–1961)
95. Baer, R. L., *Atopic Dermatitis* (New York Univ. Press, 1955)
96. Loveless, M., *Ann. Rev. Pharmacol.*, **6,** 309–26 (1966)
97. Lever, W., *Histopathology of the Skin,* 4th ed. (Lippincott, Philadelphia, 1967)
98. Nussenzweiz, R. S., Merryman, C., Benacerraf, B., *J. Exptl. Med.*, **120,** 315–29 (1964)
99. Patterson, R., Pruzansky, J. J., Chang, W. W. Y., *J. Immunol.*, **90,** 35–42 (1963)
100. Smith, J. W., Seidl, L. G., Cluff, L. E., *Ann. Internal Med.*, **65,** 629–40 (1966)
101. Siegel, B. B., Levine, B. B., *J. Allergy,* **35,** 488–98 (1962)
102. Natu, J. P., Szartz, J. A., *J. Allergy,* **40,** 202–6 (1967)
103. Parker, C. W., in *Clinical Dermatology,* (Demis, D. J., Crounse, R. G., Dobson, R. L., McGuire, J. S., Eds., Hoeber, New York, 1969)
104. Chase, M. W., *Harvey Lectures,* **61,** 169–203 (1965)
105. Fisher, A. A., *Contact Dermatitis* (Lea & Febiger, Philadelphia, 1967)
106. Epstein, W. L., Klingman, A. M., *J. Invest. Dermatol.*, **28,** 291–304 (1957)
107. Landsteiner, K., Chase, M. W., *J. Exptl. Med.*, **73,** 431–38 (1941)
108. Kligman, A. M., Epstein, W. L., in *Mechanisms of Hypersensitivity*

(Little, Brown and Co., Boston, 1959)
109. Chase, M. E., *Proc. Soc. Exptl. Biol. Med.*, **61**, 257–59 (1946)
110. Lansteiner, K., *The Specificity of Serological Reactions*, Revised (Dover Publ., New York, 1962)
111. Eisen, H., in *Cellular and Humoral Aspects of the Hypersensitive States* (Harper & Row, New York, 1959)
112. Sulzberger, M., Wolf, J., Witten, V., *Year Book of Dermatology*, 9–37 (Year Book Publishers, Chicago, 1961)
113. Fisher, A. A., *Ann. Allergy*, **24**, 406–20 (1966)
114. Domar, M., Juhlin, L., *Lancet*, **1**, 1165–66 (1967)
115. Baer, R. L., Witten, V. H., *Yearbook of Dermatology and Syphilology*, 7–46 (1957–1958)
116. Artenstein, M. S., Demis, D. J., *New Engl. J. Med.*, **270**, 1101–11 (1964)
117. Wilhelm, D. L., *Pharmacol. Rev.*, **14**, 251–80 (1962)
118. Austen, K. F., in *Immunologic Diseases*, 211–249 (Little, Brown and Co., Boston, 1965)
119. Juhlin, L., Shelley, W. B., *J. Am. Med. Assoc.*, **177**, 371–77 (1961)
120. Lobitz, W. C., Jr., in *Dermatoses Due to Environmental and Physical Factors*, 104–46 (Thomas, Springfield, Ill., 1962)
121. Calnan, C. D., *Brit. Med. J.*, **2**, 649–55 (1964)
122. Ishizaka, T., Ishizaka, K., *Proc. Soc. Exptl. Biol. Med.*, **101**, 845–50 (1959)
123. Christian, C. L., *J. Immunol.*, **84**, 117–21 (1960)
124. Ritzmann, S. E., Levin, W. C., *Arch. Internal. Med.*, **107**, 754–72 (1961)
125. Rose, B., in *Immunological Diseases*, 713–39 (Little, Brown and Co., Boston, 1965)
126. Yachnin, S., Ruthenberg, J. M., *J. Immunol.*, **94**, 12–17 (1965)
127. Landerman, N. S., Webster, M. E., Becker, E. L., Ratcliffe, H. E., *J. Allergy*, **33**, 330–41 (1962)
128. Donaldson, V. H., Evans, R. R., *Am. J. Med.*, **35**, 37–44 (1963)
129. Klemperer, P., Donaldson, V. H., Rosen, F. S., *J. Clin. Invest.*, **47**, 604–11 (1968)
130. Shulman, N. R., *Ann. Internal Med.*, **60**, 506–21 (1964)
131. Valentine, M. D., Cloch, K. J., Austen, K. F., *J. Immunol.*, **99**, 98–110 (1967)
132. Austen, K. F., Sheffer, A. L., *New Engl. J. Med.*, **272**, 649–56 (1965)
133. Rostenberg, A., Fagelson, H. J., *J. Am. Med. Assoc.*, **194**, 660–62 (1965)
134. Sutton, R., *Diseases of the Skin* (Mosby, St. Louis, Mo., 1956)
135. Yaffee, H. S., *Newer Views of Skin Diseases* (Little, Brown and Co., Boston, 1966)
136. Hellgren, L., Hersle, K., *Acta Allergol.*, **21**, 45–51 (1965)
137. Bianchine, J. R., Macaraeg, P. V. J., Jr., Lasagna, L., Azarnoff, D. L., Brunk, S. F., Hvidberg, E. F., Owen, J. A., Jr., *Am. J. Med.*, **44**, 390–405 (1968)
138. Levine, B. B., Fellner, M. J., *J. Clin. Invest.*, **44**, 1067–68 (1965)
139. DeFeo, C. P., *Arch. Dermatol.*, **94**, 545–51 (1966)
140. Stoughton, R. B., Bagatell, F., *J. Invest. Dermatol.*, **33**, 287–92 (1959)
141. Rothberg, S., Crounse, R. G., Lee, J. L., *J. Invest. Dermatol.*, **37**, 497–505 (1961)
142. Van Scott, E. J., Ekel, T., *Arch. Dermatol.*, **88**, 373–81 (1963)
143. Bullough, R., *Cancer Res.*, **10**, 1684–99 (1965)
144. Gordon, H., *Brit. J. Dermatol.*, **73**, 393–409 (1961)
145. Holcomb, F. D., *Obstet. Gynecol.*, **25**, 156–57 (1965)
146. Gammel, J. A., *Arch. Dermatol.*, **66**, 494–505 (1952)
147. Welch, A., Ede, M., *Arch. Dermatol.*, **84**, 1004, 1012 (1961)
148. Derbes, V. J., *J. Am. Med. Assoc.*, **190**, 765–66 (1964)
149. Fitzpatrick, T. B., *Arch. Dermatol.*, **92**, 484–85 (1965)
150. Goldstein, N., Leider, M., Baer, R., *Arch. Dermatol.*, **87**, 612–17 (1963)
151. Horowitz, H. I., Nashman, R. L., *Seminars Hematology* **2**, 287–312 (1965)
152. Ackroyd, J. F., *Proc. Roy. Soc. Med.*, **55**, 30–36 (1962)
153. Schulman, N. R., *Ann. Internal Med.*, **60**, 506–21 (1964)
154. Sicuteri, F., Michelacci, S., Franchi, G., *Intern. Arch. Allerg.*, **22**, 408–441 (1963)

155. Feldberg, W., Patton, W. D. M., *J. Physiol.*, **114,** 490–509 (1951)
156. Verhagen, H., *Acta Med. Scand.*, **148,** 453–62 (1954)
157. Harber, L. C., Targovik, S. E., Baer, R. L., *Arch. Dermatol.*, **96,** 646–56 (1967)
158. Jillson, O. F., Curwen, W. L., *Arch. Dermatol.*, **80,** 678–89 (1959)
159. Epstein, S., *Arch. Dermatol.*, **93,** 217–20 (1966)
160. Baer, R. L., Harber, L. C., *J. Am. Med. Assoc.*, **192,** 989–90 (1965)
161. Pathak, M. A., Danields, F., Jr., Fitzpatrick, T. B., *J. Invest. Dermatol.*, **39,** 225–39 (1962)
162. Birmingham, D. J., Key, M. M., Tubich, G. E., Perone, V. B., *Arch. Dermatol.*, **83,** 73–87 (1961)
163. Harber, L. C., Leider, M., Harris, H., Baer, R. L., *Arch. Dermatol.*, **90,** 572–76 (1964)
164. Burkick, K. H., *Arch. Dermatol.*, **93,** 424–25 (1966)
165. Crown, K. D., Alexander, E., Buck, W. H. L., Johnson, B. E., Magnus, I. A., Porter, A. D., *Brit. J. Dermatol.*, **73,** 220–28 (1961)
166. Mulloy, J. F., Mayer, J. A., *Arch. Dermatol.*, **93,** 329–31 (1966)
167. O'Quinn, S. E., Kennedy, C. B., Isbell, K. H., *J. Am. Med. Assoc.*, **199,** 125–28 (1967)
168. Knox, J. M., *Ann. Allergy,* **19,** 749–54 (1961)
169. Cahn, M. M., Levy, E. J., *Arch. Dermatol.*, **75,** 38–40 (1957)
170. Epstein, S., *Arch. Dermatol.*, **81,** 175–80 (1960)
171. Epstein, S., *J. Invest. Dermatol.*, **2,** 43–51 (1939)
172. Harber, L. C., Lashinsky, A. M., Baer, R. L., *New Engl. J. Med.*, **261,** 1378–81 (1959)
173. Miller, R. C., Beltrani, J. S., *Arch. Dermatol.*, **93,** 346–56 (1966)
174. Calnan, C. D., Harman, R. R., Wells, G. C., *Brit. Med. J.*, **2,** 1266 (1961)
175. Wilkinson, D. S., *Brit. J. Dermatol.*, **73,** 213–19 (1961)
176. Vinson, L. J., Flatt, R. S., *J. Invest. Dermatol.*, **38,** 327–28 (1962)
177. Buckley, W. R., *Arch. Dermatol.*, **78,** 454–57 (1958)
178. Hitch, J. M., *J. Am. Med. Assoc.*, **200,** 819–80 (1967)
179. Hurley, H. J., Shelley, W. B., *J. Invest. Dermatol.*, **33,** 203–20 (1959)
180. Houck, J. C., Patel, Y. M., *Nature,* **206,** 158–60 (1965)
181. Rosenfeld, S., Swiller, A. J., Shenoy, Y. M. V., Morrison, A. N., *J. Am. Med. Assoc.*, **176,** 491–93 (1961)
182. Lande, S., Lerner, A. B., *Pharmacol. Rev.*, **19,** 1–20 (1967)
183. Lerner, A. B., McGuire, J. S., *New Engl. J. Med.*, **270,** 539–46 (1964)
184. Dummett, C. D., *J. Oral Therapy,* **1,** 106–10 (1964)
185. Jeghers, H., *New Engl. J. Med.*, **231,** 181–89 (1944)
186. Greiner, A. C., Berry, K., *Can. Med. Assoc. J.*, **90,** 663–65 (1964)
187. Zelickson, A. S., Zeller, H. C., *J. Am. Med. Assoc.*, **188,** 394–96 (1964)
188. Hays, G. B., Lyle, C. B., Wheeler, C. E., Jr., *Arch. Dermatol.*, **90,** 471–76 (1964)
189. Greiner, A. C., Nicolson, G. A., *Can. Med. Assoc. J.*, **91,** 627–35 (1964)
190. Greiner, A. C., Nicolson, G. A., *Lancet,* **II,** 1165–67 (1965)
191. Blois, M. S., Jr., *J. Invest. Dermatol.*, **45,** 475–81 (1965)
192. Green, R., *Lancet,* **I,** 826–29 (1932)
193. Schechter, A. J., Taylor, H. M., *Am. J. Med. Sci.*, **192,** 645–50 (1936)
194. Maguire, A., *Proc. Roy Soc. Med.*, **53,** 563–64 (1960)
195. Tuffanelli, D., Abraham, R. K., Dubois, E. J., *Arch. Dermatol.*, **88,** 419–26 (1963)
196. Ginsberg, J. E., Shallenberger, P. L., *J. Am. Med. Assoc.*, **131,** 808–9 (1946)
197. Kierland, R. R., Sheard, C., Mason, H. L., Lobitz, W. C., *J. Am. Med. Assoc.*, **131,** 809–10 (1946)
198. Alving, A. S., Eichelberger, L., Craige, B. Jr., Jones, R. Jr., Whorton, C. M., Pullman, T. N., *J. Clin. Invest.*, **27,** Suppl. 2–5 (1948)
199. Saunders, T. S., Fitzpatrick, T. B., Seiji, M., Brunet, P., Rosenbaum, E. E., *J. Invest. Dermatol.*, **33,** 87–90 (1959)
200. Satanove, A., *J. Am. Med. Assoc.*, **191,** 263–68 (1965)
201. Kyle, R. A., Schwartz, R. S., Oliner, H. L., Demeshek, W., *Blood,* **18,** 497–510 (1961)
202. Moller, H., *Acta Dermato-Venereol.*, **46,** 423–31 (1966)
203. Cook, H. H., Gamble, C. J., Sat-

terthwaite, A. P., *Am. J. Obstet. Gynecol.*, **82,** 437–45 (1961)
204. Resnik, S., *J. Am. Med. Assoc.*, **199,** 601–5 (1967)
205. Wallman, I. S., Hilton, H. B., *Lancet* **I,** 827–29 (1962)
206. Zegarelli, E. V., Denning, C. R., Kutscher, A. H., Tuoti, F., si Sant'Agnese, P. A., *Pediatrics,* **26,** 1050–51 (1960)
207. Madison, J. F., *Arch. Dermatol.*, **88,** 58–59 (1963)
208. Kutscher, A. H., Zegarelli, E. V., Tovell, H. M. M., Hochberg, B., *J. Am. Med. Assoc.*, **184,** 586–87 (1963)
209. Witkop, C. J., Jr., Wolf, R. O., *J. Am. Med. Assoc.*, **184,** 1008–1111, (1963)
210. Loomis, W. F., *Science,* **157,** 501–6 (1967)
211. Lerner, A. B., Case, J. D., *J. Invest. Dermatol.*, **32,** 211–21 (1959)
212. Sulzberger, M., Hermann, F., *The Clinical Significance of Disturbances in the Delivery of Sweat* Thomas, Springfield, Ill., 1954)
213. Kuno, Y., *Human Perspiration* (Thomas, Springfield, Ill., 1956)
214. Goodman, L., Gilman, A., *The Pharmacological Basis of Therapeutics* (MacMillan, New York, 1965)
215. Hermann, F., Miller, O. B., *Acta Dermato-Venereol.*, **32,** 304–9 (1952)
216. Shelley, W. B., Horvath, P., Pillsbury, D., *Medicine,* **29,** 195–228 (1950)
217. Ratner, A. C., Dobson, R. L., *J. Invest. Dermatol.*, **43,** 379–81 (1964)
218. Montagna, W., Van Scott, E. J., in *Biology of Hair Growth,* 39–64 (Academic Press, New York, 1959)
219. Winkelman. R. W., Perry, H. O., Achor, R. W., Kirby, T. J., *Arch. Dermatol.*, **87,** 372–77 (1963)
220. Peters, L. (Personal communication)
221. Crounse, R., in *Clinical Dermatology,* 35–62 (Demis, D. J., Crounse, R., Dobson, R., and McGuire, J., Eds., Hoeber, New York, 1969)
222. Mereu, T. R., Kassoff, A., Goodman, A. D., *New Engl. J. Med.*, **275,** 1455–60 (1966)
223. Baker, L., Kaye, R., Root, A. W., Prasad, A. L. N., *J. Pediat.*, **71,** 494–505 (1967)
224. Demis, D. J. (In preparation)
225. Halpern, S. R., *Ann. Allergy,* **23,** 590–99 (1965)
226. Lindblad, J. H., Farr, R. S., *J. Allergy,* **32,** 392–401 (1961)
227. Holt, L. E., *New Engl. J. Med.*, **276,** 1449–54 (1967)
228. Litt, M., *Ann. N. Y. Acad. Sci.*, **116,** 964–85 (1964)
229. Rorsman, H., *Acta Dermato-Venereol.*, **42,** (Suppl. 48) 1–20 (1962)
230. Shelley, W. B., *Nature,* **195,** 1181–83 (1962)
231. Shelley, W. B., Juhlin, L., *Nature,* **191,** 1056–58 (1961)
232. Gordon, V. H., *Ann. Allergy,* **24,** 171–78 (1966)
233. Resnik, S. S., Shelley, W. B., *J. Invest. Dermatol.*, **45,** 269–74 (1965)
234. Shelley, W. B., *Ann. N. Y. Acad. Sci.*, **103,** 427–35 (1963)
235. Bobitt, J. R., Schechter, H., Pollak, V. E., *Proc. Soc. Exptl. Biol. Med.*, **117,** 608–10 (1964)
236. Friedlander, S., Friedlander, A. S., *J. Allergy,* **35,** 361–70 (1964)
237. Kravis, L. P., Lecks, H. I., Whitney, T., *J. Allergy,* **36,** 23–28 (1965)
238. Tullettt, G. L., *Brit. Med. J.*, **1,** 148–51 (1966)
239. Ridley, D. S., *Intern. J. Leprosy,* **28,** 254–59 (1960)
240. Bullough, W. S., Lawrence, E. B., Iverson, O. H., Elgjo, K., *Nature,* **214,** 578–80 (1967)
241. Bullough, W. S., Lawrence, E. B., *Exptl. Cell. Res.*, **43,** 343–50 (1966)
242. Bullough, W. S., Lawrence, E. B., *Nature,* **210,** 715–16 (1966)
243. Reed, W. B., Dexter, R., Corley, C., Fish, C., *Arch. Dermatol.*, **91,** 326–34 (1965)
244. Brown, J., Winkelmann, R. K., *Medicine,* **47,** 33–51 (1968)
245. Jacklin, H. N., *Am. J. Ophthalmol.*, **59,** 89–92 (1965)