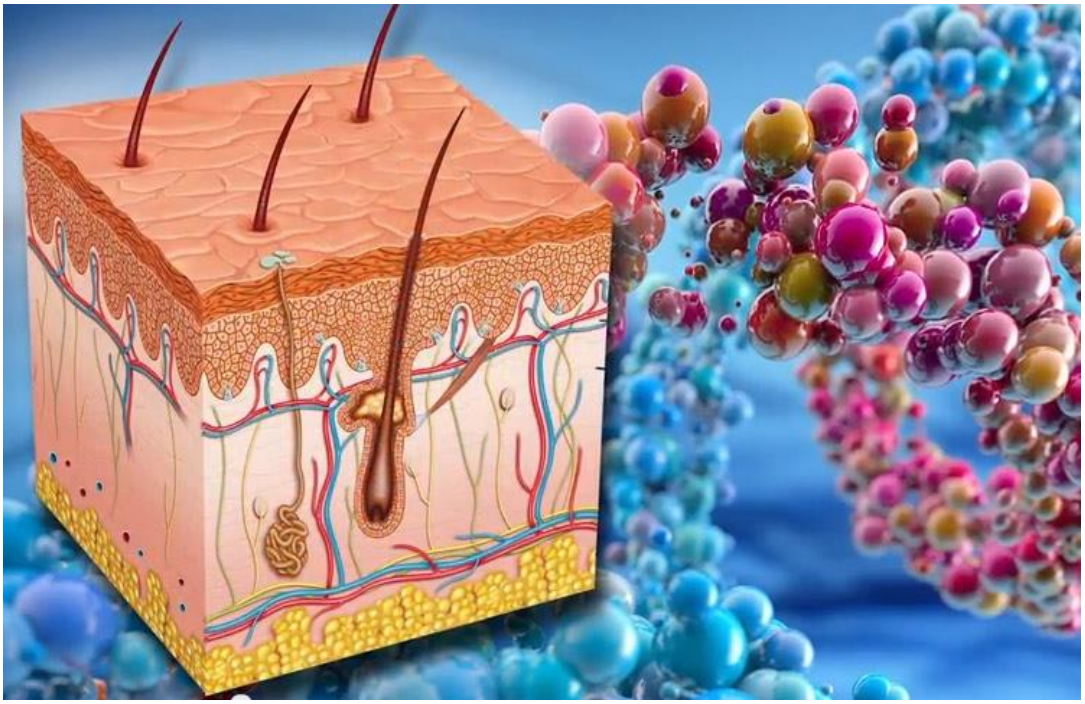
ADKHAMJON PAKIRDINOV

ATOPIC DERMATITIS, ECZEMA AND NONINFECTIOUS IMMUNODEFICIENCY DISORDERS



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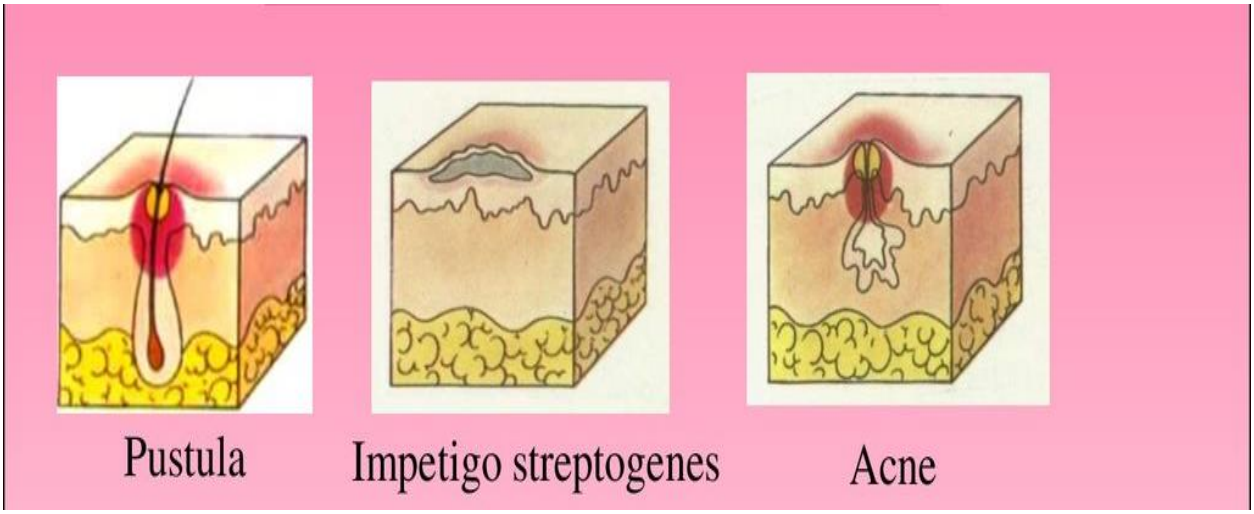
ANDIJAN STATE MEDICAL INSTITUTE

THE DEPARTMENT OF DERMATOLOGY AND VENEREOLOGY

ATOPIC DERMATITIS, ECZEMA AND NONINFECTIOUS IMMUNODEFICIENCY DISORDERS.

(FOR RESIDENTS, CLINICAL INTERNS, TREATMENT AND PEDIATRICS STUDENTS)



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PRIMARY AND SECONDARY MORFOLOGICAL

ELEMENTS OF THE SKIN.

Typically, most skin diseases produce or present with lesions that have more or less distinct characteristics. They may be uniform or diverse in size, shape, and color, and may be in different stages of evolution or involution. The original lesions are known as the primary lesions, and identification of such lesions is the most important aspect of the dermatologic physical examination. They may continue to full development or be modified by regression, trauma, or other extraneous factors, producing secondary lesions.

PRIMARY LESIONS

Primary lesions are of the following forms: macules (or patches), papules (or plaques), nodules, tumors, wheals, vesicles, bullae, and pustules.

MACULES (MACULAE, SPOTS)

Macules are variously sized, circumscribed changes in skin color, without elevation or depression (nonpalpable). They may be circular, oval, or irregular, and may be distinct in outline or fade into the surrounding skin. Macules may constitute the whole or part of the eruption, or may be merely an early phase. If the lesions become slightly raised, they are then designated papules or, sometimes, morbilliform eruptions (Fig. 1).

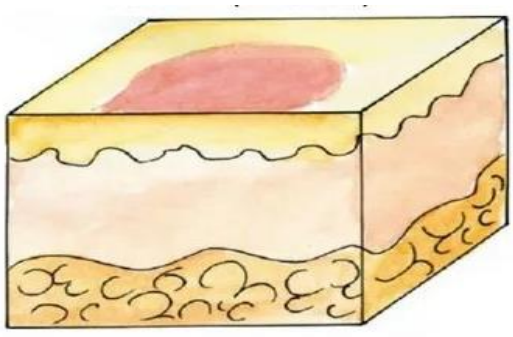


Fig. 1. Macules

PATCHES

A patch is a large macule, 1 cm or greater in diameter, as may be seen in nevus flammeus or vitiligo (Fig. 2).

Fig. 2. Patches

PAPULES

Papules are circumscribed, solid elevations with no visible fluid, varying in size from a pinhead to 1 cm. They may be acuminate, rounded, conical, flat-topped, or umbilicated, and may appear white (as in milium), red (as in eczema), yellowish (as in xanthoma), or black (as in melanoma).

Papules are generally centered in the dermis and may be concentrated at the orifices of the sweat ducts or at the hair follicles. They may be of soft or firm consistency. The surface may be smooth or rough. If capped by scales, they are known as squamous papules, and the eruption is called papulosquamous.

Some papules are discrete and irregularly distributed, as in papular urticaria, whereas others are grouped, as in lichen nitidus. Some persist as papules, whereas those of the inflammatory type may progress to vesicles and even to pustules, or may erode or ulcerate before regression takes place.

The term maculopapular should not be used. There is no such thing as a maculopapule, but there may be both macules and papules in an eruption. Most typically such eruptions are morbilliform (Fig. 3).

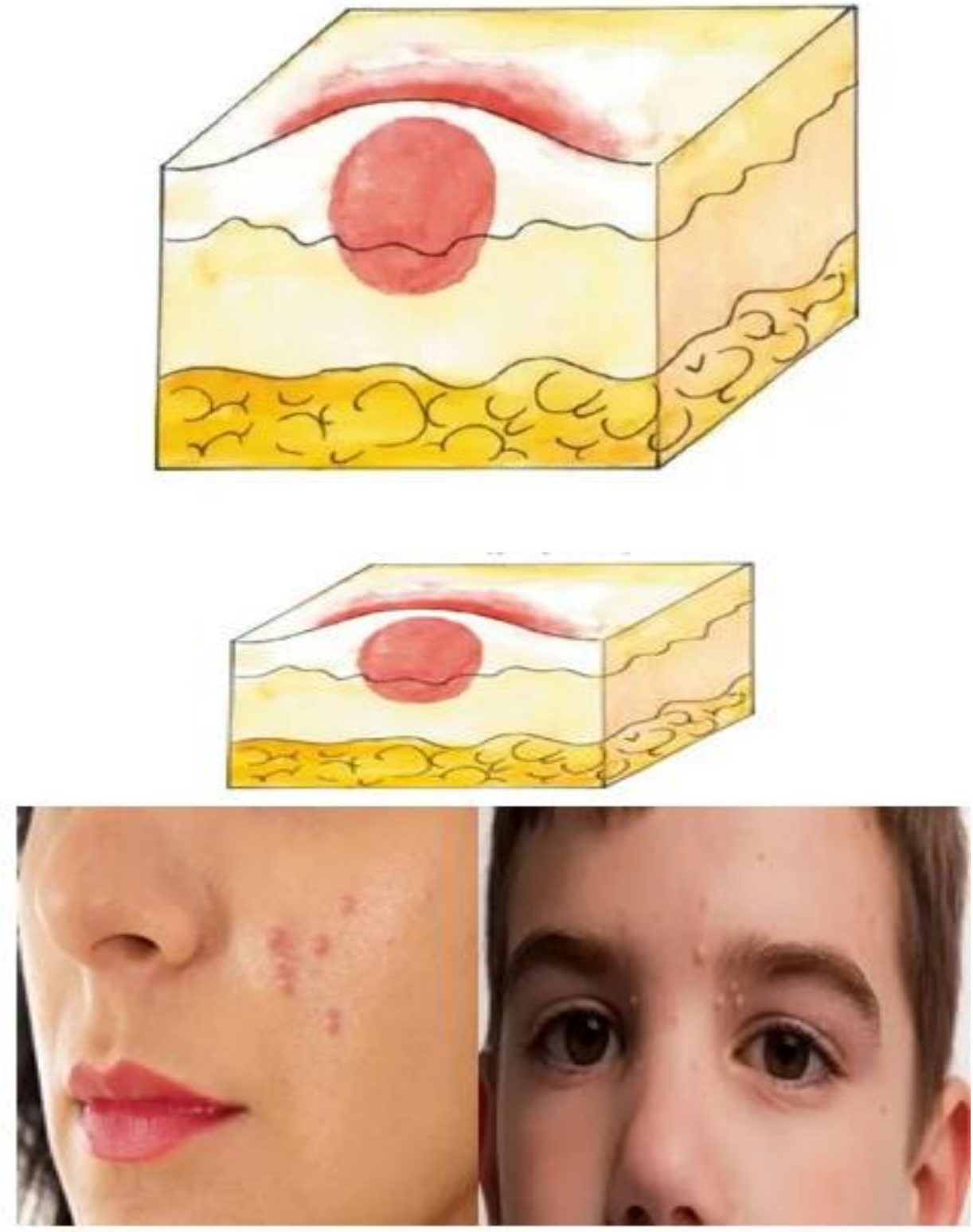


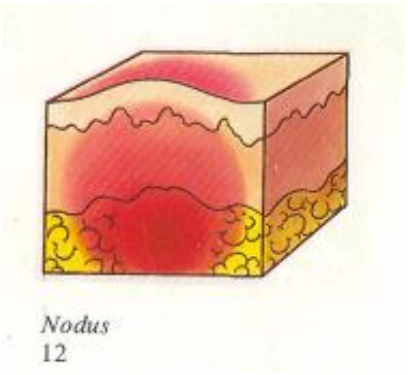
Fig. 3. Papules

PLAQUES

A plaque is a broad papule (or confluence of papules), 1 cm or more in diameter. It is generally flat, but may be centrally depressed. The center of a plaque may be normal skin.

NODULES

Nodules are morphologically similar to papules, but they are larger than 1 cm in diameter. They most frequently are centered in the dermis or subcutaneous fat (Fig. 4.).



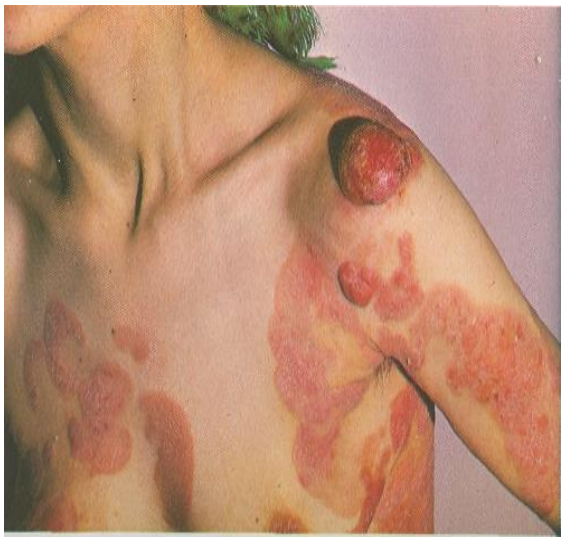


Fig. 4. Nodules

TUMORS

Tumors are soft or firm and freely movable or fixed masses of various sizes and shapes (but in general greater than 2 cm in diameter). General usage dictates that the word "tumor" means a neoplasm. They may be elevated or deep-seated, and in some instances are pedunculated (fibromas). Tumors have a tendency to be rounded. Their consistency depends on the constituents of the lesion. Some tumors remain stationary indefinitely, whereas others increase in size or break down.

WHEALS (HIVES)

Wheals are evanescent, edematous, plateau-like elevations of various sizes. They are usually oval or of arcuate contours, pink to red, and surrounded by a "flare" of macular erythema. They may be discrete or may coalesce. These lesions often develop quickly. Because the wheal is the prototypic lesion of urticaria, diseases in which wheals are prominent are frequently described as "urticarial" (e.g. urticarial vasculitis). Dermatographism, or pressure-induced whealing, may be evident **(**Fig. 5**)**.

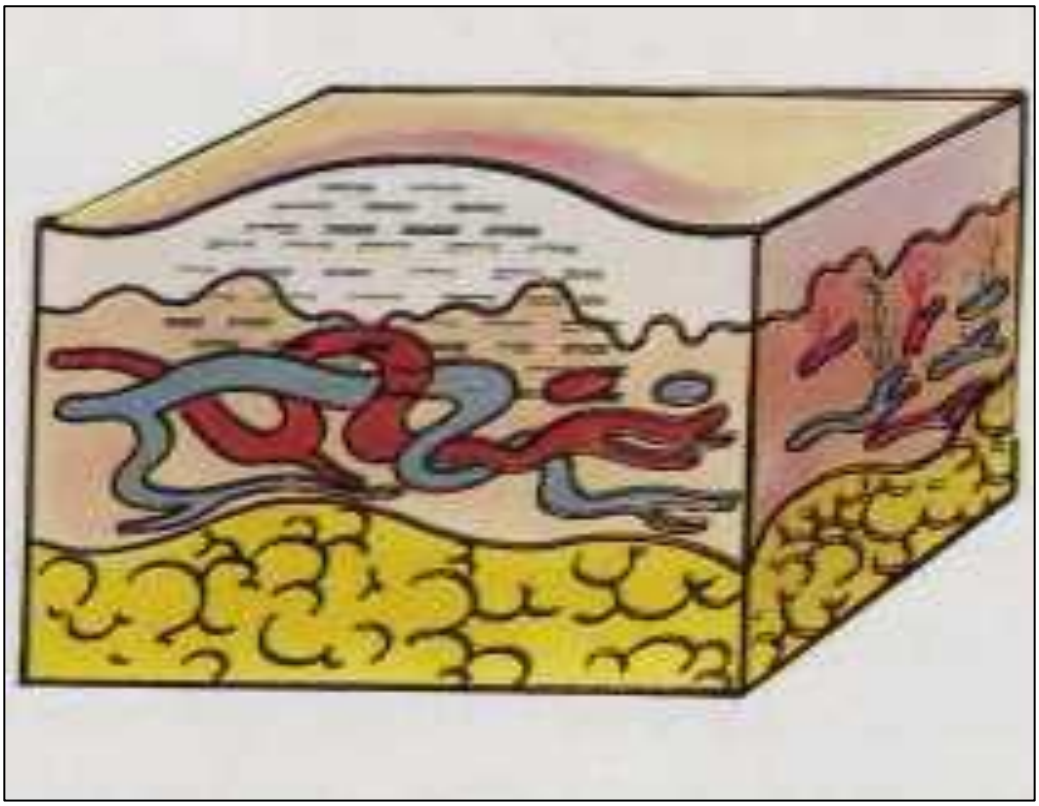


Fig. 5. Wheals

VESICLES (BLISTERS)

Vesicles are circumscribed, fluid-containing, epidermal elevations, 1-10 mm in size. They may be pale or yellow from serous exudate, or red from serum mixed with blood. The apex may be rounded, acuminate, or umbilicated as in eczema her- peticum. Vesicles may be discrete, irregularly scattered, grouped as in herpes

zoster, or linear as in allergic contact dermatitis from urushiol (poison ivy/oak). Vesicles may arise directly or from a macule or papule, and generally lose their identity in a short time, breaking spontaneously or developing into bullae through coalescence or enlargement, or developing into pustules. When the contents are of a seropuru- lent character, the lesions are known as vesicopustules. Vesicles consist of either a single cavity (unilocular) or several compartments (multilocular) containing fluid (Fig. 6).

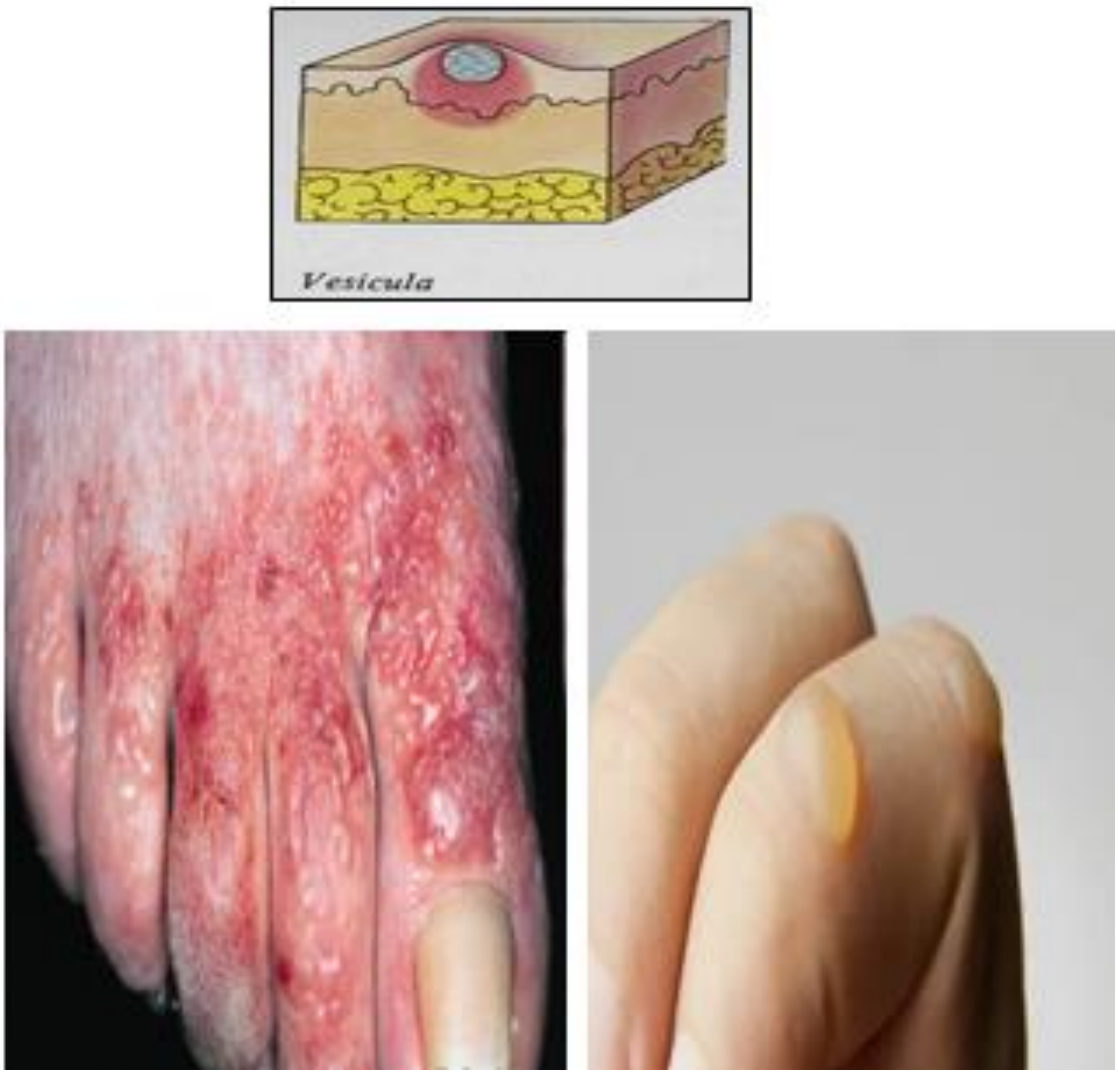


Fig. 6. Vesicles

BULLAE

Bullae are rounded or irregularly shaped blisters containing serous or seropurulent fluid. They differ from vesicles only in size, being larger than 1 cm.

They are usually unilocular but may be multilocular. Bullae may be located superficially in the epidermis, so that their walls are flaccid and thin, and subject to rupture spontaneously or from slight injury. After rupture, remnants of the thin walls may persist and, together with the exudate, may dry to form a thin crust; or the broken bleb may leave a raw and moist base, which may be covered with sero-purulent or purulent exudate. More rarely, irregular vegetations may appear on the base (as in pemphigus vegetans). When the bullae are subepidermal, they are tense, and ulcera- tion and scarring may result.

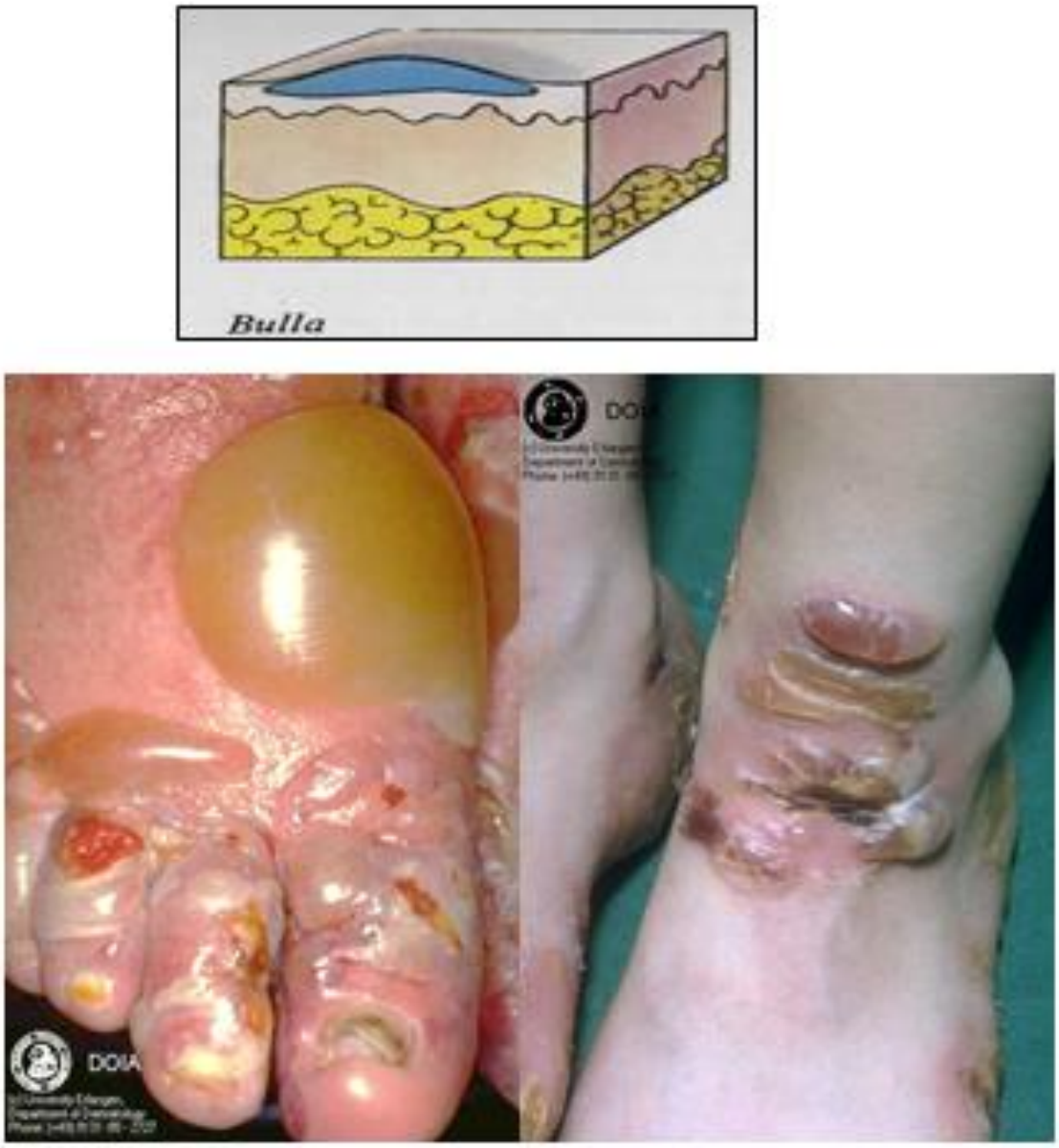


Fig. 7. Bullae

Nikolsky's sign refers to the diagnostic maneuver of putting lateral pressure on unblistered skin in a bullous eruption and having the epithelium shear off. Asboe-Hansen's sign refers to the extension of a blister to adjacent unblistered skin when pressure is put on the top of the blister. Both of these signs demonstrate the principle that in some diseases the extent of microscopic vesiculation is more than is evident by simple inspection. These findings are useful in evaluating the severity of pemphigus vulgaris and severe bullous drug reactions. Hemorrhagic bullae are common in pemphigus, herpes zoster, severe bullous drug reactions, and lichen sclerosus. The cellular contents of bullae may be useful in cytologically confirming the diagnosis of pemphigus, herpes zoster and herpes simplex (Fig. 7).

PUSTULES

Pustules are small elevations of the skin containing purulent material (usually necrotic inflammatory cells). They are similar to vesicles in shape and usually have an inflammatory areola. They are usually white or yellow centrally, but may be red if they also contain blood. They may originate as pustules or may develop from papules or vesicles, passing through transitory early stages, during which they are known as papulopustules or vesicopustules (Fig. 8).

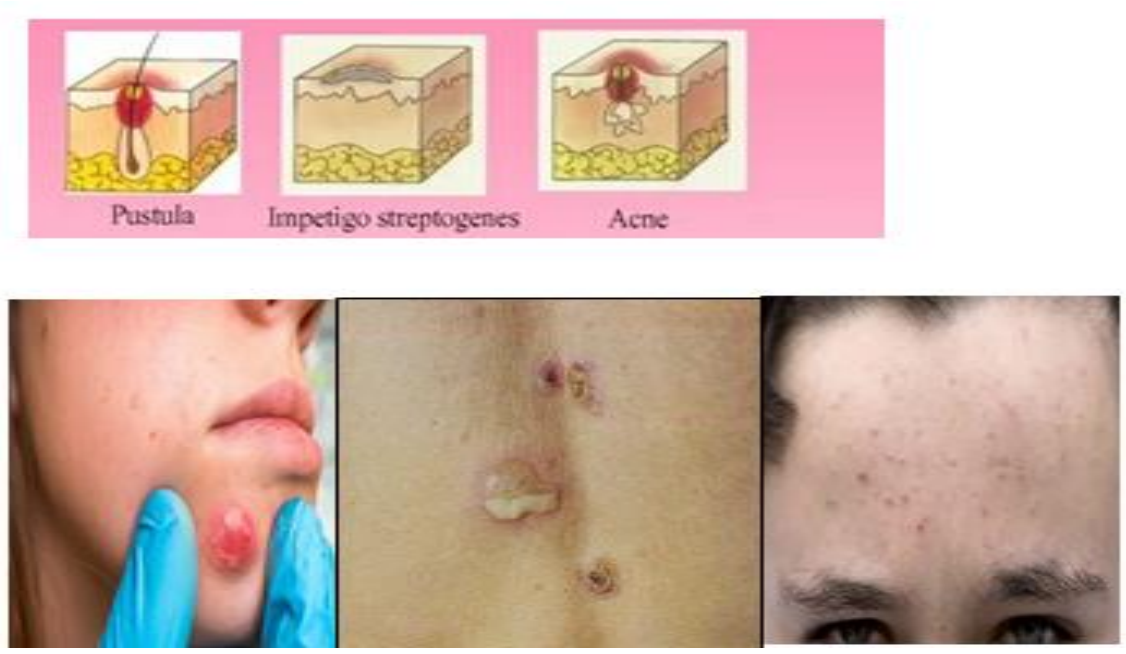


Fig. 8. Pustules

SECONDARY LESIONS

Secondary lesions are of many kinds; the most important are scales, crusts, erosions, ulcers, fissures, and scars.

SCALES (EXFOLIATION)

Scales are dry or greasy laminated masses of keratin. The body ordinarily is constantly shedding imperceptible tiny, thin fragments of stratum corneum. When the formation of epidermal cells is rapid or the process of normal keratinization is interfered with, pathologic exfoliation results, producing scales. These vary in size, some being fine, delicate, and branny, as in tinea versicolor, others being coarser, as in eczema and ichthyosis, while still others are stratified, as in psoriasis. Large sheets of desquamated epidermis are seen in toxic epidermal necrolysis, staphylococcal scalded skin syndrome, and infection-associated (toxinmediated) desquamations, such as scarlet fever. Scales vary in color from white-gray to yellow or brown from the admixture of dirt or melanin. Occasionally, they have a silvery sheen from trapping of air between their layers; these are micaceous scales, characteristic of psoriasis. When scaling occurs, it usually implies that there is some pathologic process in the epidermis, and parakeratosis is often present histologically.

CRUSTS (SCABS)

Crusts are dried serum, pus, or blood, usually mixed with epithelial and sometimes bacterial debris. They vary greatly in size, thickness, shape, and color, according to their origin, composition, and volume. They may be dry, golden yellow, soft, friable, and superficial, as in impetigo; yellowish, as in favus; thick, hard, and tough, as in thirddegree burns; or lamellated, elevated, brown, black, or green masses, as in late syphilis. The latter have been described as oystershell (ostra- ceous) crusts and are known as rupia. When crusts become detached, the base may be dry or red and moist (Fig. 9).

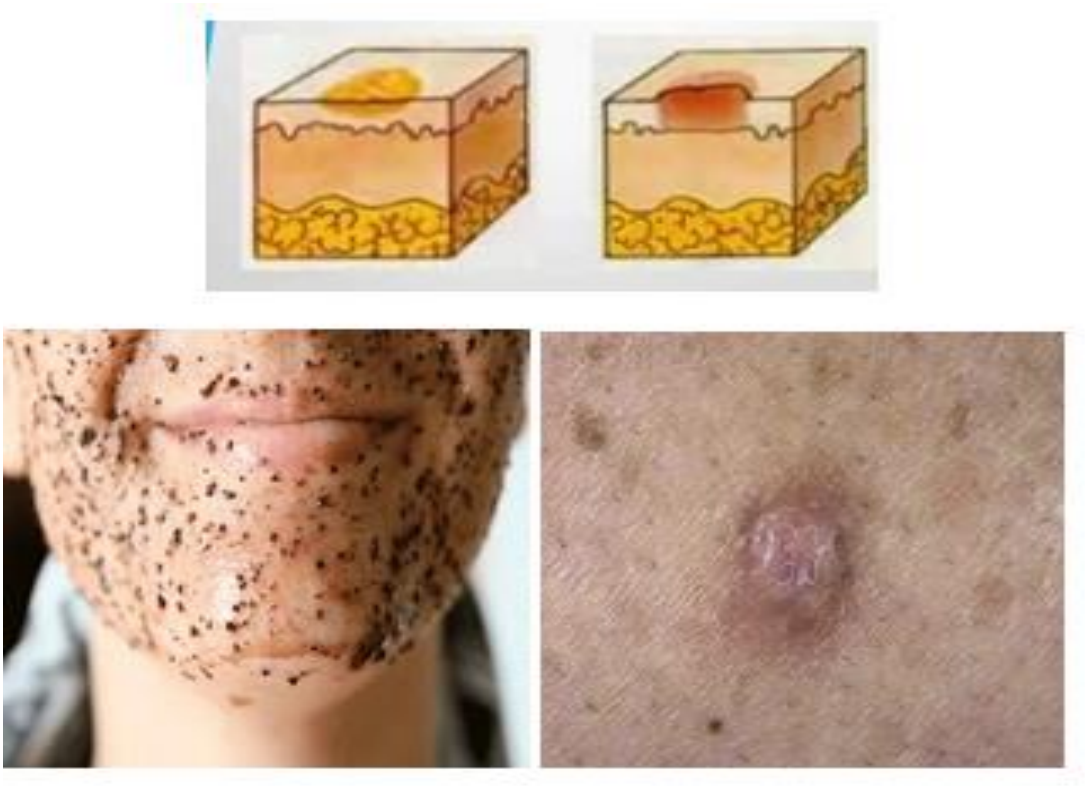


Fig. 9. Crusts

EXCORIATIONS AND ABRASIONS (SCRATCH MARKS)

An excoriation is a punctate or linear abrasion produced by mechanical means, usually involving only the epidermis but not uncommonly reaching the papillary layer of the dermis. Excoriations are caused by scratching with the fingernails in an effort to relieve itching in a variety of diseases. If the skin damage is the result of mechanical trauma or constant friction, the term abrasion may be used. Frequently there is an inflammatory areola around the excoriation or a covering of yellowish dried serum or red dried blood. Excoriations may provide access for pyogenic microorganisms and the formation of crusts, pustules, or cellulitis, occasionally associated with enlargement of the neighboring lymphatic glands. In general, the longer and deeper excoriations are, the more severe was the pruritus that provoked them. Lichen planus is an exception, however, in which pruritus is severe, but excoriations are rare (Fig. 10).

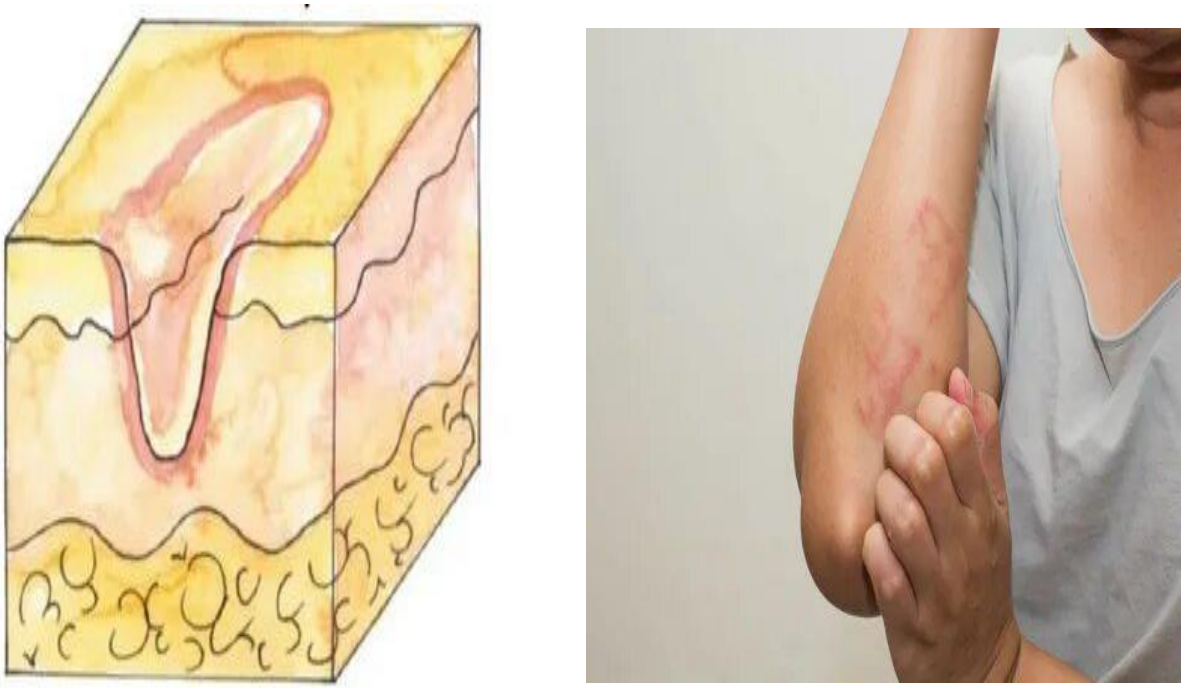
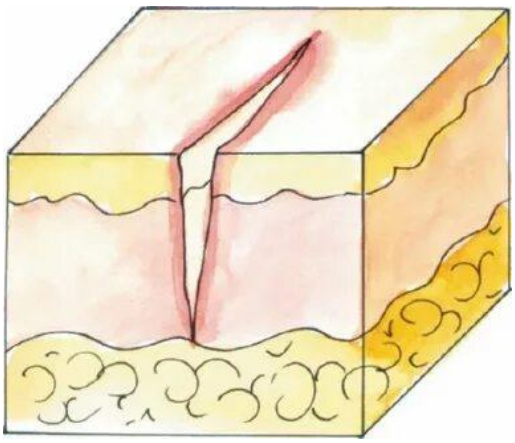


Fig. 10. Excoriations

FISSURES (CRACKS, CLEFTS)

A fissure is a linear cleft through the epidermis or into the dermis. These lesions may be single or multiple, and vary from microscopic to several centimeters in length with sharply defined margins. They may be dry or moist, red, straight, curved, irregular, or branching. They occur most commonly when the skin is thickened and inelastic from inflammation and dryness, especially in regions subjected to frequent movement. Such areas are the tips and flexural creases of the thumbs, fingers, and palms; the edges of the heels; the clefts between the fingers and toes; at the angles of the mouth; the lips; and about the nares, auricles, and anus. When the skin is dry, exposure to cold, wind, water, and cleaning products (soap, detergents) may produce a stinging, burning sensation, indicating microscopic fissuring is present. This may be referred to as chapping, as in "chapped lips." When fissuring is present, pain is often produced by movement of the parts, which opens or deepens the fissures or forms new ones (Fig. 11).



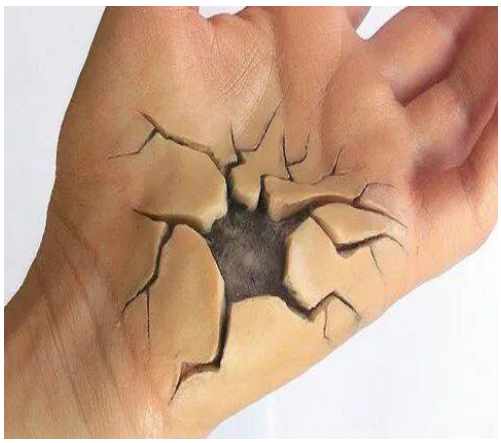
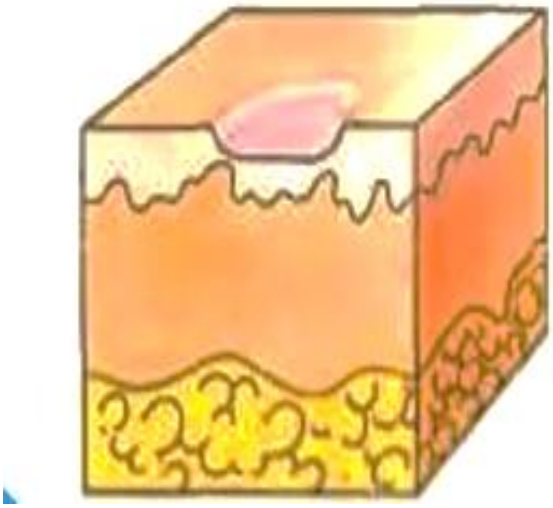


Fig. 11. Fissures

EROSIONS

Loss of all or portions of the epidermis alone, as in impetigo or herpes zoster or simplex after vesicles rupture, produces an erosion. It may or may not become crusted, but it heals without a scar (Fig. 12).



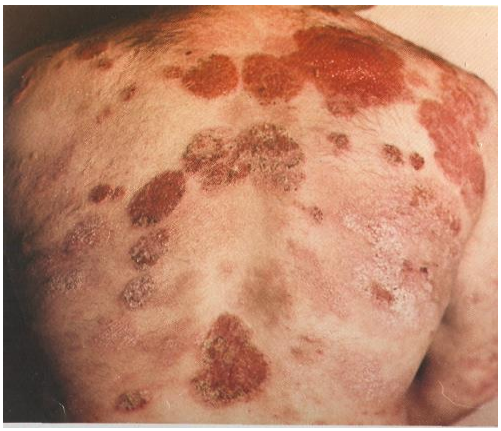
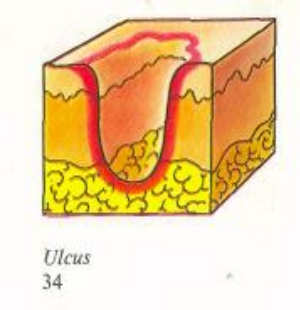


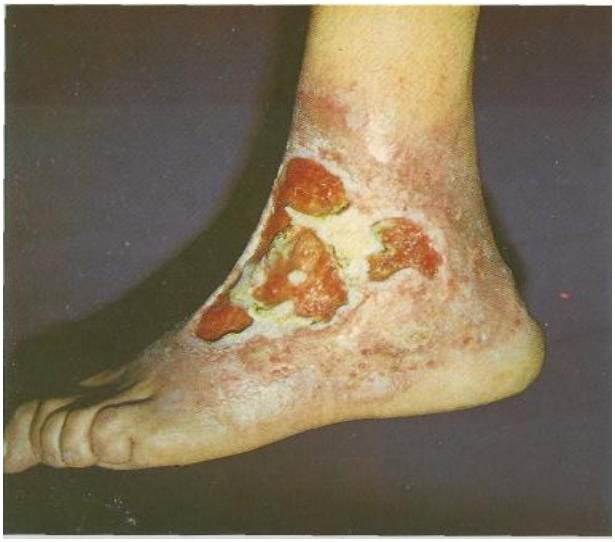
Fig. 12. Erosions

ULCERS

Ulcers are rounded or irregularly shaped excavations that result from complete loss of the epidermis plus some portion of the dermis. They vary in diameter from a few millimeters to several centimeters. They may be shallow, involving little beyond the epidermis, as in dystrophic epidermolysis bullosa, the base being formed by the papillary layer, or they may extend deep into the dermis, subcutaneous tissues, or deeper, as with leg ulcers. They heal with scarring.

ULCERS





SCARS

Scars are composed of new connective tissue that replaced lost substance in the dermis or deeper parts as a result of injury or disease, as part of the normal reparative process. Their size and shape are determined by the form of the previous destruction. Scarring is characteristic of certain inflammatory processes and is therefore of diagnostic value. The pattern of scarring may be characteristic of a particular disease. Lichen planus and discoid lupus erythematosus, for example, have inflammation that is in relatively the same area anatomically, yet discoid lupus characteristically causes scarring as it resolves, whereas lichen planus rarely results in scarring of the skin. Both processes, however, cause scarring of the hair follicles when they occur on the scalp. Scars may be thin and atrophic, or the fibrous elements may develop into neoplastic overgrowths, as in keloids. Some individuals and some areas of the body, such as the anterior chest, are especially prone to scarring. Scars may be smooth or rough, pliable or firm, and tend at first to be pink or violaceous, later becoming white, glistening, and rarely, hyperpigmented. Scars are persistent but tend to become less noticeable in the course of time. At times, and especially in certain anatomic locations (central chest), they grow thick, tough, and corded, forming a hypertrophic scar or keloid.

ATOPIC DERMATITIS

Atopic dermatitis (AD) is a chronic, inflammatory skin disease that is characterized by pruritus and a chronic course of exacerbations and remissions. It is associated with other allergic conditions, including asthma and allergic rhinoconjunctivitis. Recent studies have cast doubt on the importance of AD in the subsequent development of asthma, refuting the concept of the "atopic march." However, a common genetic defect predisposes patients to the development of AD, asthma, and allergic rhinoconjunctivitis the "atopic" disorders.

EPIDEMIOLOGY

The prevalence of AD, asthma, and allergic rhinoconjunctivitis increased dramatically in the last half of the twentieth century, becoming a major health problem in many countries. The increase began first in the most developed nations, and as nations' standards of living have increased worldwide, so has the prevalence of AD. Rates of AD are around 30% in the most developed nations and exceed 10% in many countries, resulting in a worldwide cumulative prevalence of 15-20%. In the most developed nations, the rates of AD plateaued in the 1990, whereas developing nations have rates that continue to increase. Other factors associated with high rates of AD are high latitude (perhaps associated with low levels of annual sun exposure) and lower mean annual temperature. A role for exposure to allergens thought to "trigger" AD is not supported by epidemiological studies. Iceland has a very high rate of AD (27%) yet has no dust mites, few trees, and low pet ownership. Children in Iceland, none the less, often have positive skin prick tests to environmental allergens (24%). This brings into question the value of such tests in predicting causal environmental allergens in AD. In some studies maternal smoking and the fact that two or more members of the household smoke are associated with higher rates of AD. Girls are slightly more likely to develop AD. In the US, an increased risk of AD during the first 6 months of life is noted in infants with African and Asian race/ethnicity, male gender, greater gestational age at birth, and a family history of atopy, particularly a maternal history of eczema.

About 50% of cases of AD appear in the first year of life, the vast majority within the first 5 years of life, and the remaining cases of "adult" AD usually before age 30. Atopy is now so common in the population that most individuals have a family history of atopy. Elevated IgE levels are not diagnostic of atopic disease in the adult. Therefore, elevated IgE and a family history of "atopy" in an adult with new-onset dermatitis should not be used to confirm the diagnosis of "adult" AD. Rather, a dermatologist should uncommonly make the diagnosis of adult "atopic dermatitis" for a dermatitis appearing for the first time after age 30. Adult AD should only be considered when the dermatitis has a characteristic distribution and other significant diagnoses, such as allergic contact dermatitis, photodermatitis, and cutaneous T-cell lymphoma, have been excluded.

GENETIC BASIS OF ATOPIC DERMATITIS

Eighty percent of identical twins show concordance for AD. A child is at increased risk of developing AD if either parent is affected. More than one quarter of offspring of atopic mothers develop AD in the first 3 months of life. If one parent is atopic, more than half his/her children will develop allergic symptoms by age 2. This rate rises to 79% if both parents are atopic. All these findings strongly suggested a genetic cause for AD. Filaggrin is a protein encoded by the gene FLG, which resides in the "epidermal differentiation complex" on chromosome 1q21. Ichthyosis vulgaris is caused by mutations in the FLG gene, and is frequently associated with AD. Large populationbased studies have identified more than 35 mutations in FLG that are associated with AD. Inheriting one null FLG mutation slightly increases one's risk of developing AD, and inheriting two mutations (either as a homozygote or a compound hetero- zygote) dramatically increases one's risk. Between 42% and 79% of persons with one or more FLG null mutations will develop AD. FLG mutations account for between 11% and 15% of AD cases in Europe. However, 40% of carriers with FLG null mutations never have AD. FLG mutations are associated with AD that presents early in life, tends to persist into childhood and adulthood, and is associated with wheezing in infancy, and asthma.

FLG mutations are also associated with allergic rhinitis and keratosis pilaris, independent of AD. Hyperlinear palms are strongly associated with FLG mutations, with a 71% positive predictive value for marked palmar hyperlinearity. Not all cases of AD are associated with FLG mutations, and AD patients often demonstrate clinical findings consistent with a T-helper 2 (Th2) phenotype. Polymorphisms/mutations in genes expressed by Th2 cells, especially the interleukin (IL)-4 gene promoter region, have been identified in patients with AD. Other immunomodulatory genes in which mutations have been observed in AD patients include RANTES and eotaxin, IL-13, and the Psubunit of high-affinity Fc IgE receptor on mast cells. These mutations, in and of themselves, could potentially be causal in AD. In addition, however, overexpression of Th2 cytokines downregulates filaggrin protein expression in patients with AD. This could lead to an "acquired" filaggrin deficiency, resulting in or exacerbating AD.

PREVENTION OF ATOPIC DERMATITIS

Extensive studies have been undertaken to determine whether it is possible to prevent the development of AD in children at high risk those with parents or siblings with atopy. Maternal antigen avoidance during pregnancy does not reduce the incidence of AD. Some studies have suggested that hydrolyzed protein formula milks (and even better, extensively hydrolyzed formulas) may delay the onset of AD, but a Cochrane review found no clear evidence of protective effect for AD. Soy formulas do not appear to reduce the risk of developing AD. Early introduction of solids does, in a dosedependent fashion, increase the risk of AD. Prolonged breast feeding appears to reduce the risk of AD. In two independent cohorts, cat ownership at birth substantially increases the risk of developing AD within the first year of life in children with FLG loss of function mutations, but not in those without. Dog and dust mite exposure was NOT associated with the development of AD. Filaggrindeficient individuals should avoid cat exposure early in life.

FOOD ALLERGY AND AD

The role of food allergy in AD is complicated, and the purported role of foods in AD has changed in recent years. Parents may use older Internet resources and be misinformed about food allergy. Approximately 35% of children with moderate to severe AD have food allergy. Food allergy in adults is rare. However, 85% of children with AD will have elevated IgE to food or inhalant allergens, making a diagnosis of food allergy with serum or prick tests alone inadvisable. Before food allergy testing is embarked upon, the treatment of the AD should be optimized. Parents are often seeking a "cause" for the child's AD, when in fact it could be controlled with appropriate topical measures. Since food restriction diets can be difficult and could potentially put the child at risk for malnourishment, food allergy should only be pursued in younger children or infants with more severe AD when standard treatments have failed. Prick tests have a high negative predictive value (>95%) but a positive predictive value of only 30-65%. For example, more than 8% of the US population has a positive prick test to peanut, but only 0.4% are actually clinically allergic. Possible food allergy detected by testing should be confirmed by clinical history. For instance, a positive radioallergosorbent test (RAST) or skin prick test for a food that the child rarely or never ingests is probably not causally relevant to their AD. Higher serum IgE levels and larger wheal sizes (>8-10 mm) are associated with greater likelihood of reacting to these foods when challenged. Around 90% of food allergy is due to a limited number of foods: infants: cow's milk, egg, soybean, wheat children (2-10 years): cow's milk, egg, peanut, tree nuts, fish, crustacean shellfish, sesame, and kiwi fruit older children: peanut, tree nuts, fish, shellfish, sesame, pollenassociated foods. Breast-feeding mothers must avoid the incriminated foods if their infant has been diagnosed with a food allergy.

CLINICAL MANIFESTATIONS

AD can be divided into three stages: infantile AD, occurring from 2 months to 2 years of age; childhood AD, from 2 to 10 years; and adolescent/adult AD. In

all stages, pruritus is the hallmark. Itching often precedes the appearance of lesions; hence the concept that AD is "the itch that rashes." Useful diagnostic criteria include those of Hannifin and Rajka, the UK Working Party, and the American Academy of Dermatology's Consensus Conference on Pediatric Atopic Dermatitis. These criteria have specificity at or above 90%, but have much lower sensitivities (40-100%). Therefore, they are useful for enrolling patients in studies and insuring that they have AD, but are not so useful in diagnosing a specific patient with AD.

INFANTILE ATOPIC DERMATITIS

Fifty percent or more of cases of AD present in the first year of life, but usually not until after 2 months of age. Eczema in Must have three of the following:

Pruritus

Typical morphology and distribution

Flexural lichenification in adults

Facial and extensor involvement in infancy

Chronic or chronically relapsing dermatitis

Personal or family history of atopic disease (asthma, allergic rhinitis, atopic dermatitis) Minor criteria Must also have three of the following:

Xerosis Ichthyosis/hyperlinear palms/keratosis pilaris IgE reactivity (immediate skin test reactivity, RAST test positive);

Elevated serum IgE;

Early age of onset;

Tendency for cutaneous infections (especially Staphylococcus aureus and herpes simplex virus);

Tendency to nonspecific hand/foot dermatitis;

Nipple eczema;

Cheilitis;

Recurrent conjunctivitis;

Dennie-Morgan infraorbital fold;

Keratoconus;

Anterior subcapsular cataracts;

Orbital darkening;

Facial pallor/facial erythema;

Pityriasis alba;

Itch when sweating;

Intolerance to wool and lipid solvents;

Perifollicular accentuation;

Food hypersensitivity;

Course influenced by environmental and/or emotional factors;

White dermatographism or delayed blanch to cholinergic agents.

Essential features:

- Pruritus

- Eczema

- Typical morphology and age-specific pattern

- Chronic or relapsing history Important features

Early age at onset:

Atopy;

Personal and/or family history;

IgE reactivity;

Xerosis Associated features;

Atypical vascular responses (e.g. facial pallor, white dermatographism);

Keratosis pilaris/ichthyosis/hyperlinear palms;

Orbital/periorbital changes;

Other regional findings (e.g. perioral changes/periauricular lesions).

Perifollicular accentuation/lichenification/prurigo lesions infancy usually begins as erythema and scaling of the cheeks. The eruption may extend to the scalp, neck, forehead, wrists, and extensor extremities. The areas involved correlate with the capacity of the child to scratch or rub the site, and the activities of the infant, such as crawling. There may be a significant amount of exudate, and there are many secondary effects from scratching, rubbing, and infection: crusts, infiltration, and pustules, respectively. The infiltrated plaques eventually take on a characteristic lichenified appearance. The infantile pattern of AD usually disappears by the end of the second year of life. Worsening of AD is often observed in infants after immunizations and viral infections. Partial remission may occur during the summer, with relapse in winter. This may relate to the therapeutic effects of ultraviolet (UV) B and humidity in many atopic patients, and the aggravation by wool and dry air in the winter.

CHILDHOOD ATOPIC DERMATITIS

During childhood, lesions are apt to be less exudative. The classic locations are the antecubital and popliteal fossae, flexor wrists, eyelids, face, and around the

neck. Lesions are often lichenified, indurated plaques, and in African-American patients may have a lichenoid appearance and favor the extensor surfaces. These are intermingled with isolated, excoriated 2-4 mm papules that are scattered more widely over the uncovered parts. Pruritus is a constant feature and most of the cutaneous changes are secondary to it. Itching is paroxysmal. Scratching induces lichenification and may lead to secondary infection. A vicious cycle may be established (the itchscratch cycle), as pruritus leads to scratching, and scratching causes secondary changes that in themselves cause itching. Instead of scratching causing pain, in the atopic patient the "pain" induced by scratching is perceived as itch and induces more scratching. The scratching impulse is beyond the control of the patient. Severe bouts of scratching occur during sleep, leading to poor rest and chronic tiredness in atopic children. This can affect their school performance. Severe AD involving a large percentage of the body surface area can be associated with growth retardation. Restriction diets and steroid usage may exacerbate growth retardation. Aggressive management of such children with phototherapy or systemic immunosuppressives may allow for rebound growth. Children with severe AD may also have substantial psychological disturbances. Parents should be questioned with regard to school performance and socialization.

ATOPIC DERMATITIS IN ADOLESCENTS AND ADULTS

Most adolescents and adults with AD will give a history of childhood disease. In only 6-14% of patients diagnosed with AD will it begin after age 18. One exception is the patient who moves from a humid, tropical region to a more temperate one of higher latitude. This climatic change is often associated with the appearance of AD. In older patients, AD may occur as localized erythematous, scaly, papular, exudative, or licheni- fied plaques. In adolescents, the eruption often involves the classic antecubital and popliteal fossae, front and sides of the neck, forehead, and area around the eyes. In older adults the distribution is generally less characteristic, and localized dermatitis may be the predominant feature, especially hand, nipple, or eyelid eczema). At times the eruption may

generalize, with accentuation in the flexures. The skin, in general, is dry and somewhat erythematous. Lichenification and prurigo-like papules are common. Papular lesions tend to be dry, slightly elevated, and flat-topped. They are nearly always excoriated and often coalesce to form plaques. Staphylococcal colonization is nearly universal. In darker-skinned patients, the lesions are often dramatically hyperpigmented, frequently with focal hypopigmented areas related to healed excoriations. Itching usually occurs in crises or paroxysms, often during the evening when the patient is trying to relax, or during the night. Adults frequently complain that flares of AD are triggered by acute emotional upsets. Stress, anxiety, and depression reduce the threshold at which itch is perceived and result in damage to the epidermal permeability barrier, further exacerbating AD. Atopic persons may sweat poorly, and may complain of severe pruritus related to heat or exercise. Physical conditioning and liberal use of emollients improve this component, and atopic patients can participate in competitive sports. Even in patients with AD in adolescence or early adulthood, improvement usually occurs over time, and dermatitis is uncommon after middle life. In general, these patients retain mild stigmata of the disease, such as dry skin, easy skin irritation, and itching in response to heat and perspiration. They remain susceptible to a flare of their disease when exposed to the specific allergen or environmental situation. Some will flare in response to aeroallergens, and a few patients will develop flexural dermatitis in response to niacininduced flushing. Photosensitivity develops in approximately 3% of AD patients, and may manifest as either a polymorphous light eruption-type reaction or simply exacerbation of the AD by UV exposure. Most patients (65%) are sensitive to UVA and UVB, but about 17% are sensitive to only UVA or UVB. The average age for photosensitive AD is the mid- to late thirties. Human immunodeficiency virus (HIV) infection can also serve as a trigger, and new-onset AD in an at-risk adult should lead to counseling and testing for HIV if warranted. The hands, including the wrists, are frequently involved in adults, and hand dermatitis is a common problem for adults with a history of AD. It is extremely common for atopic hand dermatitis to appear in young women after

the birth of a child, when increased exposure to soaps and water triggers their disease. Wet work is a major factor in hand eczema in general, including those patients with AD. Atopic hand dermatitis can affect both the dorsal and palmar surfaces. Keratosis punctata of the creases, a disorder seen almost exclusively in black persons, is also more common in atopics. Patients with AD have frequent exposure to preservatives and other potential allergens in the creams and lotions that are continually applied to their skin. Contact allergy may manifest as chronic hand eczema. Patch testing with clinical correlation is the only certain way to exclude contact allergy in an atopic patient with chronic hand dermatitis.

Eyelids are commonly involved. In general, the involvement is bilateral and the condition flares with cold weather. As in hand dermatitis, irritants and allergic contact allergens must be excluded by a careful history and patch testing.

ASSOCIATED FEATURES AND COMPLICATIONS CUTANEOBS STRIGMATAS STIGMATA

A linear transverse fold just below the edge of the lower eyelids, known as the Dennie-Morgan fold, is widely believed to be indicative of the atopic diathesis, but may be seen with any chronic dermatitis of the lower lids. In atopic patients with eyelid dermatitis, increased folds and darkening under the eyes is common. When taken together with other clinical findings, they remain helpful clinical signs. A prominent nasal crease may also be noted. The less involved skin of atopic patients is frequently dry and slightly erythematous, and may be scaly. Histologically, the apparently normal skin of atopics is frequently inflamed subclinically. The dry, scaling skin of AD may represent lowgrade dermatitis. Filaggrin is processed by caspase 14 during terminal keratinocyte differentiation into highly hydroscopic pyrrolidone carboxylic acid and urocanic acid, collectively known as the "natural moisturizing factor" or NMF. Null mutations in FLG lead to reduction in NMF, which probably contributes to the xerosis that is almost universal in AD. Transepidermal water loss (TEWL) is increased. This may be due to subclinical dermatitis, but is also caused by abnormal delivery of lamellar body

epidermal lipids (especially ceramide) to the interstices between the terminally differentiated keratinocytes. The defective lipid bilayers that result retain water poorly, leading to increased TEWL and clinical xerosis. Pityriasis alba is a form of subclinical dermatitis, frequently atopic in origin. It presents as poorly marginated, hypopig- mented, slightly scaly patches on the cheeks, upper arms, and trunk, typically in children and young adults. It usually responds to emollients and mild topical steroids, preferably in an ointment base. Keratosis pilaris (KP), horny follicular lesions of the outer aspects of the upper arms, legs, cheeks, and buttocks, is commonly associated with AD. The keratotic papules on the face may be on a red background, a variant of KP called keratosis pilaris rubra facei. KP is often refractory to treatment. Moisturizers alone are only partially beneficial. Some patients will respond to topical lactic acid, urea, or retinoids. Retinoids can easily irritate the skin of atopics, and treatment should begin with applications only once or twice a week. KP must be distinguished from follicular eczema, as AD and other eczemas are commonly folliculocentric, especially in black patients. Thinning of the lateral eyebrows, Hertoghe's sign, is sometimes present. This apparently occurs from chronic rubbing due to pruritus and subclinical dermatitis. Hyperkeratosis and hyperpigmentation, which produce a "dirty neck" appearance, are also frequent in AD.

VASCULAR STIGMATA

Atopic individuals often exhibit perioral, perinasal, and periorbital pallor ("headlight sign"). White dermatographism is blanching of the skin at the site of stroking with a blunt instrument. This reaction differs from the triple response of Lewis, in that it typically lacks a wheal, and the third response (flaring) is replaced by blanching to produce a white line. When 0.1 mL of a 1 : l0O 000 solution of histamine is injected intradermally, the flare phase of the triple response is absent or diminished. Atopics are at increased risk of developing various forms of urticaria, including contact urticaria. Episodes of contact urticaria may be followed by typical eczematous lesions at the affected site.

OPHTHALMOLOGIC ABNORMALITIES

Up to 10% of patients with AD develop cataracts, either anterior or posterior subcapsular ones. Posterior subcapsular cataracts in atopic individuals are indistinguishable from corticosteroidinduced cataracts. Development of cataracts is more common in patients with severe dermatitis. Keratoconus is an uncommon finding, occurring in approximately 1% of atopic patients. Contact lenses, keratoplasty, and intraocular lenses may be required to treat this condition.

SUSCEPTIBILITY TO INFECTION

More than 90% of chronic eczematous lesions contain S. aureus, often in large numbers. In addition, the apparently normal nonlesional skin of atopic patients is also commonly colonized by S. aureus. The finding of increasing numbers of pathogenic staphylococci on the skin of a patient with AD is frequently associated with weeping and crusting of skin lesions, retro- and infra-auricular and perinasal fissures, folliculitis, and adenopathy. In any flaring atopic the possibility of secondary infection must be considered. IgE antibodies directed against Staphylococcus and its toxins have been documented in some atopic individuals. Staphylococcal production of superanti- gens is another possible mechanism for staphylococcal flares of disease. Treatment of lesions of AD with topical steroids is associated with reduced numbers of pathogenic bacteria on the surface, even if antibiotics are not used. Despite the frequent observation that the presence of staphylococcal infection of lesions of AD is associated with worsening of disease, it has been impossible to prove that oral antibiotic therapy makes a long-term difference in the course of the AD. None the less, treatment of the "infected" AD patient with oral antibiotics is a community standard of dermatologists worldwide. With the widespread presence of antibiotic-resistant S. aureus, dermatologists have shifted from the chronic use of oral antibiotics in managing patients with frequent flares of AD associated with staphylococcal infection. Rather, bleach baths and reduction of nasal carriage have become the basis for controlling infection-triggered AD. In an occasional patient with AD and frequent infections, chronic

suppressive oral antibiotic therapy may stabilize the disease. Options include cepha- losporins, trimethoprim-sulfamethoxazole, clindamycin, and (in older patients) doxycycline. Identifying and treating S. aureus carriers in the family may also be of benefit. An unusual complication of S. aureus infection in patients with AD is subungual infection, with osteomyelitis of the distal phalanx. In atopic patients with fever who appear very toxic, the possibility of streptococcal infection must be considered. These children may require hospital admission and intravenous antibiotics. AD patients have increased susceptibility to generalized herpes simplex infection (eczema herpeticum), as well as widespread vaccinia infection (eczema vaccinatum) and complicated varicella. Eczema herpeticum is seen most frequently in young children and is usually associated with herpes simplex virus (HSV)-1 transmitted from a parent or sibling. Once infected, the atopic may have recurrences of HSV and repeated episodes of eczema herpeticum. Eczema herpeticum presents as the sudden appearance of vesicular, pustular, crusted, or eroded lesions concentrated in the areas of dermatitis. The lesions may continue to spread and most of the skin surface may become involved. Secondary staphylococcal infection is frequent, and local edema and regional adeno- pathy commonly occur. If lesions of eczema herpeticum occur on or around the eyelids, ophthalmologic evaluation is recommended. The severity of eczema herpeticum is quite variable, but most cases requires systemic antiviral therapy and an antistaphylococcal antibiotic. Vaccination against smallpox is contraindicated in persons with AD, even when the dermatitis is in remission. Widespread and even fatal vaccinia can occur in patients with an atopic diathesis. Atopic individuals may also develop extensive flat warts or molluscum contagiosum. Because the skin is very easily irritated, chemical treatments such as salicylic acid and canthari- din are poorly tolerated. Destruction with curettage (for molluscum), cryosurgery, or electrosurgery may be required to clear the lesions.

PATHOGENESIS

Immunologic events noted early in the development of atopic lesions include activation of the Th2 immune response, with synthesis of cytokines IL-4, IL-5, IL-10, and IL-13. These immu- nological propensities are already evident in newborns. Neonatal cord blood mononuclear cells stimulated with phyto-hemagglutinin show significantly higher IL-13 levels in children who subsequently develop AD. IL-4 and IL-5 produce elevated IgE levels and eosinophilia in tissue and peripheral blood. IL-10 inhibits delayed-type hypersensitivity. IL-4 downregulates interferon (IFN)-y production. Early lesions of AD are often urticarial in character, a manifestation of Th2 hyperreactivity. These immunologic alterations result in the reduced production of antimicrobial peptides (AMP), specifically LL-37 (cathelicidin) and P-defensins 2 and 3. This loss of AMP production may predispose atopics to widespread skin infections due to viruses (herpes, molluscum, and vaccinia) and bacteria, especially Staphylococcus. AD patients who develop eczema herpeticum are more likely to be Th2- polarized, supporting the causal relationship between reduced AMP production and cutaneous viral infection. Epicutaneous exposure to staphylococcal superantigens, to which AD patients develop IgE antibodies, further skews the immune response toward Th2 cytokine production, explaining the association of staphylococcal infection with exacerbations of AD. Staphylococcal superantigens, such as SEB, SEE, and TSST-1, cause profound reduction in steroid responsiveness of T cells. This is another possible mechanism for flares of AD associated with staphylococcal skin infection or colonization. While AD begins as a Th2-mediated disorder, in its chronic phase, cutaneous inflammation is characterized by Th1 cytokines. This explains why chronic AD histologically resembles other chronic dermatoses. Monocytes in the peripheral blood of patients with AD produce elevated levels of prostaglandin E2 (PGE2). PGE2 reduces IFN-y production but not IL-4 from helper T cells, enhancing the Th2 dominance. PGE2 also directly enhances IgE production from B cells. Abnormalities of cutaneous nerves and the products they secrete (neuropeptides) have been identified in atopic patients. These

may explain the abnormal vascular responses, reduced itch threshold, and perhaps some of the immunologic imbalances seen in atopic skin. Decreased activation of peripheral pruriceptors has been demonstrated in patients with atopy, suggesting that itch in lesional skin might have a central component (central sensitization) based on altered spinal impulses rather than in primary afferent neurons. The acetylcholine content of atopic skin is markedly elevated, and acetylcholine may play a role in atopic signs and symptoms. In subjects with AD, acetylcholine injected intradermally will produce marked pruritus, while it produces pain in control patients. Epidermal nerve fibers are "stretched" in the acanthotic, lichenified lesions of AD, reducing their threshold for stimulation. Fissures in the skin in AD expose these epidermal nerve fibers, perhaps triggering pruritus, and explaining the rapid reduction of pruritus by simple emollients in some lesions. In addition, in chronic AD, mu opiate receptors are absent from the surface of keratinocytes. This may allow endogenous opiates in the epidermis to bind directly to epidermal nerves, triggering itch. In fact, topical opiate antagonists can reduce itch in AD. In atopic patients, the epidermal barrier is abnormal, even in apparently normal skin. An increase in TEWL correlates with the severity of the disease. AD usually worsens in the winter due to decreased ambient humidity. Stress also results in poor formation of epidermal lipid bilayers, worsening TEWL. This is mediated by endogenous corticoid production, and systemic corticosteroid therapy of AD results in similar abnormalities in epidermal lipid bilayer synthesis. This could explain the flares of AD seen with stress and following systemic steroid therapy. Correction of barrier dysfunction is critical to improving AD; hence the value of skin hydration, ointments, and occlusion. Optimizing this component of AD treatment appears to have the greatest benefit in reducing the severity of AD.

DIFFERENTIAL DIAGNOSIS

Typical AD in infancy and childhood is not difficult to diagnose because of its characteristic morphology, predilection for symmetric involvement of the face, neck, and antecubital and popliteal fossae, and association with food allergy,

asthma, and allergic rhinoconjunctivitis. Dermatoses that may resemble AD include seborrheic dermatitis (especially in infants), irritant or allergic contact dermatitis, nummular dermatitis, photodermatitis, scabies, and cases of psoriasis with an ecze- matous morphology. Certain immunodeficiency syndromes (see below) may exhibit a dermatitis remarkably similar or identical to AD.

HISTOPATHOLOGY

The histology of AD varies with the stage of the lesion, with many of the changes induced by scratching. Hyperkeratosis, acanthosis, and excoriation are common. Staphylococcal colonization may be noted histologically. Although eosinophils may not be seen in the dermal infiltrate, staining for eosinophil major basic protein (MBP) reveals deposition in many cases. Heavy MBP deposition is often seen in specimens from patients with AD and a personal or family history of respiratory atopy.

GENERAL MANAGEMENT

Education and support

Parental and patient education is of critical importance in the management of AD. In the busy clinic setting dermatologists frequently have insufficient time to educate patients adequately regarding the multiple factors that are important in managing AD. Educational formats that have proved effective have been immediate nursing education on the correct use of medications, weekly evening educational sessions, and multi- disciplinary day treatment venues. In all cases, "written action plans" outlining a "stepwise approach" have been important for parent/patient education. In addition, patients with chronic disease often become disenchanted with medical therapies or simply "burn out" from having to spend significant amounts of time managing their skin disease. The psychological support that can be piggy-backed into educational sessions can help motivate parents/patients and keep them engaged in the treatment plan. Having a child with AD is extremely stressful and generates significant stress within the family. Sleep

is lost by both the patient and the parents. Supportive educational techniques can help the family cope with this burden. Finally, the dermatologist must consider the complexity and time commitment of any prescribed regimen and make sure the parents/patient both understand and are committed to undertaking the treatments proposed.

Barrier repair

In virtually all cases of AD, there is xerosis and an impaired epidermal barrier. The cornerstone of treatment and prevention of AD lies in addressing this problem. Patients should moisturize daily, especially after bathing. This may be with petrolatum or a petrolatum-based product, an oilbased product, vegetable shortening, or a "barrier repair" moisturizer that contains the essential lipids of the epidermal barrier. These special barrier repair moisturizers have similar benefits in AD to low-potency topical steroids. They are easier to apply and, if they are available to the patient, may enhance compliance. Petrolatum and petrolatum-based moisturizers are most commonly recommended and are the cheapest and most effective for most patients. However, men with significant body hair, AD patients triggered by heat, and the rare patient with true allergic contact dermatitis to petrolatum may not be able to tolerate petrolatumbased agents. Patients should be instructed on the barrier-damaging properties of soaps, hot water, and scrubbing. Synthetic detergents that have a more acidic pH are preferred to harsh soaps. Detergent use should be restricted to the axilla, groin, face, soles, and scalp. Oil- based cleansers can be used to "wash" the skin without water. For flares of AD, the soak and smear technique (soak in a tub then seal in the water with a heavy moisturizer or medicated ointments) or wet dressings (wet wraps) with topical steroids can be very effective. In dry climates, AD patients may note some benefit with humidifiers. Alpha-hydroxy acidcontaining products (lactic acid, glycolic acid) can be irritating and can exacerbate inflamed AD. These products should only be used for the xerosis of AD when there is absolutely no inflammation or pruritus.

Antimicrobial therapy

When there is evidence of infection, treatment with topical or systemic antibiotics may be appropriate. Rather than treating once an infection occurs, it appears that the key in AD is to reduce nasal staphylococcal carriage pre-emptively and to keep the skin decolonized from Staphylococcus. Bleach bathes have rapidly become a mainstay in AD patients. Twice-weekly bathing in a tepid bath with % cup of standard household bleach (6%) diluted into 40 gallons of water dramatically improves AD on the trunk and extremities, but less so on the face. This treatment combines decolonization of the skin with hydration, addressing two of the major factors in worsening of AD. Adequate moisturization following bathing is critical. Intranasal application of mupirocin is beneficial in reducing nasal carriage and improving the AD. In 80% of families, at least one parent is carrying the same staphylococcal strain as a colonized AD child. If recurrent infections afflict a patient with AD, look for other carriers in the family and treat them aggressively. Recurrent infections, especially furunculosis, are a cardinal feature of children and adults with AD who have systemic immunological abnormalities, especially hyper-IgE syndrome.

Environmental factors

Stress, heat, sweating, and external irritants may precipitate an attack of itching and flare AD. Wool garments should be avoided. Addressing these triggers may improve the AD. Exercise may need to be limited in patients with significant flares to swimming or walking during cool times of the day to avoid triggering sweating. Itch nerves are more active at higher temperatures, so overheating should be avoided. Irritants and allergens in the numerous products that AD patients may use can lead to flares of AD. Patients should avoid products that contain common allergens, and should be evaluated for allergic contact dermatitis if a topical agent is associated with worsening of their AD.

Antipruritics

Sedating antihistamines are optimally used nightly (not as needed) for their antipruritic and sedative effects. Diphenhydramine, hydroxyzine, and Sinequan can all be efficacious. Cetirizine and fexofenadine have both demonstrated efficacy in managing the pruritus of AD in children and adults, respectively. These can be added without significant sedation if standard firstgeneration antihistamines are not adequate in controlling pruritus. Applying ice during intense bouts of itch may help to "break" an itch paroxysm. Moisturizing lotions containing menthol, phenol, or pramocaine can be used between steroid applications to moisturize and reduce local areas of severe itch. More widespread use of topical Sinequan is limited by systemic absorption and sedation.

SPECIFIC TREATMENT MODALITIES TOPICAL CORTICOSTEROID THERAPY

Topical corticosteroids are the most commonly used class of medications, along with moisturizers, for the treatment of AD. They are effective and economical. In infants, low-potency steroid ointments, such as hydrocortisone 1% or 2.5%, are preferred. Emphasis must be placed on regular application of emollients. Once corticosteroid receptors are saturated, additional applications of a steroid preparation contribute nothing more than an emollient effect. In most body sites, once-a-day application of a corticosteroid is almost as effective as more frequent applications, at lower cost and with less systemic absorption. In some areas, twice-a-day applications may be beneficial, but more frequent applications are almost never of benefit. Steroid phobia is common in parents and patients with AD. Less frequent applications of lowerconcentration agents, with emphasis on moisturizing, address these concerns. Application of topical corticosteroids under wet wraps or vinyl suit occlusion (soak and smear) can increase efficiency. For refractory areas, a stronger corticosteroid, such as desonide, aclomethasone, or triamcinolone, may be used. A more potent molecule is more appropriate than escalating concentrations of a weaker molecule because the effect of the latter

plateaus rapidly as receptors become saturated. Do not undertreat! This leads to loss of faith on the part of the patient/ parents and prolongs the suffering of the patient. For severe disease, use more potent topical steroids in short bursts of a few days to a week to gain control of the disease. In refractory and relapsing AD, twice-weekly steroid application may reduce flares. In older children and adults, mediumpotency steroids such as triamcinolone are commonly used, except on the face, where milder steroids or calcineurin inhibitors are preferred. For thick plaques and lichen simplex chronicus-like lesions, very potent steroids may be necessary. These are generally applied on weekends, with a milder steroid used during the week. Ointments are more effective, due to their moisturizing properties, and require no preservatives, reducing the likelihood of allergic contact dermatitis. If an atopic patient worsens or fails to improve after the use of topical steroids and moisturizers, the possibility of allergic contact dermatitis to a preservative or the corticosteroids must be considered. Contact allergy to the corticosteroid itself is not uncommon. Corticosteroid allergy seldom manifests as acute worsening of the eczema. Instead, it manifests as a flare of eczema whenever the corticosteroid is discontinued, even for a day. This may be difficult to differentiate from stubborn AD. Although the potential for local and even systemic toxicity from corticosteroids is real, the steroid must be strong enough to control the pruritus and remove the inflammation. Even in small children, strong topical steroids may be necessary in weekly pulses to control severe flares. Weekend pulses are always preferable to daily application of a potent steroid. Monitoring of growth parameters should be carried out in infants and young children.

TOPICAL CALCINEURIN INHIBITORS (TCIS)

Topical calcineurin inhibitors, such as tacrolimus or pimecrolimus, offer an alternative to topical steroids. Systemic absorption is generally not significant with either of these agents. Although a 0.03% tacrolimus ointment is marketed for use in children, it is unclear whether it really offers any safety advantage over the 0.1% formulation. Tolerability is improved if the ointment is applied to bone-dry skin.

Patients experience less burning if eczematous patches are treated initially with a corticosteroid, with transition to a calcineurin inhibitor after partial clearing. Improvement tends to be steady, with progressively smaller areas requiring treatment. These agents are particularly useful on the eyelids and face, in areas prone to steroid atrophy, when steroid allergy is a consideration, or when systemic steroid absorption is a concern. Tacrolimus is more effective than pimecrolimus, with tacrolimus 0.1% ointment equivalent to triamcinolone acetonide 0.1%, and pime- crolimus equivalent to a class V or VI topical corticosteroid.

Tar

Crude coal tar 1-5% in white petrolatum or hydrophilic ointment USP, or liquor carbonis detergens (LCD) 5-20% in hydrophilic ointment USP, is sometimes helpful for an area of refractory AD. Tar preparations are especially beneficial when used for intensive treatment for adults in an inpatient or daycare setting, especially in combination with UV phototherapy.

PHOTOTHERAPY

If topical modalities fail to control AD, phototherapy is the next option on the therapeutic ladder. Narrow-band UVB (NB- UVB) is highly effective and has replaced broadband UV for treating AD. When acutely inflamed, AD patients may tolerate UV poorly. Initial treatment with a systemic immunosuppres- sive can cool off the skin enough to institute UV treatments. Patients with significant erythema must be introduced to UV at very low doses to avoid nonspecific irritancy and flaring of the AD. Often the initial dose is much lower and the dose escalation much slower than in patients with psoriasis. In acute flares of AD, UVA-1 can be used. In patients in whom NB-UVB fails, photochemotherapy (PUVA) can be effective. It requires less frequent treatments, and can be given either topically (soak/bath PUVA) or systemically (oral PUVA). Goeckerman therapy with tar and UVB in a day treatment setting will lead to improvement in more than 90% of patients with refractory AD, and a prolonged remission can be induced.

SYSTEMIC THERAPY

Systemic corticosteroids

In general, systemic steroids should be used only to control acute exacerbations. In patients requiring systemic steroid therapy, short courses (3 weeks or less) are preferred. If repeated or prolonged courses of systemic corticosteroids are required to control the AD, phototherapy or a steroid-sparing agent should be considered. Chronic corticosteroid therapy for AD frequently results in significant corticosteroid-induced side effects. Osteoporosis in women requires special consideration and should be addressed with a bisphosphonate early in the course of therapy when bone loss is greatest. Preventive strategies, such as calcium supplements, vitamin D supplementation, bisphosphonates, regular exercise, and stopping smoking, should be strongly encouraged. Dual energy x-ray absorptiometry (DEXA) scans are recommended.

Cyclosporine

Cyclosporine is highly effective in the treatment of severe AD, but the response is rarely sustained after the drug is discontinued. It is very useful to gain rapid control of severe AD. It has been shown to be safe and effective in both children and adults, although probably tolerated better in children. Potential long-term side effects, especially renal disease, require careful monitoring, with attempts to transition the patient to a potentially less toxic agent if possible. The dose range is 3-5 mg/kg, with a better and more rapid response at the higher end of the dose range.

Other immunosuppressive agents

Several immunosuppressive agents have demonstrated efficacy in patients with AD. There are no comparative trials, so the relative efficacy of these agents is unknown. They do not appear to be as effective or quick to work as cyclosporine. However, over the long term, they may have a better safety profile, so patients requiring long-term immunosuppression may benefit from one of these agents.

They include azathioprine (Immuran), mycophenolate mofetil (Cellcept), and methotrexate (Rheumatrex). The dosing of azathioprine is guided by the serum thiopurine methyltransferase level. Mycophenolate mofetil is generally well tolerated and, like azathioprine, takes about 6 weeks to begin to reduce the AD. Low-dose weekly methotrexate is very well tolerated in the elderly and may have special benefit in that population. Intravenous immunoglobulin (IVIG) has had some limited success in managing AD, but its high cost precludes it use, except when other reasonable therapeutic options have been exhausted. IFN-y given by daily injection has demonstrated efficacy in both children and adults with severe AD. The onset of response can be delayed. It is well tolerated but can cause flu-like symptoms. Omalizumab can be considered in refractory cases, but only 20% of patients achieve a 50% or greater reduction of their AD. Infliximab has not been beneficial in AD. Traditional Chinese herb mixtures have shown efficacy in children and in animal models for AD. The active herbs appear to be ophiopogon tuber and schisandra fruit. Chinese herbs are usually delivered as a brewed tea to be drunk daily. Their bitter taste makes them unpalatable to most Western patients. However, this option should be considered in patients who might accept this treatment approach.

Management of an acute flare

Initially, the precipitating cause of the flare should be sought. Recent stressful events may be associated with flares. Secondary infection with S. aureus should be assumed in most cases. Less commonly, herpes simplex or coxsackie virus may be involved. Pityriasis rosea may also cause AD to flare. The development of contact sensitivity to an applied medication or photosensitivity must be considered. In the setting of an acute flare, treating triggers (see above) may lead to improvement. A short course of systemic steroids may be of benefit, but patients should be counseled that prolonged systemic corticosteroid therapy must be avoided. "Home hospitalization" may be useful. The patient goes home to bed, isolated from work and other stressors; large doses of an antihistamine are

given at bedtime; the patient soaks in the tub twice daily, then applies a topical steroid ointment under wet pajamas and a sauna suit (soak and smear). Often, 3-4 days of such intensive home therapy will break a severe flare.

ECZEMA

The word eczema seems to have originated in AD 543 and is derived from the Greek work ekzein, meaning to "to boil forth" or "to effervesce." In its modern use, the term refers to a broad range of conditions that begin as spongiotic dermatitis and may progress to a lichenified stage. The term encompasses such disorders as dyshidrotic eczema and nummular eczema. The acute stage generally presents as a red edematous plaque that may have grossly visible, small, grouped vesicles. Subacute lesions present as erythematous plaques with scale or crusting. Later, lesions may be covered by a dryer scale or become lichenified. In most eczematous reactions, severe pruritus is a prominent symptom. The degree of irritation at which itching begins (the itch threshold) is lowered by stress. Itching is often prominent at bedtime and commonly results in insomnia. Heat and sweating may also provoke episodes of itching. Histologically, the hallmark of all eczematous eruptions is a serous exudate between cells of the epidermis (spongiosis), with an underlying dermal perivascular lymphoid infiltrate and exocytosis (lymphocytes noted within spongiotic foci in the dermis). Spongiosis is generally out of proportion to the lymphoid cells in the epidermis. This is in contrast to mycosis fungoides, which demonstrates minimal spongiosis confined to the area immediately surrounding the lymphocytes.

In most eczematous processes, spongiosis is very prominent in the acute stage, where it is accompanied by little acanthosis or hyperkeratosis. Subacute spongiotic dermatitis demonstrates epidermal spongiosis with acanthosis and hyperkeratosis. Chronic lesions may have little accompanying spongiosis, but it is not uncommon for acute and chronic stages to overlap, as episodes of eczematous dermatitis follow one another. Scale corresponds to foci of parakeratosis produced by the inflamed epidermis. A crust is composed of serous exudate, acute

inflammatory cells, and keratin. Eczema, regardless of cause, will manifest similar histologic changes if allowed to persist chronically. These features are related to chronic rubbing or scratching, and correspond clinically to lichen simplex chronicus or prurigo nodularis. Histologic features at this stage include compact hyperkeratosis, irregular acanthosis, and thickening of the collagen bundles in the papillary portion of the dermis. The dermal infiltrate at all stages is predominantly lymphoid, but an admixture of eosinophils may be noted. Neutrophils generally appear in secondarily infected lesions. Spongiosis with many intraepidermal eosinophils may be seen in the early spongiotic phase of pemphigoid, pemphigus, and incontinentia pigmenti, as well as some cases of allergic contact dermatitis.

Regional eczemas Ear eczema

Eczema of the ears or otitis externa may involve the helix, postauricular fold, and external auditory canal. By far the most frequently affected site is the external canal, where it is often a manifestation of seborrheic dermatitis or allergic contact dermatitis. Secretions of the ear canal derive from the specialized apocrine and sebaceous glands, which form cerumen. Rubbing, wiping, scratching, and picking exacerbate the condition. Secondary bacterial colonization or infection is common. Infection is usually caused by staphylococci, streptococci, or Pseudomonas. Contact dermatitis from neomycin, benzocaine, and preservatives may be caused by topical remedies. Pseudomonas aeruginosa can result in malignant external otitis with ulceration and sepsis. Earlobe dermatitis is virtually pathognomonic of metal contact dermatitis (especially nickel) and occurs most frequently in women who have pierced ears. Treatment should be directed at removal of causative agents, such as topically applied allergens. Scales and cerumen should be removed by gentle lavage with an ear syringe. Antibiotic- corticoid preparations, such as Cortisporin otic suspension, have frequently been prescribed, and ingredients such as neo- mycin are therefore frequently found as relevant contact allergens. A combination of ciprofloxacin plus a topical steroid (Ciprodex) is preferred to neomycin-containing products. Corticosteroids alone can be effective for

noninfected dermatitis. For very weepy lesions, Domeboro optic solution may be drying and beneficial.

EYELID DERMATITIS

Eyelid dermatitis is most commonly related to atopic dermatitis or allergic contact dermatitis, or both. Allergic conjunctivitis in an atopic patient may lead to rubbing and scratching of the eyelid and result in secondary eyelid dermatitis. Seborrheic dermatitis, psoriasis, and airborne dermatitis are other possible causes. Ninety percent of patients with eyelid dermatitis are female. When an ocular medication contains an allergen, the allergen passes through the nasolacrimal duct, and dermatitis may also be noted below the nares in addition to the eyelids. Some cases of eyelid contact dermatitis are caused by substances transferred by the hands to the eyelids. If eyelid dermatitis occurs without associated atopic dermatitis, an allergen is detected in more than 50% of cases. More than 25% of patients with atopic dermatitis and eyelid dermatitis will also have allergic contact dermatitis contributing to the condition. Fragrances and balsam of Peru, metals (nickel and gold), paraphenylenediamine, thiomersal, quaternium 15, oleamidopropyl di-methlyamine, thiuram (in rubber pads used to apply eyelid cosmetics), and tosylamide formaldehyde (in nail polish) are common environmental allergens causing eyelid dermatitis. In medications, preservatives such as cocamidopropyl betaine and active agents such as phenylephrine hydrochloride, sodium cromoglycate, papaine, and idoxuridine have all been implicated.

Eyelid dermatitis requires careful management, often in collaboration with an ophthalmologist. The most important aspect is to identify and eliminate any possible triggering allergens as noted above. Patch testing for standard allergens, as well as the patient's ocular medications, is required. Preservativefree eye medications should be used. The ophthalmologist should monitor the patient for conjunctival complications, measure the intraocular pressure, and monitor for the development of cataracts, especially in patients with atopic dermatitis who have an increased risk for cataracts, Initially, topical corticosteroids and petrolatum-based

emollients are recommended. If the dermatitis is persistent, the patient may be transitioned to TCIs to reduce the long-term risk of ocular steroid complications. The TCIs are often not initially tolerated on inflamed eyelids due to the burning. If there is an associated allergic conjunctivitis, or in patients who fail treatment with topical medications applied to the eyelid, ocular instillation of cyclosporine ophthalmic emulsion (Restasis) can be beneficial. Cromolyn sodium ophthalmic drops may be used to stabilize mast cells in the eyelid and reduce pruritus. In balsam of Peru-allergic patients, a balsam of Peru elimination diet may benefit.

Breast eczema (nipple eczema)

Eczema of the breasts usually affects the areolae, and may extend on to the surrounding skin. The area around the base of the nipple is usually spared, and the nipple itself is less frequently affected. The condition is rarely seen in men. Usually, eczema of the nipples is of the moist type with oozing and crusting. Painful fissuring is frequently seen, especially in nursing mothers. Atopic dermatitis is a frequent cause, and nipple eczema may be the sole manifestation of atopic dermatitis in adult women. It frequently presents during breastfeeding. The role of secondary infection with bacteria and Candida should be considered in breastfeeding women. Other causes of nipple eczema are allergic contact dermatitis and irritant dermatitis. Irritant dermatitis occurs from friction (jogger's nipples), or from ill-fitting brassieres with seams in women with asymmetrical and large breasts. In patients in whom eczema of the nipple or areola has persisted for more than 3 months, especially if it is unilateral, a biopsy is mandatory to rule out the possibility of Paget's disease of the breast. Topical corticosteroids or TCIs are often effective in the treatment of non-Paget eczema of the breast. Nevoid hyperkerato- sis of the nipples is a chronic condition that may mimic nipple eczema, but is not steroidresponsive. Nipple eczema in the breastfeeding woman is a therapeutic challenge. The dermatitis may appear in an atopic woman when her child begins to ingest solid foods. This may signal contact dermatitis to a food. Allergic contact dermatitis may develop to topically applied protective creams

(containing vitamin A and E, aloe, chamomile, or preservatives). Staphylococcal superinfection may develop, and can be identified by culture. Oral antibiotics are the preferred treatment for bacterial secondary infection. Candidal infection of the areola may present as normal skin, erythema, or an acute or chronic eczema. The area of the areola immediately adjacent to the nipple tends to be involved, sometimes with fine hairline cracks. Patients frequently complain of severe pain, especially with nursing. Analgesia may be required, and breastfeeding may need to be suspended for a period. Pumping and the use of a silicone nipple shield may be helpful. Associated conditions include oral thrush in the infant, antibiotic use, and a personal history of vaginal candidiasis. Cultures may or may not be positive from the affected areola/nipple. The child's mouth should also be cultured, even if the examination is completely normal, as candidal colonization of the breastfeeding infant's mouth may be asymptomatic with no findings on clinical examination. A positive culture from the infant in the setting of nipple eczema in the mother would warrant therapy of the mother and infant. Therapy with topical or systemic antifungal agents may be required to determine whether Candida is pathogenic. Oral fluconazole can be dramatically effective in these patients. Topical gentian violet 0.5%, applied once daily to the nipple, or all-purpose nipple ointment [(mupirocin 2% (10 g), nystatin 100 000 units/mL ointment (10 g), clotrimazole 10% (vaginal cream) (10 g), and betamethasone 0.1% ointment (10 g)] is an effective topical agent. The child's thrush should also be treated. A lactation consultant or nurse may be helpful in managing these patients, since poor positioning during breastfeeding is a common cofactor in the development of nipple eczema.

Hand eczema

Hand eczema is a common and important skin condition. Every year, about 10% of the population has at least one episode of hand dermatitis, and at any time about 5% of the population is affected. The genetic risk factors for the development of hand dermatitis are unknown. Even among patients with atopic dermatitis,

it is unclear whether patients with null mutations for FLG are at increased risk. Hand eczema is the most common occupational skin condition, accounting for more than 80% of all occupational dermatitis. Tobacco smoking and alcohol consumption do not appear to be risk factors for the development of hand eczema. Women are at increased risk for the development of hand eczema. Most of this increased risk is accounted for by a "spike" in the rate of hand eczema in the 20-29-year age group, when increased environmental exposures increase women's risk (childcare, housecleaning, etc). Chronic hand eczema, especially if severe, significantly reduces the patient's quality of life and is associated with symptoms of depression. A significant portion of patients with hand eczema will still be affected 15 years later. The risk for persistence of the hand eczema is doubled if there is associated eczema at other sites at presentation, if there is a childhood history of atopic dermatitis, and if the onset of the hand eczema was before age 20. Preventive interventions have been successful on two fronts: Persons at high risk for hand eczema can be identified and counseled to avoid high-risk occupations. Once occupational hand eczema develops, there are some occupation-specific strategies that can lead to improvement and prevent recurrence. The evaluation and management of hand eczema have been hampered by the lack of a uniform classification system and a dearth of controlled therapeutic trials. The diagnostic dilemma in hand dermatitis is in part related to two factors. The clinical appearance of the skin eruption on the palms and soles may be very similar, independent of the etiology. In addition, virtually all chronic hand dermatitis demonstrates a chronic dermatitis histologically, again independent of pathogenic cause. Psoriasis, specifically, on the palms and soles, may show spon- giosis and closely resemble a dermatitis. As a consequence, the proposed classification schemes rely on a combination of morphological features, history of coexistent illnesses, occupational exposure, and results of patch testing. The different types of hand eczema are: allergic contact dermatitis (with or without an additional irritant component) irritant hand dermatitis atopic hand eczema (with or without an additional irritant component) vesicular (or vesiculobullous) endogenous hand

eczema hyperkeratotic endogenous hand eczema. A complete history, careful examination of the rest of the body surface, and, at times, patch testing are essential in establishing a diagnosis. The importance of patch testing cannot be overemphasized. Allergens in the environment (especially shower gels and shampoos), in the workplace, and in topical medications may be important in any given patient. Patch testing must include broad screens of common allergens or cases of allergic contact dermatitis will be missed. The role of ingested nickel in the development of hand eczema in nickel-allergic patients is controversial. Some practitioners treat such patients with low-nickel diets and even disulfiram chelation with reported benefit. However, the risk of development of hand eczema in adulthood is independent of nickel allergy. Similarly, the role of lowbalsam diets in the management of balsam of Peru-allergic patients with hand eczema is unclear. Wet work (skin in liquids or gloves for more than 2 hours per day, or handwashing more than 20 times per day) is a strong risk factor for hand eczema. High-risk occupations include those that entail wet work, and those with exposure to potential allergens. These nine "highrisk" occupations include bakers, hairdressers, dental surgery assistants, kitchen workers/cooks, butchers, healthcare workers, cleaners, doctors/dentists/veterinarians, and laboratory technicians. In about 5% of patients with hand eczema, especially if this is severe, it is associated with prolonged missed work, job change, and job loss. In healthcare workers, the impaired barrier poses a risk for infection by blood-borne pathogens.

Almost onethird of baker's apprentices develop hand dermatitis within 12 months of entering the profession. Among hairdressers, the incidence approaches 50% after several years. Both irritant dermatitis and allergic contact dermatitis are important factors, with glyceryl monothioglycolate and ammonium persulfate being the most common allergens among hairdressers. Among those with preservative allergy, the hands are preferentially involved in patients allergic to isothiazolinones and formaldehyde, while the hands and face are equally involved with paraben allergy. Cement workers have a high rate of hand dermatitis related to contact allergy, alkalinity, and hygroscopic effects of cement. Dorsal hand der-

matitis in a cement worker suggests contact allergy to chro- mate or cobalt. The addition of ferrous sulfate to cement has no effect on irritant dermatitis, but reduces the incidence of allergic chromate dermatitis by two-thirds. Among patients with occupational hand dermatitis, atopic patients are disproportionately represented. Hand dermatitis is frequently the initial or only adult manifestation of an atopic diathesis. The likelihood of developing hand eczema is greatest in patients with atopic dermatitis, more common if the atopic dermatitis was severe, but still increased in incidence in patients with only respiratory atopy. Atopic patients should receive career counseling in adolescence to avoid occupations that are likely to induce hand dermatitis. Contact urticaria syndrome may present as immediate burning, itching, or swelling of the hands, but a chronic eczematous phase may also occur. Latex is an important cause of the syndrome, but raw meat, lettuce, garlic, onion, carrot, tomato, spinach, grapefruit, orange, radish, fig, parsnip, cheese, or any number of other foods may be implicated.

VESICULOBULLOUS HAND ECZEMA (POMPHOLYX, DYSHIDROSIS)

Idiopathic acute vesicular hand dermatitis is not related to blockage of sweat ducts, although palmoplantar hyperhidrosis is common in these patients and control of hyperhidrosis improves the eczema. Acute pompholyx, also known as cheiropompholyx if it affects the hands, presents with severe, sudden outbreaks of intensely pruritic vesicles. Primary lesions are macroscopic, deep-seated multilocular vesicles resembling tapioca on the sides of the fingers, palms, and soles. The eruption is symmetrical and pruritic, with pruritus often preceding the eruption. Coalescence of smaller lesions may lead to bulla formation severe enough to prevent ambulation. Individual outbreaks resolve spontaneously over several weeks. Bullous tinea or an id reaction from a dermatophyte should be excluded, and patch testing should be considered to rule out allergic contact dermatitis.

CHRONIC VESICULOBULLOUS HAND ECZEMA

In chronic cases the lesions may be hyperkeratotic, scaling, and fissured, and the "dyshidrosiform" pattern may be recognized only during exacerbations. There is a tendency for the pruritic 1-2 mm vesicles to be most pronounced at the sides of the fingers. In long-standing cases the nails may become dys- trophic. The distribution of the lesions is, as a rule, bilateral and roughly symmetrical.

HYPERKERATOTIC HAND DERMATITIS

Males outnumber females by 2 : 1, and the patients are usually older adults. The eruption presents as hyperkeratotic, fissure- prone, erythematous areas of the middle or proximal palm. The volar surfaces of the fingers may also be involved. Plantar lesions occur in about 10% of patients. Histologically, the lesions show chronic spongiotic dermatitis. The most important differential diagnosis is psoriasis, and some of the patients with chronic hyperkeratotic hand dermatitis will ultimately prove to be psoriatic. The presence of sharply demarcated plaques, nail pitting, or occasional crops of pustules is an important clue to psoriatic hand involvement.

TREATMENT

The hands are essential for work both in and out of the home. Treatment regimens must be practical and allow patients to function as normally as possible. There are few controlled treatment trials for hand dermatitis, and only recently has the type of hand eczema been identified in the trial. As one might suspect, the efficacy of some of the treatments depends on the morphology of the eruption and the diagnostic classification (see above). Protection Vinyl gloves may be worn during wet work, especially when detergents are used. Although vinyl gloves protect against chemicals, they do not prevent exposure to heat through the glove or the macerating effect of sweat, which accumulates under the gloves. They are also far less durable than rubber gloves. Rubber gloves may be used at home if patients do not exhibit allergy to rubber chemicals or latex. Wearing white cotton

gloves under the vinyl gloves is beneficial. For rough work, such as gardening, wearing protective cloth or leather gloves is essential. Cotton can adsorb allergens in the environment, and cotton gloves worn throughout the day offer little protection from many allergens. Barrier repair Moisturizing is a critical component of the management of hand dermatitis. Application of a protective moisturizing cream or ointment after each handwashing or water exposure is recommended. Creams require a preservative and have a higher risk of contact sensitivity. Ointments tend to have few ingredients and do not generally require a preservative. At night, even during periods of remission, a heavy moisturizing ointment should be applied to the hands after soaking in water. If palmar dryness is present, occlusion of the moisturizer with a plastic bag or vinyl gloves is recommended. White petrolatum is cheap and nonsensitizing, and remains a valuable agent in the treatment of hand dermatitis. Topical agents Superpotent and potent topical steroid agents are first-line pharmacologic therapy. Their efficacy is enhanced by presoaking and occlusion (soak and smear technique or wet dressings). A single application with occlusion at night is often more effective than multiple daytime applications. As in the treatment of atopic dermatitis, once steroid receptors are saturated, additional applications of a corticosteroid contribute only an emollient effect. Triamcinolone 0.1% ointment is available in a nonsensitizing white petrolatum base. It is fairly potent and inexpensive, does not irritate, and has a low incidence of sensitization. In refractory cases, superpotent steroids may be used for a period of 2-3 weeks, then on weekends, with a milder corticosteroid applied during the week. The addition of 2.5% zinc sulfate to clobetasol seemed to enhance efficacy of the topical steroid. Chronic use of potent fluorinated corticosteroids may be associated with skin atrophy. TCIs may be of benefit in some mildly affected patients. Soaks with a tar bath oil or applications of 20% liquor carbonis detergens or 2% crude coal tar in an ointment base may be of benefit, especially in those patients with the hyperkeratotic type of hand eczema. Bexarotene gel can be beneficial in up to 50% of patients with refractory hand eczema. Phototherapy Phototherapy in the form of high-dose UVA-1, soak or cream PUVA, and oral

PUVA can be effective. Given the thickness of the palms, UVA irradiation should be delivered 30 min after soaking, as opposed to bath PUVA, which can be done immediately after bathing. Relatively few phototoxic reactions are seen with regimens that use a 1520 min soak in a 3 mg/L solution of 8-methoxypsoralen, starting with 0.25-0.5 J/cm2 and increasing by 0.25-0.5 J/cm2 three times a week. Superficial Grenz ray radiotherapy remains a viable modality, but wellmaintained machines are few in number. The depth of penetration is limited, so it is best used after acute crusting and vesiculation have been cleared with other treatment. Doses of 200 cG are delivered at weekly intervals for a total of 800-1000 cG. Therapy may be repeated after 6 months. The total lifetime dose should not exceed 5000 cG. Botulinum toxin In patients with palmoplantar hyperhidrosis and associated hand eczema, treatment of the hyperhidrosis with intradermal injections of botulinum toxin leads to both dramatic resolution of the sweating and clearing of the hand eczema. The hand eczema returns when the sweating returns. Iontophoresis, which also reduces sweating, can similarly improve hand dermatitis. This illustrates the importance of wetness in the exacerbation of hand eczema. Systemic agents The systemic agents used to treat severe chronic hand dermatitis are identical to those used for atopic dermatitis. The use of systemic corticosteroids usually results in dramatic improvement. Unfortunately, relapse frequently occurs almost as rapidly, so systemic steroids are recommended only to control acute exacerbations. For instance, patients with infrequent, but severe, outbreaks of pompholyx may benefit from a few weeks of systemic steroids, starting at about 1 mg/kg/day. Patients with persistent severe hand dermatitis should be considered for alternative, steroid-sparing therapy. Methotrexate, in psoriatic doses, azathioprine, and myco- phenolate mofetil (in doses of 1-1.5 g twice a day for an adult) can all be considered. Cyclosporine can be effective, but given the chronicity of hand eczema, its use is best reserved for severe outbreaks. Oral retinoids may have a place in the management of hand dermatitis. Alitretinoin, at a dose of 30 mg per day, will lead to complete or near-complete clearance of chronic refractory hand eczema in about 50% of cases. The onset of response is delayed,

with some patients achieving optimal benefit only after more than 6 months of treatment. Workplace modifications The incidence of hand dermatitis in the workplace can be reduced by identifying major irritants and allergens, preventing exposure through engineering controls, substituting less irritating chemicals when possible, enforcing personal protection and glove use, and instituting organized worker education. Hand eczema classes have been documented to reduce the burden of occupational dermatitis. It is important to note that prevention of exposure to a weak but frequent irritant can have more profound effects than removal of a strong but infrequently contacted irritant. Proper gloves are essential in industrial settings. Nitrile gloves are generally less permeable than latex gloves. Gloves of ethylene vinyl alcohol copolymer sandwiched with polyethylene are effective against epoxy resin, methyl methacrylate, and many other organic compounds. Latex and vinyl gloves offer little protection against acrylates. The 4H (4 h) glove and nitrile are best in this setting. As hospitals transition to nonlatex gloves, it is important to note that even lowprotein, powderfree latex gloves reduce selfreported skin problems among health workers. Barrier products can improve hand dermatitis if used in the appropriate setting. Foams containing dimethicone and glycerin can reduce hand dermatitis related to wet work.

DIAPER (NAPKIN) DERMATITIS

Diaper dermatitis has dramatically decreased due to highly absorbable disposable diapers. None the less, dermatitis of the diaper area in infants remains a common cutaneous disorder. The highest prevalence occurs between 6 and 12 months of age. Diaper dermatitis is also seen in adults with urinary or fecal incontinence who wear diapers. Irritant diaper dermatitis is an erythematous dermatitis limited to exposed surfaces. The folds remain unaffected, in contrast to intertrigo, inverse psoriasis, and candidiasis, where the folds are frequently involved. In severe cases of irritant dermatitis there may be superficial erosion or even ulceration. The tip of the penis may become irritated and crusted, with the result that the baby urinates frequently and spots of blood appear on the diaper.

Complications of diaper dermatitis include punchedout ulcers or erosions with elevated borders (Jacquet erosive diaper dermatitis); pseudoverrucous papules and nodules; and violaceous plaques and nodules (granuloma gluteale infantum). The importance of ammonia in common diaper dermatitis has been overstated, but constant maceration of the skin is critical. The absence of diaper dermatitis in societies in which children do not wear diapers clearly implicates the diaper environment as the cause of the eruption. Moist skin is more easily abraded by friction of the diaper as the child moves. Wet skin is more permeable to irritants. Skin wetness also allows the growth of bacteria and yeast. Bacteria raise the local pH, increasing the activity of fecal lipases and proteases. Candida albicans is frequently a secondary invader and, when present, produces typical satellite erythematous lesions or pustules at the periphery as the dermatitis spreads. Napkin psoriasis, seborrheic dermatitis, atopic dermatitis, Langerhans cell histiocytosis, tinea cruris, allergic contact dermatitis, acrodermatitis enteropathica, aminoacidurias, biotin deficiency, and congenital syphilis should be included in the differential diagnosis. Given the skill of most pediatricians in the management of diaper dermatitis, dermatologists should think about these conditions in infants who have failed the standard interventions used by pediatricians. Refractory diaper dermatitis may require a biopsy to exclude some of the above conditions. Prevention is the best treatment. Diapers that contain superabsorbent gel have been proved effective in preventing diaper dermatitis in both neonates and infants. They work by absorbing the wetness away from the skin and by buffering the pH. Cloth diapers and regular disposable diapers are equal to each other in their propensity to cause diaper dermatitis and are inferior to the superabsorbent gel diapers. The frequent changing of diapers is also critical. Protecting the skin of the diaper area is of great benefit in all forms of diaper dermatitis. Zinc oxide paste is excellent. Zinc oxide paste with 0.25% miconazole may be considered if Candida may be present. If simple improved hygiene and barrier therapy are not effective, the application of a mixture of equal parts nystatin ointment and 1% hydrocortisone ointment at each

diaper change offers both anticandidal activity and an occlusive protective barrier from urine and stool, and can be very effective.

CIRCUMOSTOMY ECZEMA

Eczematization of the surrounding skin frequently occurs after an ileostomy or colostomy. It is estimated that some 75% of ileostomy patients have some postoperative sensitivity as a result of the leakage of intestinal fluid on to unprotected skin. As the consistency of the intestinal secretion becomes viscous, the sensitization subsides. Proprietary medications containing karaya powder have been found to be helpful. Twenty percent cholestyramine (an ionexchange resin) in Aquaphor, and topical sucralfate as a powder or emollient at 4 g% concentration, are both effective treatments. Psoriasis may also appear at ostomy sites. Topical treatment may be difficult, as the appliance adheres poorly after the topical agents are applied. A topical steroid spray may be used, and will not interfere with appliance adherence. Contact dermatitis to the ostomy bag adhesive can be problematic, as even supposed hypoallergenic ostomy bags may still trigger dermatitis in these patients.

AUTOSENSITIZATION AND CONDITIONED IRRITABILITY

The presence of a localized, chronic, and usually severe focus of dermatitis may affect distant skin in two ways. Patients with a chronic localized dermatitis may develop dermatitis at distant sites from scratching or irritating the skin. This is called "conditioned irritability." The most common scenario is distant dermatitis in a patient with a chronic eczematous leg ulcer. Autoeczematization refers to the spontaneous development of widespread dermatitis or dermatitis distant from a local inflammatory focus. The agent causing the local inflammatory focus is not the direct cause of the dermatitis at the distant sites. Autoeczematization most commonly presents as a generalized acute vesicular eruption with a prominent dys-hidrosiform component on the hands. The most common associated condition is a chronic eczema of the legs, with or without ulceration. The "angry back" or

"excited skin" syndrome observed with strongly positive patch tests, and the local dermatitis seen around infectious foci (infectious eczematoid dermatitis), may represent a limited form of this reaction.

ID REACTIONS

Patients with a variety of infectious disorders may present with eczematous dermatitis. The classic example is the vesicular id reactions of the hands in response to an inflammatory tinea of the feet. Similarly, inflammatory tinea capitis is often associated with a focal or diffuse dermatitis, primarily of the upper half of the body. Nummular eczematous lesions or pityriasis rosea-like lesions may occur in patients with head or pubic louse infestation. Id reactions clear when the focus of infection or infestation is treated.

JUVENILE PLANTAR DERMATOSIS

Juvenile plantar dermatosis is an eczematous disorder of children, first described by Enta and Moller in 1972, and named by Mackie in 1976. It is probably the same disease as symmetrical lividity of the soles described by Pernet in 1925. It usually begins as a patchy, symmetrical, smooth, red, glazed macule on the base or medial surface of the great toes, sometimes with fissuring and desquamation, in children aged 3 to puberty. Lesions evolve into red scaling patches involving the weightbearing and frictional areas of the feet, usually symmetrically. The forefoot is usually much more involved than the heel. Toe webs and arches are spared. The eruption is disproportionately more common in atopic children. In some patients, a similar eruption occurs on the fingers. The disease is caused by the repeated maceration of the feet by occlusive shoes, especially athletic shoes, or by the abrasive effects of pool surfaces or diving boards. The affected soles remain wet in the rubber bottoms of the shoes or are macerated by pool water. Thin, nonabsorbent, synthetic socks contribute to the problem. Histologically, there is psoriasiform acanthosis and a sparse, largely lymphocytic infiltrate in the upper dermis, most dense around sweat ducts at their

point of entry into the epidermis. Spongiosis is commonly present and the stratum corneum is thin but compact. The diagnosis is apparent on inspection, especially if there is a family or personal history of atopy and the toe webs are spared. Allergic contact dermatitis to shoes and dermatophy- tosis should be considered in the differential diagnosis. Allergic shoe dermatitis usually involves the dorsal foot, but some patients with rubber allergy have predominant involvement of the soles. Treatment involves avoidance of maceration. Foot powders, thick absorbent socks, absorbent insoles, and having alternate pairs of shoes to wear to allow the shoes to dry out are all beneficial. Topical steroid medications are of limited value and often are no more effective than occlusive barrier protection. Petrolatum or urea preparations can sometimes be of benefit. Most cases clear within 4 years of diagnosis.

XEROTIC ECZEMA

Xerotic eczema is also known as winter itch, eczema craquele, and asteatotic eczema. These vividly descriptive terms are all applied to dehydrated skin showing redness, dry scaling, and fine crackling that may resemble crackled porcelain or the fissures in the bed of a dried lake or pond. The primary lesion is an erythematous patch covered with an adherent scale. As the lesion enlarges, fine cracks in the epidermis occur. Nummular lesions may occur. Xerotic "nummular" eczema is less weepy than classic nummular dermatitis. Favored sites are the anterior shins, extensor arms, and flank. Elderly persons are particularly predisposed, and xerosis appears to be the most common cause of pruritus in older individuals. Xerotic eczema is seen most frequently during the winter, when there is low relative humidity. Bathing with hot water and harsh soaps contributes. The epidermal water barrier is impaired and TEWL is increased. Epidermal barrier repair begins to decrease after age 55. It is correlated with an increase in epidermal pH. This is why older patients complain that they have not changed their bathing routine or soaps, yet have developed xerotic dermatitis. The loss of barrier repair ability is improved by acidifying the epidermis; hence the benefit of mild acids in treating xerosis.

Short tepid baths, limitation of the use of soap to soiled and apocrine-bearing areas, juvenile plantar dermatosis.

NUMMULAR ECZEMA (DISCOID ECZEMA)

Nummular eczema usually begins on the lower legs, dorsa of the hands, or extensor surfaces of the arms. A single lesion often precedes the eruption and may be present for some time before other lesions appear. The primary lesions are discrete, coin-shaped, erythematous, edematous, vesicular, and crusted patches. Most lesions are 2-40 cm in diameter. Lesions may form after trauma (conditioned hyperirritability). As new lesions appear, the old lesions expand as tiny papulo-vesicular satellite lesions appear at the periphery and fuse with the main plaque. In severe cases the condition may spread into palmsized or larger patches. Pruritus is usually severe and of the same paroxysmal, compulsive quality and nocturnal timing seen in atopic dermatitis and prurigo nodularis. Atopic dermatitis frequently has nummular morphology in adolescents, but in atopy the lesions tend to be more chronic and lichenified. Histologically, nummular eczema is characterized by acute or subacute spongiotic dermatitis. Initial treatment consists of simple soaking and greasing with an occlusive ointment, and once or twice a day application of a potent or superpotent topical steroid cream or ointment. Ointments are more effective and occlusion may be necessary. If secondary staphylococcal infection is present, an antibiotic with appropriate coverage is recommended. Sedating antihistamines at bedtime are useful to help with sleep and reduce night-time scratching. In some cases refractory to topical agents, intralesional or systemic corticosteroid therapy may be required. In cases failing topical steroids, phototherapy with NB-UVB, or soak or oral PUVA can be effective. For refractory plaques, the addition of topical tar as 2% crude coal tar or 20% LCD may be beneficial.

PRURITIC DERMATITIS IN THE ELDERLY

Pruritic skin conditions are common in elderly patients. They begin to appear around age 60 and increase in severity with age. Males are more commonly affected. The dermatoses seen in this age group are typically either eczematous or papular. The eczematous plaques may resemble nummular dermatitis, a feature recognized by Marion Sulzberger when he coined the phrase "exudative discoid and lichenoid chronic dermatitis" or "oidoid disease." The pathogenic basis of this component of dermatitis in the elderly may be related to barrier failure due to loss of acidification of the epidermis. In addition, patients often have urticarial papules on the trunk and proximal extremities that resemble insect bites. These lesions are termed "subacute prurigo." Histologically, they demonstrate features of an arthropod assault, with superficial and deep perivascular lymphohistiocytic infiltrates, dermal edema, and at times interstitial eosinophils. Lesions may also show features of transient acantholytic dermatitis or eosinophilic fol- liculitis. This component of the eruption may be related to the tendency of the elderly to have immune systems that skew toward Th2, due to loss of Th1 function. At times patients will have both types of eruption, either simultaneously or sequentially. The combination of barrier failure and an immune system skewed toward Th2 is parallel to what occurs in the setting of atopic dermatitis. For this reason, some practitioners consider this "adult atopic dermatitis." However, it is unknown whether these conditions have a genetic basis, or more likely, given the time of onset, are due to acquired barrier and immune system abnormalities. In these patients, allergic contact dermatitis and photodermatitis may be present or develop. Patch testing may identify important allergens, avoidance of which leads to improvement. Calcium channel blockers may be associated with this condition, but stopping them will clear only about one-quarter of patients on that class of medication. Treatment for these patients is similar to treatment of atopic dermatitis, with antihistamines, emollients, and topical steroids (soak and smear) as the first line. In refractory cases, phototherapy (UVB or PUVA), Goeckerman therapy (UVB plus crude coal tar) in a day-treatment setting, and immunosuppressive

agents can be effective. Inadvertent use of phototherapy in the patient with coexistent photosensitivity will lead to an exacerbation of the disorder.

HORMONE-INDUCED DERMATOSES

Autoimmune progesterone dermatitis may appear as urticar- ial papules, deep gyrate lesions, papulovesicular lesions, an eczematous eruption, or targetoid lesions. Urticarial and erythema multiformelike lesions are most characteristic. Lesions typically appear 5-7 days before menses, and improve or resolve a few days following menses. Biopsies show dense superficial and deep dermal lymphocytic infiltration, with involvement of the follicles, and an admixture of eosinophils. There may be an accompanying mild interface component, as seen in drug eruptions. Pruritus is common. Onset is typically in the third and fourth decades. Familial cases have been reported. When urticaria is the predominant skin lesion, there is a generalized distribution, and it may be accompanied by laryngospasm. Anaphylactoid reactions may occur. Oral erosions may be present. The eruption typically appears during the luteal phase of the menstrual period, and spontaneously clears following menstruation, only to return in the next menstrual period. Many of the reported patients had received artificial progestational agents before the onset of the eruption. In some it appeared during a normal pregnancy. The eruption may worsen or clear during pregnancy. Rarely, it can occur in males and adolescent females. Progesterone luteal phase support during in vitro fertilization has exacerbated the disease. In most cases, diagnosis has been confirmed by intradermal testing with 0.01 mL of aqueous progesterone suspension (50 mg/mL). A positive test may be immediate (30 min) or delayed (24-96 h). Flares may be induced by intramuscular or oral progesterone. The most commonly used treatment is an oral contraceptive to suppress ovulation, thereby reducing progesterone levels. Topical steroids, antihistamines (cetirizine plus hydroxyzine), conjugated estrogen, leuprolide acetate, danazol, and tamoxifen may be effective in some cases. Autoimmune estrogen dermatitis also presents as a cyclic skin disorder that may appear eczematous, papular, bullous, or urticarial.

Pruritus is typically present. Skin eruptions may be chronic but are exacerbated premenstrually or occur only immediately before the menses. Characteristically, the derma- tosis clears during pregnancy and at menopause. Intracutaneous skin testing with estrone produces a papule lasting longer than 24 h or an immediate urticarial wheal (in cases with urticaria). Injections of progesterone yield negative results, ruling out autoimmune progesterone dermatitis. Tamoxifen is effective in some cases.

IMMUNODEFICIENCY SYNDROMES

Primary immunodeficiency diseases (PIDs), although rare, are important to the dermatologist. They may present with skin manifestations, and the dermatologist may be instrumental in referring appropriate patients for immunodeficiency evaluations. These conditions have also given us tremendous insight into the genetic makeup and functioning of the immune system. The PIDs are still classified as those with predominantly antibody deficiency, impaired cell-mediated immunity (cellular immunodeficiencies, T cells, natural killer (NK) cells), combined B- and T-cell deficiencies, defects of phagocytic function, complement deficiencies, and wellcharacterized syndromes with immunodeficiency. More than 120 PIDs were identified, as of the 2005 classification. While many PIDs will present within the first year of life, adult presentations can occur. The dermatologist should suspect a PID in certain situations. Skin infections, especially chronic and recurrent bacterial skin infections, are often the initial manifestation of a PID. Fungal (especially Candida) and viral infections (warts, molluscum) less commonly are the dermatological presentation of a PID. Eczematous dermatitis and erythroderma, at times closely resembling severe atopic dermatitis or seborrheic dermatitis, may affect the skin of PID patients. They may be refractory to standard therapies. Granuloma formation, autoimmune disorders, and vasculitis are other cutaneous manifestations seen in some forms of primary immunodeficiency. The PIDs in which a specific infection or finding is the more common presentation are discussed in other chapters (for

example, chronic mucocutaneous candidiasis; Hermansky - Pudlak, Chediak-Higashi, and Griscelli syndromes with pigmentary anomalies, and cartilagehair hypoplasia syndrome with disorders of hair. The conditions described below are the most important PID conditions with which dermatologists should be familiar.

DISORDERS OF ANTIBODY DEFICIENCY X-LINKED AGAMMAGLOBULINEMIA (XLA)

Also known as Bruton syndrome, this rare hereditary immu- nologic disorder usually only becomes apparent between 4 and 12 months of life, since the neonate obtains adequate immunoglobulin from the mother to protect it from infection in young infancy. The affected boys present with infections of the upper and lower respiratory tracts, gastrointestinal tract, skin, joints, and central nervous system (CNS). The infections are usually due to Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, and Pseudomonas. Recurrent skin staphylococcal infection may be a prominent component of this condition. Atopic-like dermatitis and pyoderma gan- grenosum have been described. Hepatitis B, enterovirus, and rotavirus infections are common in XLA patients and one- third develop a rheumatoid-like arthritis. Enterovirus infection may result in a dermatomyositis-meningoencephalitis syndrome. An absence of palpable lymph nodes is characteristic. IgA, IgM, IgD, and IgE are virtually absent from the serum, although IgG may be present in small amounts. The spleen and lymph nodes lack germinal centers, and plasma cells are absent from the lymph nodes, spleen, bone marrow, and connective tissues. In XLA B cells usually only make up 0.1% of circulating peripheral blood lymphocytes (normal 5-20%). More than 500 different mutations have been identified in the Btk gene in XLA patients. Some of these mutations only partially compromise the gene, so some patients may have milder phenotype and up to 7% circulating B cells, making differentiation from common variable immunodeficiency difficult. The Bruton tyrosine kinase (Btk) is essential for the development of B lymphocytes. Treatment with relatively highdose gamma globulin has enabled many patients to live into adulthood. Chronic sinusitis and

pulmonary infection remain problematic due to the lack of IgA. Chronic pulmonary disease affects 76% of XLA patients over the age of 20 years.

ISOLATED IGA DEFICIENCY

An absence or marked reduction of serum IgA occurs in approximately 1 in 600, making it the most common immunodeficiency state. Autosomal-dominant, autosomal - recessive, and sporadic cases have been reported. Certain medications appear to induce selective IgA deficiency, including phenytoin, sulfasalazine, cyclosporine, nonsteroidal anti - inflammatory drugs (NSAIDs), and hydroxychloroquine. The genetic cause in most cases is unknown, but a few cases have a mutation in the tumor necrosis factor (TNF) receptor family member TACI. Common variable immunodeficiency (CVID) may develop in patients with IgA deficiency, or other members of IgA - deficient patients' families may have CVID. Ten to fifteen percent of all symptomatic immunodeficiency patients have IgA deficiency. Most IgA-deficient patients are entirely well, however. Of those with symptoms, half have repeated infections of the gastrointestinal and respiratory tracts, and one-quarter have autoimmune disease. Allergies such as anaphylactic reactions to transfusion or IVIG, asthma, and atopic dermatitis are common in the symptomatic group. There is an increased association of celiac disease, dermatitis herpetiformis, and inflammatory bowel disease. Vitiligo, alopecia areata, and other autoimmune diseases such as systemic lupus erythematosus, dermatomyositis, scleroderma, thyroiditis, rheumatoid arthritis, polyarteritislike vasculitis and Sjogren syndrome have all been reported to occur in these patients. Malignancy is increased in adults with IgA deficiency.

COMMON VARIABLE IMMUNODEFICIENCY

Common variable immunodeficiency (CVID), also known as acquired hypogammaglobulinemia, is a heterogeneous disorder and is the most common immunodeficiency syndrome after IgA deficiency. Patients have low levels of IgG and IgA, and 50% also have low levels of IgM. The genetic defect is unknown.

These patients do not form antibodies to bacterial antigens, and have recurrent sinopulmonary infections. They have a predisposition to autoimmune disorders, such as vitil- igo and alopecia areata, gastrointestinal abnormalities, lymphoreticular malignancy, and gastric carcinoma. Cutaneous, as well as visceral, granulomas have been reported in as many as 22% of patients. These can involve both the skin and the viscera, creating a sarcoidosis-like clinical syndrome. Replacement of the reduced immunoglobulins with IVIG may help reduce infections. Topical, systemic, and intralesional corticosteroids may be used for the granulomas, depending on their extent. Infliximab and etanercept have been effective in steroid-refractory cases.

CLASS-SWITCH RECOMBINATION DEFECTS (FORMERLY IMMUNODEFICIENCY WITH HYPER-IGM)

This group of diseases includes disorders which are combined T- and B-cell abnormalities, such as CD40 deficiency and CD40 ligand deficiency, and disorders of primary B cells, such as cytidine deaminase and uracil-DNA glycosylase deficiencies. They are rare, and the different genetic diseases included in this group appear to have different clinical manifestations. These patients experience recurrent sinopulmonary infections, diarrhea, and oral ulcers. Neutropenia may be associated with the ulcers. Recalcitrant human papillomavirus infections may occur.

THYMOMA WITH IMMUNODEFICIENCY

Thymoma with immunodeficiency, also known as Good syndrome, occurs in adults in whom profound hypogammaglobulinemia and benign thymoma appear almost simultaneously. It is now classified predominantly as an antibody deficiency disorder. There is a striking deficiency of B and pre-B cells. One patient developed vulvovaginal gingival lichen planus. Myelodysplasia and pure red cell aplasia may occur. Patients are at risk for fatal opportunistic pulmonary infections with fungi and Pneumocystis. Thymectomy does not prevent the development of

the infectious or lymphoreticular complications. Supportive therapy with IVIG, GM-CSF, and transfusions may be required.

DISORDERS WITH T-CELL DEFICIENCY

T-cell deficiency states can occur due to lack of thymic tissue, enzyme defects toxic to T lymphocytes (purine nucleoside phosphorylase deficiency), failure to express surface molecules required for immune interactions (CD3, major histocom- patibility complex (MHC) class I and II), or defects in signaling molecules (ZAP-70).

DIGEORGE SYNDROME

DiGeorge syndrome is also called congenital thymic hypopla- sia, the velocardiofacial syndrome, and III and IV pharyngeal pouch syndrome. It is an autosomal-dominant disorder, which, in 50% of cases, is due to hemizygous deletion of 22q11- pter and rarely due to deletions in 10p. Many cases are sporadic. Most DiGeorge syndrome patients have the congenital anomalies and only minor thymic anomalies. They present with hypocalcemia or congenital heart disease. The syndrome includes congenital absence of the parathyroids and an abnormal aorta. Aortic and cardiac defects are the most common cause of death. DiGeorge syndrome is characterized by a distinctive facies: notched, low-set ears, micrognathia, shortened philtrum, and hypertelorism. Patients with these DiGeorge congenital malformations and complete lack of thymus are deemed to have "complete DiGeorge syndrome." Cellmediated immunity is absent or depressed, and few T cells with the phenotype of recent thymus emigrants are found in the peripheral blood or tissues. Opportunistic infections commonly occur despite normal immunoglobulin levels. Maternally derived graftversus - host disease (GVHD) may occur in these patients. A small subset of patients with complete DiGeorge syndrome develop an eczematous dermatitis, lymphadenopathy, and an oligoclonal T-cell proliferation. The condition may present as an atopic-like dermatitis, severe and extensive seborrheic dermatitis, or an erythroderma. This is

called "atypical complete DiGeorge syndrome." Biopsies show features of a spongiotic dermatitis with eosinophils, necrotic keratinocytes with satellite necrosis, and characteristically peri- and intraeccrine inflammation. This resembles the histology of grade 1-2 GVHD, lichen striatus, and some cases of mycosis fungoides. One African American patient with DiGeorge syndrome developed a granulomatous dermatitis. The treatment for complete DiGeorge syndrome is thymic transplantation.

PURINE NUCLEOSIDE PHOSPHORYLASE DEFICIENCY

This very rare autosomal-recessive enzyme defect leads to greatly reduced T-cell counts and depressed cell-mediated immunity. B-cell numbers are normal, but immunoglobulins may be normal or decreased. Mutation in the gene for the enzyme located on chromosome 14q13 is responsible. Accumulation of purines in cells of the lymphoid system and CNS leads to the clinical findings of T-cell deficiency and neurological impairment. Patients usually present at between 3 and 18 months of age with recurrent infections involving the upper and lower respiratory tracts, spasticity, ataxia, developmental delay, and autoimmune hemolytic anemia. They usually die from overwhelming viral infections. Bone marrow transplant may be life-saving.

MISCELLANEOUS T-CELL DEFICIENCIES

TAP 1 and TAP 2 gene deficiencies are very, very rare autosomal-recessive disorders that result in severe reduction of MHC class I expression on the surface of cells. CD8 cells are decreased but CD4 cells are normal, as are B-cell numbers and serum immunoglobulins. Three forms of disease occur. One phenotype develops severe bacterial, fungal, and parasitic infection, and dies by age 3. The second phenotype is completely asymptomatic. The third group is the most common. Group 3 patients present in childhood with recurrent and chronic bacterial respiratory infections. These lead to bronchiectasis and eventually fatal respiratory failure in adulthood. The skin abnormalities appear in late childhood or

more commonly in young adulthood. Necrotizing granulomatous lesions appear as plaques or ulcerations on the lower legs and on the midface around the nose. The perinasal lesions are quite destructive and resemble "lethal midline granuloma" or Wegener's granulomatosis. Nasal polyps with necrotizing granulomatous histology also occur. One patient also developed leukocytoclastic vasculitis. MHC class II deficiency is due to mutations in transcription factors for MHC class II proteins (C2TA, RFX5, RFXAP, RFSANK genes). It is inherited in an autosomal-recessive manner and results in decreased CD4 cells. ZAP-70 deficiency is an autosomal-recessive disorder of considerable heterogeneity. This enzyme is required for T-cell receptor intracellular signaling. Patients present before age 2 with recurrent bacterial, viral, and opportunistic infections, diarrhea, and failure to thrive. They have a lymphocytosis with normal CD4 cells and decreased CD8 cells. Some patients develop an exfoliative erythroderma, eosinophilia, and elevated IgE levels. Omenn syndrome is a rare autosomalrecessive disorder that presents at birth or in the neonatal period. Clinical features are exfoliative erythroderma, eosinophilia, diarrhea, hepatosplenomegaly, lymphadenopathy, hypogammaglobulinemia with elevated IgE, recurrent infections, and early death (usually by 6 months of age). Both antibody production and cell-mediated immune function are impaired. T-cell receptor rearrangements are severely restricted in patients with Omenn syndrome. Mutations in RAG1, RAG2, Artemis, and IL-7Ralpha genes may result in Omenn syndrome. Anhidrotic ectodermal dysplasia with immunodeficiency is an X-linked recessive disorder with lymphocytosis and elevated CD3 and CD4 cells, and low levels of NK cells. It is due to a mutation in the gene that codes for nuclear factor κ B essential modulator (NEMO). The mother may have mild stigmata of incontinentia pigmentii. The mutations are hypomor- phic (some NEMO function is preserved). These male infants present within the first few months of life with hypohidrosis, delayed tooth eruption, and immunodeficiency. Hair may be absent. Frequent infections of the skin and respiratory tract are common. The eruption has been characterized as an "atopic dermatitislike eruption," although some cases may have prominent intertriginous lesions resembling seborrheic dermatitis. Treatment

is bone marrow transplantation. A similar autosomaldominant syndrome is caused by a mutation in the gene IKBA (inhibitory κ B kinase y). IPEX syndrome (immune dysregulation, polyendocrinopa- thy, enteropathy, X-linked syndrome) is a rare disorder with neonatal autoimmune enteropathy, diabetes, thyroiditis, food allergies, and skin eruptions. IPEX is caused by mutations in FOXP3, the master control gene for regulatory T-cell (Treg) development. Patients present with diffuse and severe erythematous exudative plaques resembling atopic dermatitis. The skin eruption may be follicularly based or lead to prurigo nodularis. The scalp develops hyperkeratotic psoriasiform plaques. Cheilitis and onychodystrophy can occur. Staphylococcal sepsis may develop.

SEVERE COMBINED IMMUNODEFICIENCY DISEASE

This heterogeneous group of genetic disorders is characterized by severely impaired humoral and cellular immunity. Moniliasis of the oropharynx and skin, intractable diarrhea, and pneumonia are the triad of findings that commonly lead to the diagnosis of severe combined immunodeficiency disease (SCID). In addition, severe recurrent infections may occur, caused by Pseudomonas, Staphylococcus, Enterobacteriaceae, or Candida. Overwhelming viral infections are the usual cause of death. Engraftment of maternally transmitted or transfusion- derived lymphocytes can lead to GVHD. The initial seborrheic dermatitis-like eruption may represent maternal engraftment GVHD. This cutaneous eruption may be asymptomatic but tends to generalize. More severe eczematous dermatitis and erythroderma may develop with alopecia. Cutaneous granulomas have been reported in a Jak-3-deficient SCID patient. SCID is characterized by deficiency or total absence of circulating T lymphocytes. Immunoglobulin levels are consistently very low, but B-cell numbers may be reduced, normal, or increased. The thymus is very small; its malformed architecture at autopsy is pathognomonic. The inheritance may be autosomalrecessive or X-linked; the most common type of SCID is X-linked. A deficiency of a common y-chain that is an essential component of the IL-2 receptor is responsible for the profound lymphoid

dysfunction in X-linked SCID. This abnormality also causes defects in IL-4, 7, 9, 15, and 21. The mutation has been mapped to Xq13.1. About half the autosomal-recessive cases have a deficiency of adenosine deaminase, the gene for which is located on chromosome 20q13. Mutations in Jak-3, IL-7Ralpha, CD45, CD3delta/CD3epsilon, RAG1 or RAG2, and Artemis (DCLREC1C) can all also cause the SCID phenotype. Reticular dysgenesis causes SCID, granulocytopenia, and thrombocytopenia. Prenatal diagnosis and carrier detection are possible for many forms of SCID. The definitive treatment is hematopoietic stem cell transplantation (HSCT, bone marrow transplantation). This should ideally be carried out before 3 months of age for optimal outcome. The success rate is less than 90%. In utero hematopoietic stem cell transplantation has been successful in X-linked SCID. SCID patients rarely live longer than 2 years without transplantation. On average, 8 years after successful HSCT, SCID patients may develop severe human papilloma- virus (HPV) infection with common warts, flat warts, or even epidermodysplasia verruciformis. The development of HPV infections in SCID patients following HSCT is only seen in patients with either JAK-3 or y-chain (gamma c) deficiency, but in those patients more than 50% may develop this complication.

WHIM SYNDROME

WHIM (warts, hypogammaglobulinemia, infections, myelokathexis) syndrome is an autosomaldominant syndrome with hypogammaglobulinemia, reduced B cell numbers, and neutropenia. The most common genetic cause is a truncation mutation of CXCR4, which leads to gain of function in that gene. Additional mutations that are not in the CXCR4 gene can also cause WHIM, but all of them lead to functional hyper- activity of CXCR4. CXCR4 causes retention of neutrophils in the bone marrow and is the basis of the neutropenia and myelokathexis (increased apoptotic neutrophils in the bone marrow). There is profound loss of circulating CD27+ memory B cells, resulting in hypogammaglobulinemia, and the observation that WHIM patients have normal

antibody response to certain antigens, but fail to maintain this antibody production. However, normal immunoglobulin levels do not exclude the diagnosis of WHIM. Almost 80% of WHIM patients have warts at the time of their diagnosis. These include common and genital wart types. A significant number of female WHIM patients have cervical and vulval dysplasia, which can progress to carcinoma. WHIM patients have disproportionately more HPV infections than SCID patients, yet WHIM patients have little problem resolving other viral infections. They may develop Epstein-Barr virus (EBV)-induced lymphomas, however. The vast majority of patients in early childhood suffer recurrent sinopulmonary infections, skin infections, osteomyelitis, and urinary tract infections. Recurrent pneumonias lead to bronchiectasis. Treatment is G-CSF, IVIG, prophylactic antibiotics, and aggressive treatment of infections. The HPV infections can progress to fatal carcinomas and therefore male patients must be regularly examined by dermatologists and female ones by gynecologists; a low threshold for biopsy of genital lesions is required. Hematopoietic cells in response to external stimuli. The hematopoietic cells of affected patients cannot polarize or migrate in response to physiologic stimuli, accounting for the protean clinical features of the syndrome. Wiskott-Aldrich syndrome occurs when mutations in WASP lead to absence or truncation of the WASP protein (WASP-mutations). Mutations that result in normal length but some loss of function in the WASP protein (WASP+ mutations) result in three different syndromes: X-linked thrombocytopenia (XLT), intermittent X-linked thrombocytopenia, and X-linked neutropenia. Patients with XLT may also have an atopic-like dermatitis, but this is usually milder than the severe and difficult to control eczema affecting patients with the full Wiskott-Aldrich syndrome. WASP/XLT patients may also develop autoimmune disease, especially autoimmune hemolytic anemia, vasculitis, Henoch-Schonleinlike purpura, and inflammatory bowel disease. High IgM is associated with the development of autoimmune disease. Treatment is with platelet transfusions, antibiotics, and IVIG, if required. Often splenectomy is performed to help control bleeding, but this leads to increased risk of sepsis and is not routinely

recommended. Immunosuppressive therapy or rituximab may be used to control autoimmune complications. Bone marrow transplantation from a human leukocyte antigen (HLA)-identical sibling as early as possible in the disease course provides complete reversal of the platelet and immune dysfunction, as well as improvement or clearing of the eczematous dermatitis. Survival at 7 years with a matched sibling donor transplant approaches 90%.

WISKOTT-ALDRICH SYNDROME

Wiskott-Aldrich syndrome, an X-linked recessive syndrome, consists of a triad of chronic eczematous dermatitis resembling atopic dermatitis; increased susceptibility to bacterial infections, such as pyoderma or otitis media; and thrombocytopenic purpura with small platelets. There are normal levels of IgM and IgG, but elevated levels of IgA and IgE. T cells progressively decline in number and activity. Untreated survival is about 15 years, with death from infection, bleeding, or lymphoma. The genetic cause of Wiskott-Aldrich syndrome is a mutation in the WASP gene. This gene codes for a protein called WASP, which is universally expressed in hematopoietic cells and is critical in the reorganization of the actin cytoskeleton in.

ATAXIA TELANGIECTASIA

Ataxia telangiectasia is an autosomal-recessive condition that is due to mutations in a single gene on chromosome 11 (ATM), which encodes a protein called ATM. This protein is critical in cell cycle control. When ATM is absent, the cell cycle does not stop to repair DNA breaks or for B(D)J recombination of immu- noglobulin and T-cell receptor genes. This results in immunodeficiency and an increased risk for malignancy. The clinical features of the patients are progressive ocular and cutaneous telangiectasias, premature aging, and progressive neuro- degeneration. Skin changes that are characteristic are cutaneous non-infectious granulomas (which can be ulcerative and painful), loss of subcutaneous fat, premature gray hair, large irregular café aulait spots, vitiligo, seborrheic

dermatitis, atopic dermatitis, recurrent impetigo, and acanthosis nigricans. Late tightening of the skin can occur and resembles acral sclerosis. Sinopulmonary infections are common, especially otitis media, sinusitis, bronchitis, and pneumonia. Varicella, at times severe, herpes simplex, molluscum contagiosum, and herpes zoster can occur. Refractory warts occur in more than 5% of patients. Aside from candidal esophagitis, unusual opportunistic infections are rare. Childhood immunizations, including liver viral vaccines, are well tolerated. Lymphopenia is common, with reduction of both B and T cells occurring in the majority of patients. Helper T-cell counts can be below 200. IgA, IgG4, IgG2, and IgE deficiencies can all be present. Paradoxically, IgM, IgA, and IgG can be elevated in some patients, including the presence of monoclonal gammopathy in more than 10% of cases. The immunological abnormalities are not progressive. Lymphoma risk is increased more than 200-fold (especially B-cell lymphoma), and leukemia (especially T-cell chronic lymphocytic leukemia) is increased 70-fold. Treatment includes high vigilance for infection and malignancy. In patients with low CD4 counts, prophylaxis to prevent Pneumocystis pneumonia can be considered. When IgG deficiency is present and infections are frequent, IVIG may be beneficial. IVIG and intralesional corticosteroids may be used for the cutaneous granulomas. Carriers of ataxia telangiectasia have an increased risk for hematologic and breast malignancies. Due to the accumulation of chromosomal breaks following radiation exposure, both the ataxia telangiectasia patients and the carriers should minimize radiation exposure.

DEFECTS OF PHAGOCYTE NUMBER, FUNCTION, OR BOTH

CHRONIC GRANULOMATOUS DISEASE

Chronic granulomatous disease (CGD) is a rare disorder caused by mutations in one of the genes that encode the subunits of the superoxidegenerating phagocyte NADPH oxidase system responsible for the respiratory burst involved in organism killing. CGD is characterized by repeated and recurrent bacterial and fungal infections of the lungs, skin, lymph nodes, and bones. Gingivostomatitis

(aphthous-like ulcerations) and a seborrheic dermatitis of the periauricular, perinasal, and perianal area are characteristic. The dermatitis is frequently infected with S. aureus, and regional adenopathy and abscesses may complicate the infections. The term "suppurative dermatitis" is used in the immunology literature to describe this seborrheic-like dermatitis with secondary infection (very analogous to the "infective dermatitis" seen in human T-cell lymphotropic virus (HTLV)-1 infection). In addition to S. aureus, Serratia species are commonly isolated from skin abscesses, liver abscesses, and osteomyelitis. Aspergillus is the most common agent causing pneumonia in CGD patients. In tuberculosis-endemic areas, CGD patients frequently develop active tuberculosis or prolonged scarring, abscesses, or disseminated infection following BCG immunization. There are four types of CGD, one X-linked and three autosomal-recessive. The X-linked form is the most common (65-75% of CGD patients) and is due to a mutation in the CYBB gene, which leads to absence of the high molecular weight subunit of cytochrome b 558 (gp 91-phox) and a total absence of NADPH oxidase activity. In autosomal-recessive forms, mutations in the genes encoding for the remaining three oxidase components have been described: p22-phox (CYBA), p47-phox (NCF-1), and p67-phox (NCF-2). The X-linked variant has the most severe phenotype. Compared to the autosomal- recessive CGD patients, the X-linked patients present at an earlier age (14 months vs 30 months), and are diagnosed at an earlier age (3 years vs 6 years). The lack of superoxide generation apparently causes disease, not because the bacteria are not being killed by the superoxide, but because the superoxide is required to activate proteases in phagocytic vacuoles that are needed to kill infectious organisms. Granuloma formation is characteristic of CGD and can occur in the skin, gastrointestinal tract, liver, bladder, bone, and lymph node. Up to 40% of biopsies from these organs will demonstrate granulomas, at times with identifiable fungal or mycobacterial organisms. Since these patients are often on prophylactic antibiotics, organisms are frequently not found, however. Subcorneal pustular eruptions can also be seen in CGD patients. In the intestinal tract an inflammatory bowel disease-like process occurs, with granulomas in the colon.

This can cause significant gastrointestinal symptoms. The diagnosis of CGD is made by demonstrating low reduction of yellow nitro-blue tetrazolium (NBT) to blue formazan in the "NBT test." Dihydrorhodamine 123 flow cytometry, chemiluminescence production, and the ferricytochrome C reduction assay are also confirmatory and may be more accurate. Female carriers of the X-linked form of CGD have a mixed population of normal and abnormal phagocytes, and therefore show intermediate NBT reduction. The majority of carriers have skin complaints. Raynaud phenomenon can occur. More than half will report a photosensitive dermatitis, 40% have oral ulcerations, and a third have joint complaints. Skin lesions in carriers have been described as DLE- like (Discoid lupus erythematosus), but histologically there is often an absence of the interface component and they resemble tumid lupus. DIF examination is usually negative, as is common in tumid lupus erythematosus (LE). Less commonly, CGD patients themselves have been described as having similar LE-like lesions, or "arcuate dermal erythema." Despite these findings, the vast majority of patients with LE-like skin lesions, both carriers and CGD patients, are antinuclear antibody (ANA)-negative. Treatment of infections should be early and aggressive. There should be a low threshold to biopsy skin lesions, as they may reveal important and potentially life-threatening infections. Patients usually receive chronic trimethoprim-sulfamethoxazole prophylaxis, chronic oral itraconazole or another anti-Aspergillus agent, and IFN-y injections. Bone marrow or stem cell transplantation has been successful in restoring enzyme function, reducing infections, and improving the associated bowel disease. However, survival is NOT increased with bone marrow transplantation, so it is not routinely undertaken.

LEUKOCYTE ADHESION MOLECULE DEFICIENCY

This rare autosomalrecessive disorder has three types. Leukocyte adhesion molecule deficiency (LAD) type I is due to a mutation in the common chain (CD18) of the P2 integrin family. It is characterized by recurrent bacterial infections of the skin and mucosal surfaces, especially gingivitis and perio-

dontitis. Skin ulcerations from infection may continue to expand. Cellulitis and necrotic abscesses, especially in the perirectal area, can occur. Minor injuries may lead to pyoderma gangrenosumlike ulcerations that heal slowly. Infections begin at birth, and omphalitis with delayed separation of the cord is characteristic. Neutrophilia is marked, usually 5-20 times normal, and the count may reach up to 100 000 during infections. Despite this, there is an absence of neutrophils at the sites of infection, demonstrating the defective migration of neutrophils in these patients. LAD type I patients are either severely (<1% normal CD18 expression) or moderately affected (2.5-10% of normal expression.) Patients with moderate disease have less severe infections and survive into adulthood, whereas patients with severe disease often die in infancy. LAD type II is due to a mutation in FUCT1, which results in a general defect in fucose metabolism and causes the absence of SLeX and other ligands for the selectins. Severe mental retardation, short stature, a distinctive facies, and the rare hh blood phenotype are the features. Initially, these patients have recurrent cellulitis with marked neutrophilia, but the infections are not life-threatening. After age 3 years, infections become less of a problem and patients suffer from chronic periodontitis. LAD type III is due to mutation in the gene KINDLIN3 (FERMT3) and is characterized by severe recurrent infections, bleeding tendency (due to impaired platelet function), and marked neutrophilia. Bone marrow transplantation is required for patients with severe LAD type I and LAD type III. There are at least two types of hyperimmunoglobulin E syndrome (HIES): an autosomaldominant form caused by mutations in STAT3, and an autosomal-recessive form, for which the genetic cause is still unknown. The two forms of HIES are clinically somewhat different and will be described separately. Autosomal-dominant HIES was first called Job's syndrome. The classic triad is eczema, recurrent skin and lung infections, and high serum IgE. The skin disease is the first manifestation of STAT3 deficiency and begins at birth in 19% of cases, within the first week of life in more than 50%, and in the first month in 80%. The initial eruption is noted first on the face or scalp, but quickly generalizes to affect the face, scalp, and body. Dermatitis of the body only

is distinctly uncommon. The body rash favors the shoulder, arms, chest, and buttocks. The newborn rash begins as pink papules that may initially be diagnosed as "neonatal acne." The papules develop quickly into pustules, then coalesce into crusted plaques. Histologically, these papules are intraepidermal eosinophilic pustules. The dermatitis evolves to bear a close resemblance to atopic dermatitis, often very severe. Staphylococcal infection of the dermatitis is frequent, and treatment of the staphy- lococcal infection with antibiotics and bleach baths leads to improvement. Since only about 8% of children with IgE levels below 2000 actually have HIES, other features must be used to confirm the diagnosis. Abscesses, sometimes cold, are characteristic. Recurrent pyogenic pneumonia is the rule, starting in childhood. Due to the lack of neutrophilic inflammation in the pneumonia, symptoms may be lacking and lead to a delay in diagnosis. Although antibiotic treatment clears the pneumonia, healing is abnormal, with the formation of bronchiectasis and pneumatoceles, a characteristic feature of HIES. Mucocutaneous candidiasis is common, typically thrush, vaginal candidiasis, and candida onychomycosis. Musculo- skeletal abnormalities are common, including scoliosis, osteo- penia, minimal trauma fractures, and hyperextensibility, leading to premature degenerative joint disease. Retention of some or all of the primary teeth is a characteristic feature. Other oral manifestations include median rhomboid glossitis, high-arch palate, and abnormally prominent wrinkles on the oral mucosa. Arterial aneurysms are common, including berry and coronary aneurysms. The coronary aneurysms can cause myocardial infarction. Autosomal-dominant HIES patients have a characteristic facies, developing during childhood and adolescence. Features include facial asymmetry, broad nose, deepset eyes, and a prominent forehead. The facial skin is rough, with large pores. There is an increased risk of malignancy, predominantly B-cell non-Hodgkin lymphoma. Laboratory abnormalities are limited to eosinophilia and an elevated IgE. In adults, the IgE levels may become normal. Th17 cells are lacking from the peripheral blood of STAT3 mutation patients. A scoring system developed at the National Institutes of Health (NIH) can accurately identify patients with HIES, selecting those in whom

genetic testing could be considered. Autosomalrecessive HIES is much less common. These patients also suffer from severe eczema and recurrent skin and lung infections. The lung infections resolve without pneumatoceles, however. Autosomal-recessive HIES patients are predisposed to cutaneous viral infections, especially molluscum contagiosum, herpes simplex, and varicella zoster. They also contract mucocutaneous candidiasis. Neurological disease is much more common in autosomal-recessive HIES, ranging from facial paralysis to hemiplegia. Autosomal-recessive HIES has normal facies, no fractures, and normal shedding of primary dentition. Treatment for HIES is currently traditional. Infections are suppressed with bleach baths and chronic antibiotic prophylaxis (usually with trimethoprim/sulfamethoxazole).

COMPLEMENT DEFICIENCY

The complement system is an effector pathway of proteins that results in membrane damage and chemotactic activity. Four major functions result from complement activation: cell lysis, opsonization/phagocytosis, inflammation, and immune complex removal. In the "classic" complement pathway, complement is activated by an antigen-antibody reaction involving IgG or IgM. Some complement components are directly activated by binding to the surface of infectious organisms; this is called the "alternate" pathway. The central component common to both pathways is C3. In the classic pathway, antigen-antibody complexes sequentially bind and activate three complement proteins, C1, C4, and C2, leading to the formation of C3 convertase, an activator of C3. The alternate pathway starts with direct activation of C3. From activated C3, C5-C9 are sequentially activated. Cytolysis is induced mainly via the "membrane attack complex," which is made up of the terminal components of complement. Opsonization is mainly mediated by a subunit of C3b, and inflammation by subunits of C3, C4, and C5. Inherited deficiencies of complement are usually autosomal- recessive traits. Deficiencies of all 11 components of the classic pathway, as well as inhibitors of this pathway, have been described. Genetic

deficiency of the C1 inhibitor is the only autosomal-dominant form of complement deficiency and results in hereditary angioedema. In general, deficiencies of the early components of the classic pathway result in connective tissue disease states, while deficiencies of the late components of complement lead to recurrent neisserial sepsis or meningitis. Overlap exists, and patients with late- component deficiencies may exhibit connective tissue disease, while patients with deficiencies of early components, such as C1q, may manifest infections. Deficiency of C3 results in recurrent infections with encapsulated bacteria such as Pneumococcus, H. influenzae, and Streptococcus pyogenes. C3 inactivator deficiency, like C3 deficiency, results in recurrent pyogenic infections. Properdin (a component of the alternate pathway) dysfunction is inherited as an X-linked trait and predisposes to fulminant meningococcemia. Deficiency of C9 is the most common complement deficiency in Japan but is uncommon in other countries. Most patients appear healthy. MASP2 deficiency, resulting in absent hemolytic activity by the lectin pathway, is considered a complement deficiency and results in a syndrome resembling systemic lupus erythematosus (SLE) and increased pyogenic infection. Factor I deficiency results in recurrent infections, including Neisseria meningitides. Partially deficient family members may also have increased infections. C2 deficiency is the most common complement deficiency in the US and Europe. Most patients are healthy, but SLE-like syndromes, disseminated cutaneous lupus erythematosus, frequent infections, anaphylactoid purpura, dermatomyositis, vasculitis, and cold urticaria may be seen. C1q-, C4-, and C2-deficient patients have SLE at rates of 90%, 75%, and 15% respectively. Complement deficiency-associated SLE typically has early onset, photosensitivity, less renal disease, and Ro/ La autoantibodies in two-thirds. C2- and C4-deficient patients with LE commonly have subacute annular morphology. Sjogren syndrome, arthralgias, and oral ulcerations. Renal disease, anti-dsDNA antibodies, and anticardiolipin antibodies are uncommon. Patients with C4 deficiency may have lupus and involvement of the palms and soles. Many of the complement component deficiencies can be acquired as an autoimmune phenomenon or a paraneoplastic

finding. Examples include acquired angioedema, as when C1 inhibitor is the target, or lipodystrophy and nephritis, when C3 convertase is the target. When complement deficiency is suspected, a useful screening test is a CH50 (total hemolytic complement) determination, because deficiency of any of the complement components will usually result in CH50 levels that are dramatically reduced or zero.

GRAFT-VERSUS-HOST DISEASE

Graft-versus-host disease (GVHD) occurs most frequently in the setting of hematopoietic stem cell transplantation (HSCT), but may also occur following organ transplantation or in the rare situation of transfusion of active lymphoid cells into an immunodeficient child postpartum or even in utero. Blood transfusions with active lymphocytes (non-radiated whole blood) from family members or in populations with minimal genetic variability, given to an immunodeficient patient, can result in GVHD. HSCT from a monozygotic twin (syngeneic) or even from the patient's own stem cells (autologous) can induce a mild form of GVHD. GVHD requires three elements. First, the transplanted cells must be immunologically competent. Second, the recipient must express tissue antigens that are not present in the donor and therefore are recognized as foreign. Third, the recipient must be unable to reject the transplanted cells. Immunological competence of the transplanted cells is important, since ablating them too much may lead to failure of engraftment, or more commonly incomplete eradication of the recipient's malig- nancy (graft vs tumor effect). Therefore, some degree of immu- nological competence of the transplanted cells is desired. For this reason, the prevalence of GVHD still remains about 50% following HSCT. Another important factor in determining the development and severity of the GVHD is the preconditioning regimen. Chemotherapy and radiation cause activation of dendritic cells (antigen-presenting cells, APCs) in tissues with high cell turnover - the skin, gut, and liver. These APCs increase their expression of HLA and other minor cell surface antigens, priming them to interact with transplanted lym- phoid cells. Host APCs

are important in presenting these antigens to the active lymphoid donor cells. Cytokines, especially IL-2, TNF-a, and IFN-y, are important in enhancing this host- donor immunological interaction. Reducing this early inflammatory component in GVHD can delay the onset of the GVHD, but may not reduce the prevalence. The indications for HSCT, the age limits, and the degree of HLA incompatibility allowed have all increased over the last decade, increasing the number of persons at risk for GVHD. While initially only reactions that occurred within the first 100 days after transplantation were considered acute GVHD, it is now recognized that classical acute GVHD can occur up to a year or more following HSCT. Acute GVHD is based on the clinical presentation, NOT the duration following transplantation. In acute GVHD the cutaneous eruption (Fig. 5-17) typically begins between the 14th and 42nd days after transplantation, with a peak at day 30. Acute GVHD is characterized by an erythematous morbilliform eruption of the face and trunk, which may become confluent and result in exfoliative erythroderma. It often begins with punctate lesions corresponding to hair follicles and eccrine ducts. Even when morbilliform, darker punctate areas are a helpful clinical sign. In children, the diaper area is often involved. The eruption may appear papular and eczematous, involving web spaces, periumbilical skin, and ears. The appearance bears some resemblance to scabies. The differential diagnosis for the eruption of acute GVHD includes the eruption of lymphocyte recovery, engraftment syndrome (see below), a viral exanthema, and a drug eruption. The cutaneous histology in the early phases of acute GVHD may not be able to distinguish these entities. Grade IV GVHD is characterized by fullthickness slough and may resemble toxic epidermal necrolysis. The mucous membranes and the conjunctivae can be involved as well, which can be difficult to distinguish from chemotherapy-induced and infectious mucositis. Often around the same time, the patient develops the other characteristic features of acute GVHD, a cholestatic hepatitis with elevated bilirubin and a highvolume diarrhea. Syngeneic/autologous GVHD usually involves only the skin and is self-limited. The preconditioning regimens are felt to result in loss of "selftolerance." Engraftment syndrome is a

combination of symptoms that occur around the time of engraftment and neutrophil recovery. Patients develop fever (without an infectious source), diarrhea, pulmonary infiltrates with hypoxia, and capillary leak syndrome with edema and weight gain. It occurs as soon as 7 days after autologous HSCT, and between 11 and 16 days after allogeneic transplants. The associated skin eruption is clinically and histologically identical to acute GVHD, but at the time of presentation is usually diagnosed as a "drug eruption" and antibiotic therapy is frequently changed. Ocular involvement with keratitis can occur. This syndrome occurs in 7-59% of patients following HSCT, and is a significant cause of morbidity and mortality in the setting of autologous peripheral blood progenitor cell transplants. In one series it accounted for 45% of all transplantrelated mortality. It is mediated by cytokine production and neutrophil infiltration of the organs damaged by the conditioning chemotherapy, especially the lungs. Administration of G-CSF and autologous transplantation are risk factors for the development of engraftment syndrome. The relationship of engraftment syndrome to eruption of lymphocyte recovery is unclear. The treatment of engraftment syndrome is high-dose systemic steroids. With improved support for patients following HSCT, more people are surviving and developing chronic GVHD. It is the second most common cause of death in HSCT patients. It is unclear whether chronic GVHD is mediated by the same pathological mechanisms as acute GVHD. Chronic GVHD has features more typical of an "autoimmune" disease. Diagnostic criteria have been adopted. There are "diagnostic" and "distinctive" cutaneous manifestations. The most common diagnostic feature, which occurs in 80% of patients who develop chronic GVHD, is a lichen planus-like eruption. It typically occurs 3-5 months after grafting, usually beginning on the hands and feet, but becoming generalized. It may present with a malar rash resembling LE. The chronic interface dermatitis can leave the skin with a poikilodermatous appearance. Similar lichen planus-like lesions may occur on the oral mucosa and can result in pain and poor nutrition. Sclerosis is the other "diagnostic" family of skin lesions. This can include lesions resembling superficial morphea/lichen sclerosus. The

morphealike lesions demonstrate an isomorphic response, favoring areas of pressure, especially the waist-band and brassiere-band areas. Sclerosis can occur on the genital mucosa, and complete fusion of the labia minora may occur, requiring surgical correction. Deeper sclerotic lesions resembling eosinophilic fasciitis and restriction of the oral commissure due to sclerosis can occur. These sclerotic plaques may ulcerate, especially during therapy with PUVA. The extent of involvement of the deep tissues, such as muscle and fascia, cannot be easily defined by clinical examination, and may be aided by magnetic resonance imaging (MRI). Rarely, the myositis of chronic GVHD may be accompanied by a skin eruption very similar to dermatomyositis. The "distinctive" features include depigmentation resembling vitiligo; scarring or non-scarring alopecia; nail dystrophy (longitudinal ridging, brittle thin nails, pterygium, and nail loss); and xerostomia and other Sjogren-like mucosal symptoms. Histologically, acute GVHD demonstrates vacuolar interface dermatitis. Individual keratinocyte necrosis with adjacent lymphocytes (satellite necrosis) is typically present, suggesting cellmediated cytotoxicity. The extent of necrosis, bulla formation, and slough is used in grading schemes. In early acute GVHD, the findings may be focal and restricted to hair follicles and sweat ducts. The histologic findings in very early disease may be nonspecific, and many treatment protocols do not depend on histologic features to initiate therapy. A background of epidermal disorder and atypia resembling bowenoid actinic keratosis is almost universally present in later lesions of acute GVHD, and is a helpful diagnostic feature. Similar epidermal changes may be seen with cancer chemotherapy, especially in acral erythema or after busulfan. Chronic GVHD demonstrates lichenoid dermatitis or dermal sclerosis with hyalinization of collagen bundles and narrowing of the space between the collagen bundles. Prevention of post-transfusion GVHD is most safely achieved by irradiating the blood before transfusion in high- risk individuals. Acute GVHD is managed on the skin with topical steroids, TCIs, and UV phototherapy. When systemic symptoms appear, a glucocorticoid, cyclosporine, or tacrolimus is instituted. Blocking the cytokine storm with monoclonal antibodies

such as etanercept, infliximab, and others can be beneficial in some patients. Extracorporeal photopheresis can be considered in acute and chronic GVHD that fails to respond to these first-line therapies. Bath PUVA, with or without isotretinoin, can improve sclerodermatous chronic GVHD. Imatinib can be beneficial in refractory scleroderma- tous chronic GVHD.

GVHD IN SOLID ORGAN TRANSPLANTATION

Transplantation of a solid organ into a partially immunosuppressed host may result in GVHD, since the organ may contain immune cells. The prevalence of GVHD following transplantation is related to the type of organ transplanted and is dependent upon the amount of lymphoid tissue that the organ contains. The risk profile is small intestine > liver > kidney > heart. In liver and small intestine transplants the risk is 1-2%, but when it occurs the mortality is 85%. Close matching increases the risk of GVHD in organ transplantation, since the immunocompetent recipient cells are less likely to recognize the donor lymphocytes as "non-self" and destroy them. The onset is usually 1-8 weeks following transplantation, but can be delayed for years. Fever, rash, and pancytopenia are the cardinal features. The skin is the first site of involvement and only cutaneous disease occurs in 15% of cases. Both acute and chronic GVHD skin findings can occur. Skin biopsies tend to show more inflammation than in HSCT-associated GVHD. In GVHD accompanying liver transplantation, the liver is unaf- fected, since it is syngeneic with the donor lymphocytes. In these patients pancytopenia can occur and is a frequent cause of mortality. The diagnosis of GVHD in the setting of organ transplantation can be aided by documenting macrochimer- ism in the peripheral blood and skin after the first month of transplantation.

CONTACT DERMATITIS AND DRUG ERUPTIONS

CONTACT DERMATITIS

There are two types of dermatitis caused by substances coming in contact with the skin: irritant dermatitis and allergic contact dermatitis. Irritant dermatitis is an inflammatory reaction in the skin resulting from exposure to a substance that causes an eruption in most people who come in contact with it. Allergic contact dermatitis is an acquired sensitivity to various substances that produce inflammatory reactions in those, and only those, who have been previously sensitized to the allergen.

IRRITANT CONTACT DERMATITIS

Many substances act as irritants that produce a nonspecific inflammatory reaction of the skin. This type of dermatitis may be induced in any person if a sufficiently high concentration is used. No previous exposure is necessary and the effect is evident within minutes, or a few hours at most. The concentration and type of the toxic agent, the duration of exposure, and the condition of the skin at the time of exposure produces the variation in the severity of the dermatitis from person to person, or from time to time in the same person. The skin may be more vulnerable by reason of maceration from excessive humidity, or exposure to water, heat, cold, pressure, or friction. Dry skin is less likely to react to contactants. Thick skin is less reactive than thin. Repeated exposure to some of the milder irritants may, in time, produce a hardening effect. This process makes the skin more resistant to the irritant effects of a given substance. Symptomatically, pain and burning are more common in irritant dermatitis, contrasting with the usual itch of allergic reactions.

ALKALIS

Irritant dermatitis is often produced by alkalis such as soaps, detergents, bleaches, ammonia preparations, lye, drain pipe cleaners, and toilet bowl and oven cleansers. Alkalis penetrate and destroy deeply because they dissolve keratin.

Strong solutions are corrosive and immediate application of a weak acid such as vinegar, lemon juice, or 0.5% hydrochloric acid solution will lessen their effects. The principal compounds are sodium, potassium, ammonium, and calcium hydroxides. Occupational exposure is frequent among workers in soap manufacturing. Alkalis in the form of soaps, bleaching agents, detergents, and most household cleansing agents figure prominently in the causes of hand eczema. Sodium silicate (water glass) is a caustic used in soap manufacture and paper sizing, and for the preservation of eggs. Alkaline sulfides are used as depilatories. Calcium oxide (quicklime) forms slaked lime when water is added. Severe burns may be caused in plasterers. The powerful acids are corrosive, whereas the weaker ones are astringent. Hydrochloric acid produces burns that are less deep and more liable to form blisters than injuries from sulfu- ric and nitric acids. Hydrochloric acid burns are encountered in those who handle or transport the product, and in plumbers and those who work in galvanizing or tinplate factories. Sulfuric acid produces a brownish charring of the skin, beneath which is an ulceration that heals slowly. Sulfuric acid is used more widely than any other acid in industry; it is handled principally by brass and iron workers and by those who work with copper or bronze. Nitric acid is a powerful oxidizing substance that causes deep burns; the tissue is stained yellow. Such injuries are observed in those who manufacture or handle the acid or use it in the making of explosives in laboratories. Hydrofluoric acid is used widely in rust remover, in the semiconductor industry, and in germicides, dyes, plastics, and glass etching. It may act insidiously at first, starting with erythema and ending with vesiculation, ulceration, and, finally, necrosis of the tissue. It is one of the strongest inorganic acids, capable of dissolving glass. Oxalic acid may produce paresthesia of the fingertips, with cyanosis and gangrene. The nails become discolored yellow. Oxalic acid is best neutralized with limewater or milk of magnesia to produce precipitation. Phenol (carbolic acid) is a protoplasmic poison that produces a white eschar on the surface of the skin. It can penetrate deep into the tissue. If a large surface of the skin is treated with phenol for cosmetic peeling effects, the absorbed phenol may produce glomerulonephritis

and arrhythmias. Locally, temporary anesthesia may also occur. Phenol is readily neutralized with 65% ethyl or isopropyl alcohol. Titanium hydrochloride is used in the manufacture of pigments. Application of water to the exposed part will produce severe burns. Therefore, treatment consists only of wiping away the noxious substance. Other strong acids that are irritants include acetic, trichloracetic, arsenious, chlorosulfonic, chromic, fluoroboric, hydriodic, hydrobromic, iodic, perchloric, phosphoric, salicylic, silicofluoric, sulfonic, sulfurous, tannic, and tungstic acids. Treatment of acid burns consists of immediate rinsing with copious amounts of water and alkalization with sodium bicarbonate, calcium hydroxide (limewater), or soap solutions. Some chemicals require unusual treatment measures. Fluorine is best neutralized with magnesium oxide. Periungual burns should be treated intralesionally with 10% calcium gluconate solution, which deactivates the fluoride ion and averts more tissue damage. Hypocalcemia, hypomagnesemia, hyperkalemia, and cardiac dysrhythmias may complicate hydrofluoric acid burns. Phosphorus burns should be rinsed off with water followed by application of copper sulfate to produce a precipitate.

AIRBAG DERMATITIS

Airbags are deployed as a safety feature on cars when rapid deceleration occurs. Activation of a sodium azide and cupric oxide propellant cartridge releases nitrogen gas, which expands the bag at speeds exceeding 160 km/h. Talcum powder, sodium hydroxide, and sodium carbonate are released into the bag. Abrasions, thermal, friction, and chemical burns, and an irritant contact dermatitis may result. Superficial erythema may respond well to topical steroids, but full-thickness burns may occur and require debridement and grafting.

OTHER IRRITANTS

Some metal salts that act as irritants are the cyanides of calcium, copper, mercury, nickel, silver, and zinc, and the chlorides of calcium and zinc. Bromine, chlorine, fluorine, and iodine are also irritants. Occupational exposure to methyl

bromide may produce erythema and vesicles in the axillary and inguinal areas. Insecticides, including 2, 2-dichlorovinyl dimethyl phosphate used in roach powder and fly repellents and killers, can act as irritants.

FIBERGLASS DERMATITIS

Fiberglass dermatitis is seen after occupational or inadvertent exposure. The small spicules of glass penetrate the skin and cause severe irritation with tiny erythematous papules, scratch marks, and intense pruritus. Usually, there is no delayed hypersensitivity reaction. Wearing clothes that have been washed together with fiberglass curtains, handling air conditioner filters, or working in the manufacture of fiberglass material may produce severe folliculitis, pruritus, and eruptions that may simulate scabies or insect or mite bites. Fiberglass is also used in thermal and acoustic installations, padding, vibration isolation, curtains, draperies, insulation for automobile bodies, furniture, gasoline tanks, and spacecraft. Talcum powder dusted on the flexure surfaces of the arms prior to exposure makes the fibers slide off the skin. A thorough washing of the skin after handling fiberglass is helpful. Patch testing to epoxy resins should be done when evaluating workers in fiberglass/reinforced plastics operations, as an allergic contact dermatitis may be difficult to discern from fiberglass dermatitis.

DUSTS

Some dusts and gases may irritate the skin in the presence of heat and moisture, such as perspiration. The dusts of lime, zinc, and arsenic may produce folliculitis. Dusts from various woods, such as teak, may incite itching and dermatitis. Dusts from cinchona bark, quinine, and pyrethrum produce widespread dermatitis. Tobacco dust in cigar factories, powdered orris root, lycopodium, and dusts of various nutshells may cause swelling of the eyelids and dermatitis of the face, neck, and upper extremities, the distribution of an airborne contact dermatitis. Dusts formed during the manufacture of high explosives may cause erythematous,

vesicular, and eczematous dermatitis that may lead to generalized exfoliative dermatitis.

CAPSAICIN

Hand irritation produced by capsaicin in hot peppers used in Korean and North Chinese cuisine (Hunan hand) may be severe and prolonged. Pepper spray, used by police in high concentrations, and by civilians in less concentrated formulas, contains capsaicin and may produce severe burns. Cold water is not much help; capsaicin is insoluble in water. Acetic acid 5% (white vinegar) or antacids (Maalox) may completely relieve the burning even if applied an hour or more after the contact. Application should be continued until the area can be dried without return of the discomfort.

TEAR GAS DERMATITIS

Lacrimators such as chloroacetophenone in concentrated form may cause dermatitis, with a delayed appearance some 2472 h after exposure. Irritation or sensitization, with erythema and severe vesiculation, may result. Treatment consists of lavage of the affected skin with sodium bicarbonate solution and instillation of boric acid solution into the eyes. Contaminated clothing should be removed. Sulfur mustard gas, also known as yperite, has been used in chemical warfare such as in the Iraq-Iran war. Erythema, vesicles, and bullae, followed by healing with hyperpigmentation over a 1-week period, result from mild to moderate exposure. Toxic epidermal necrolysis (TEN)-like appearance may follow more concentrated contact. The earliest and most frequently affected sites are areas covered by clothing and humidified by sweat, such as the groin, axilla, and genitalia.

Mace is a mixture of tear gas (chloroacetophenone) in trichloroethane and various hydrocarbons resembling kerosene. It is available in a variety of self-defense sprays. It is a potent irritant and may cause allergic sensitization.

Treatment consists of changing clothes, then washing with oil or milk, followed by washing with copious amounts of water.

CHLORACNE

Workers in the manufacture of chlorinated compounds may develop chloracne, with small straw-colored follicular plugs and papules, chiefly on the malar crescent, retroauricular areas, earlobes, neck, shoulders, and scrotum. The synthetic waxes chloronaphthalene and chlorodiphenyl, used in the manufacture of electric insulators and in paints, varnishes, and lacquers, similarly predispose workers engaged in the manufacture of these synthetic waxes to chloracne. Exposure to 2, 6-dichlorobenzonitrile during the manufacture of a herbicide, and to 3,4,3',4'-tetrachloroazooxybenzene, which is an unwanted intermediate byproduct in the manufacture of a pesticide, may also produce chloracne. A contaminant in the synthesis of herbicides and hexachlorophene, 2,3,7,8-tetracholorodibenzopdioxin, produces a chemical burn in the acute stage, but chloracne, hyperpigmentation, hirsutism, and skin fragility (with or without criteria for porphyria cutanea tarda) are manifestations of chronic toxicity. Gastrointestinal tract cancer and malignancies of the lymphatic and hematopoietic systems are suspected to result but the studies are still inconclusive. While contact is the usual method of exposure, inhalation, ingestion, or contact with contaminated clothing may also result in chloracne. Chloracne may persist for long periods because dioxin is stored in the liver and released slowly into the circulation. Treatment is with medications used in acne vulgaris, including isotretinoin.

HYDROCARBONS

Many hydrocarbons produce skin eruptions. Crude petroleum causes generalized itching, folliculitis, or acneiform eruptions. The irritant properties of petroleum derivatives are directly proportional to their fat-solvent properties and inversely proportional to their viscosity. Oils of the naphthalene series are more irritating than those of the paraffin series. Refined fractions from petroleum are

less irritating than the unrefined products, although benzene, naphtha, and carbon disulfide may cause a mild dermatitis. Lubricating and cutting oils are causes of similar cutaneous lesions. They represent a frequent cause of occupational dermatoses in machine tool operators, machinists, layout men, instrument makers, and set-up men. Insoluble (neat) cutting oils are responsible for a follicular acneiform eruption on the dorsa of the hands, the forearms, face, thighs, and back of the neck. Hyperpigmentation, keratoses, and scrotal cancer have been found in those exposed to insoluble cutting oils. Soluble oils and synthetic fluids used in metalworking do not result in acne, but rather an eczematous dermatitis, usually of the dorsal forearms and hands. Approximately 50% of the time it is irritant and in the remainder it is allergic. Allergic contact dermatitis arises from various additives, such as biocides, coloring agents, and deodorizers. Coal briquette makers develop dermatitis as a result of a tarry residue from petroleum used in their trade. Paraffin exposure leads to pustules, keratoses, and ulcerations. Shale oil workers develop an erythematous, follicular eruption that eventually leads to keratoses, which may become the sites of carcinoma. It is estimated that 50% of shale oil workers have skin problems. Impure and lowgrade paraffins and mineral oils cause similar skin eruptions. Initially, the skin changes are similar to those in chloracne. In due time, a diffuse erythema with dappled pigmentation develops. Gradually, keratoses appear, and after many years some of these are the sites of carcinoma. Melanoderma may occur from exposure to mineral oils and lower-grade petroleum, from creosote, asphalt, and other tar products. Photosensitization may play a role. Creosote is a contact irritant, sensitizer, and photosensitizer. Allergy is demonstrated by patch testing with 10% creosote in oil. Petrolatum dermatitis may appear as a verrucous thickening of the skin caused by prolonged contact with impure petroleum jelly or, occasionally, lubricating oil. A follicular centered process may occur in which erythematous horny nodules are present, usually on the anterior and inner aspects of the thighs. There are no comedones and the lesions are separated by apparently normal skin. Acne corne consists of follicular keratosis and pigmentation resulting from crude petroleum, tar oils, and

paraffin. The dorsal aspects of the fingers and hands, the arms, legs, face, and thorax are the areas usually involved. The lesions are fol- licular, horny papules, often black, and are associated at first with a follicular erythema and later with a dirty brownish or purplish spotty pigmentation, which in severe cases becomes widespread and is especially marked around the genitals. This syndrome may simulate pityriasis rubra pilaris or lichen spinulosus. Coal tar and pitch and many of their derivatives produce photosensitization and an acneiform folliculitis of the forearms, legs, face, and scrotum. Follicular keratoses (pitch warts) may develop and later turn into carcinoma. Soot, lamp black, and the ash from peat fires produce dermatitis of a dry, scaly character, which in the course of time forms warty outgrowths and cancer. Chimney sweep's cancer occurs under a soot wart and is usually located on the scrotum, where soot, sebum, and dirt collect in the folds of the skin. This form of cancer has virtually disappeared. Acquired perforating disease may occur in oil field workers who use drilling fluid containing calcium chloride. Patients develop tender, umbilicated papules of the forearms that microscopically show transepidermal elimination of calcium.

SOLVENTS

These cause approximately 10% of occupational dermatitis. When they are applied to the hands to cleanse them, the surface oil is dissolved and a chronic fissured dermatitis results. Additionally, peripheral neuropathy and chemical lymphangitis may occur after the solvents are absorbed through the fissured skin. Solvent sniffers may develop an eczematous eruption about the mouth and nose. There is erythema and edema. It is a direct irritant dermatitis caused by the inhalation of the solvent placed on a handkerchief. Trichloroethylene is a chlorinated hydrocarbon solvent and degreasing agent, and is also used in the dry-cleaning and refrigerant industry. Inhalation may produce exfoliative erythroderma, mucous membrane erosions, eosinophilia, and hepatitis. Allergic contact dermatitis caused by alcohol is rarely encountered with lower aliphatic alcohols. A severe case of bullous and hemorrhagic dermatitis on the fingertips and

deltoid region was caused by isopropyl alcohol. Though rare, ethyl alcohol dermatitis may also be encountered. Cetyl and stearyl alcohols may provoke contact urticaria.

ALLERGIC CONTACT DERMATITIS

Allergic contact dermatitis results when an allergen comes into contact with previously sensitized skin. It is due to a specific acquired hypersensitivity of the delayed type, also known as cell-mediated hypersensitivity or immunity. Occasionally, dermatitis may be induced when the allergen is taken internally by a patient first sensitized by topical application; this occurs, for example, with substances such as cinnamon oil or various medications. The anamnestic response is termed systemic contact dermatitis. It may appear first at the site of the prior sensitization or past positive patch test, but may spread to a generalized morbilliform or eczematous eruption. Additional morphologic patterns include vesicular hand eczema, urticaria, erythema multiforme, vasculitis, or the baboon syndrome. The latter is a deep red-violet eruption on the buttocks, genital area, inner thighs, and sometimes axilla. The most common causes of contact dermatitis in the US are: toxicodendrons (poison ivy, oak, or sumac), nickel, balsam of Peru (Myroxylon pereirae), neomycin, fragrance, thimerosal, gold, formaldehyde and the formaldehyde-releasing preservatives, bacitracin, and rubber compounds. Frequent positive reactions to thimerosal do not often correlate with clinical exposure histories. These reactions are probably related to its use as a preservative in commonly administered vaccines and skintesting material. It also serves as a marker for piroxicam photosensitivity. These sensitizers do not cause demonstrable skin changes on initial contact. Persons may be exposed to allergens for years before finally developing hypersensitivity. Once sensitized, however, subsequent outbreaks may result from extremely slight exposure.

When allergens are applied to the skin, Langerhans cells in the epidermis process them and display them in a complex with human leukocyte antigen (HLA)-DR on their surface. This is presented to a CD4+ T cell, interaction with the T-cell

receptor-CD3 complex occurs, and the allergen is recognized. This leads to proliferation and recruitment of lymphocytes with release of vasoactive substances and direct inflammatory mediators. Genetic variability in these processes and other factors, such as concentration of the allergen applied, its vehicle, timing and site of the exposure, presence of occlusion, age, sex, and race of the patient, and presence of other skin or systemic disorders, likely determine whether any given exposure will result in sensitization. Eczematous delayedtype hypersensitivity reaction, as exemplified by allergic contact dermatitis and the patch test, must be distinguished from immediate-type hypersensitivity reactions. The latter presents within minutes of exposure with urticaria and is proven with a scratch test. It should be kept in mind, however, that persons who develop contact urticaria to a substance may concomitantly have a type IV delayedtype sensitization and eczema from the same allergen. In some instances, impetigo, pustular folliculitis, and irritations or allergic reactions from applied medications are superimposed on the original dermatitis. A particularly vexing situation is when allergy to topical steroids complicates an eczema, in which case the preexisting dermatitis usually does not flare, but simply does not heal as expected. The cutaneous reaction may also provoke a hypersusceptibility to various other previously innocuous substances, which continues the eczematous inflammatory response indefinitely. These eruptions resolve when the cause is identified and avoided. For acute generalized allergic contact dermatitis treatment with systemic steroidal agents is effective, beginning with 40-60 mg/day prednisone in a single oral dose, and tapering slowly to topical steroids. When the eruption is limited in extent and severity, local application of topical corticosteroid creams, lotions, or aerosol sprays is preferred.

TESTING FOR SENSITIVITY

PATCH TEST

The patch test is used to detect hypersensitivity to a substance that is in contact with the skin so that the allergen may be determined and corrective measures taken. So many allergens can cause allergic contact dermatitis that it is

impossible to test a person for all of them. In addition, a good history and observation of the pattern of the dermatitis, its localization on the body, and its state of activity are all helpful in determining the cause. The patch test is confirmatory and diagnostic, but only within the framework of the history and physical findings; it is rarely helpful if it must stand alone. Interpretation of the relevance of positive tests and the subsequent education of patients are challenging in some cases. The Contact Allergen Avoidance Database (CARD) provides names of alternative products that may be used by patients when an allergen is identified. This is available through the American Contact Dermatitis Society. The patch test consists of application of substances suspected to be the cause of the dermatitis to intact uninflamed skin. Patch testing may be administered by the thinlayer rapid-use epicutaneous (TRUE) test or by individually prepared aluminum (Finn) chambers mounted on Scanpor tape. The TRUE test has resulted in more screening for allergic contact dermatitis than in the past; however, if this test does not reveal the allergen for a highly suspect dermatitis, testing with an expanded series by the Finn chamber technique may yield relevant allergens in more than half of these patients. Test substances are applied usually to the upper back, although if only one or two are applied, the upper outer arm may be used. Each patch should be numbered to avoid confusion. The patches are removed after 48 h (or sooner if severe itching or burning occurs at the site) and read. The patch sites need to be evaluated again at day 4 or 5 because positive reactions may not appear earlier. Some allergens may take up to day 7 to show a reaction and the patient should be advised to return if such a delayed reaction occurs. Erythematous papules and vesicles with edema are indicative of allergy. Occasionally, patch tests for potassium iodide, nickel, or mercury will produce pustules at the site of the test application. Usually no erythema is produced; therefore, the reaction has no clinical significance. Strong patch-test reactions may induce a state of hyperirritability ("excited skin syndrome") in which negative tests appear as weakly positive. Weakly positive tests in the presence of strong ones do not prove sensitivity. There is wide variation in the ability of the skin and mucous membranes to react to antigens. The oral

mucosa is more resistant to primary irritants and is less liable to be involved in allergic reactions. This may be because the keratin layer of the skin more readily combines with haptens to form allergens. Also, the oral mucosa is bathed in saliva, which cleanses and buffers the area and dilutes irritants. However, patch testing for various types of oral signs and symptoms, such as swelling, tingling and burning, perioral dermatitis, and the appearance of oral lichen planus, is useful in determining a cause in many cases. The ability of the skin to react to allergens also depends on the presence of functional antigenpresenting cells, the Langerhans cells. Potent topical steroids, ultraviolet (UV) light, various immunosuppressants such as oral prednisone and the acquired immunodeficiency syndrome (AIDS) have been reported to interfere with the number and function of these key cells. False-negative reactions may result; the value of testing in such circumstances is that if a positive reaction occurs, a diagnosis may be made. Vitiliginous skin is less reactive than normally pigmented adjacent skin.

PROVOCATIVE USE TEST

The provocative use test will confirm a positive closed patchtest reaction to ingredients of a substance, such as a cosmetic; it is used to test products that are made to stay on the skin once applied. The material is rubbed on to normal skin of the inner aspect of the forearm several times a day for 5 days.

PHOTOPATCH TEST

The photopatch test is used to evaluate for contact photoallergy to such substances as sulfonamides, phenothiazines, p-aminobenzoic acid, oxybenzone, 6-methyl coumarin, musk ambrette, or tetrachlorsalicylanilide. A standard patch test is applied for 48 h; this is then exposed to 5-15 J/m2 of UVA and read after another 48 h. To test for 6-methyl coumarin sensitivity, the patch is applied in the same manner but for only 30 min before light exposure, rather than for 48 h. A duplicate set of nonirradiated patches is used in testing for the presence of routine delayed hypersensitivity reactions. Also, a site of normal skin is given an identical

dose of UVA to test for increased sensitivity to light without prior exposure to chemicals. There is a steady increase in incidence of photoallergy to sunscreening agents and a falling incidence of such reactions to fragrance.

REGIONAL PREDILECTION

Familiarity with certain contactants and the typical dermatitis they elicit on specific parts of the body will assist in diagnosis of the etiologic agent.

HEAD AND NECK

The scalp is relatively resistant to the development of contact allergies; however, involvement may be caused by hair dye, hair spray, shampoo, or permanent wave solutions. The surrounding glabrous skin, including the ear rims and backs of the ears, may be much more inflamed and suggestive of the cause. Persistent otitis of the ear canal may be caused by sensitivity to the neomycin that is an ingredient of most aural medications. The eyelids are the most frequent site for nail polish dermatitis. Volatile gases, falseeyelash adhesive, fragrances, preservatives, mascara, rubber in sponges used to apply cosmetics, and eyeshadow are also frequently implicated. Perioral dermatitis and cheilitis may be caused by flavoring agents in dentifrices and gum, as well as fragrances, shellac, medicaments, and sunscreens in lipstick and lip balms. Perfume dermatitis may cause redness just under the ears or on the neck. Earlobe dermatitis is indicative of nickel sensitivity. Photocontact dermatitis may involve the entire face and may be sharply cut off at the collar line or extend down on to the sternum in a V shape. There is a typical clear area under the chin where there is little or no exposure to sunlight. In men, in whom shaving lotion fragrances may be responsible, the left cheek and left side of the neck (from sun exposure while driving) may be the first areas involved.

TRUNK

The trunk is an infrequent site; however, the dye or finish of clothing may cause dermatitis. The axilla may be the site of deodorant and clothingdye

dermatitis. Involvement of the axillary vault suggests the former; of the axillary folds, the latter. In women, brassieres cause dermatitis from either the material itself, the elastic, or the metal snaps or underwires.

ARMS

The wrists may be involved because of jewelry or the backs of watches and clasps, all of which may contain nickel. Wristbands made of leather are a source of chrome dermatitis.

HANDS

Innumerable substances may cause allergic contact dermatitis of the hands, which typically occurs on the backs of the hands and spares the palms. Florists will often develop fingertip or palmar lesions. A hand dermatitis that changes from web spaces to fingertips or from palms to dorsal hands should trigger patch testing. Poison ivy and other plant dermatitides frequently occur on the hands and arms. Rubber glove sensitivity must be kept constantly in mind. Usually irritancy is superimposed on allergic contact dermatitis of the hands, altering both the morphologic and histologic clues to the diagnosis.

ABDOMEN

The abdomen, especially the waistline, may be the site of rubber dermatitis from the elastic in pants and undergarments. The metallic rivets in blue jeans may lead to periumbilical dermatitis in nickelsensitive patients, as may piercings of the umbilicus.

GROIN

The groin is usually spared, but the buttocks and upper thighs may be sites of dermatitis caused by dyes. The penis is frequently involved in poison ivy dermatitis. Condom dermatitis may also occur. The perianal region may be involved from the "caine" medications in suppositories, as well as preservatives and fragrances in cleansing materials. Nearly half of women with pruritus vulvae

have one or more relevant allergens; often these are medicaments, fragrances, or preservatives.

LOWER EXTREMITIES

The shins may be the site of rubber dermatitis from elastic stockings. Feet are sites for shoe dermatitis, most often attributable to rubber sensitivity, chrometanned leather, dyes, or adhesives. Application of topical antibiotics to stasis ulcers commonly leads to sensitivity and allergic contact dermatitis.

DERMATITIS RESULTING FROM PLANTS

A large number of plants, including trees, grasses, flowers, vegetables, fruits, and weeds, are potential causes of dermatitis. Eruptions from them vary considerably in appearance but are usually vesicular and accompanied by marked edema. After previous exposure and sensitization to the active substance in the plant, the typical dermatitis results from re-exposure. The onset is usually a few hours or days after contact. The characteristic linearly grouped lesions are probably produced by brushing the skin with a leaf edge or a broken twig, or by carriage of the allergen under the nails. Contrary to general belief, the contents of vesicles are not capable of producing new lesions.

TOXICODENDRON (POISON IVY)

Toxicodendron dermatitis includes dermatitis from members of the Anacardiaceae family of plants: poison ivy, poison oak, poison sumac, Japanese lacquer tree, cashew nut tree (the allergen is in the nutshell), mango (the allergen is in the rind, leaves, or sap), Rengas tree, and Indian marking nut tree. The ginkgo (the allergen is in the fruit pulp), spider flower or silver oak, Gluta species of trees and shrubs in Southeast Asia, Brazilian pepper tree, also known as Florida holly, and poisonwood tree contain nearly identical antigens. Toxicodendron dermatitis appears within 48 h of exposure of a person previously sensitized to the plant. It usually begins on the backs of the fingers, interdigital spaces, wrists, and eyelids, although it may begin on the ankles or other parts that have been exposed. Marked

pruritus is the first symptom; then. Poison ivy species found commonly in the eastern US. (Courtesy of James WD [ed]: Textbook of Military Medicine. Office of the Surgeon General, United States Army, 1994) inflammation, vesicles, and bullae may appear. The vesicles are usually grouped and often linear. Large bullae may be present, especially on the forearms and hands. The eyelids are puffy; they will be worst in the morning and improve as the day progresses. Pruritus ani and involvement of the genital areas occur frequently. A black lacquer deposit may occur in which the sap of the plant has been oxidized after being bound to the stratum corneum. Untreated toxicodendron dermatitis usually lasts 2-3 weeks. The fingers transfer the allergen to other parts, especially the forearms and the male prepuce, which become greatly swollen. However, once the causative oil has been washed off, there is no spreading of the allergen and no further spread of the dermatitis. Some persons are so susceptible that direct contact is not necessary, the allergen apparently being carried by the fur of their pets or by the wind. It can also be acquired from golf clubs or fishing rods, or even from furniture that a dog or cat might have occupied after exposure to the catechol. Occasionally, eating the allergen, as occurred in a patient who ingested raw cashew nuts in an imported pesto sauce, may result in the baboon syndrome (a deep red-violet eruption on the buttocks, genital area, inner thighs, and sometimes axilla), or a systematized allergic contact dermatitis with the morphology of a generalized erythematous papular eruption. The cause is an oleoresin known as urushiol, of which the active agent is a mixture of catechols. This and related resorcinol allergens are present in many plants and also in phi- lodendron species, wood from Persoonia elliptica, wheat bran, and marine brown algae. The most striking diagnostic feature is the linearity of the lesions. It is rare to see vesicles arranged in a linear fashion except in plant-induced dermatitis. A history of exposure in the country or park to plants that have shiny leaves in groups of three, followed by the appearance of vesicular lesions within 2 days, usually establishes the diagnosis. Persons with known susceptibility not only should avoid touching plants having the grouped "leaves-of-three," but should also exercise care in handling articles of clothing, tools, toys,

and pets that have come in contact with such plants. Eradication of these plants growing in frequented places is one easy preventive measure, as is recognition of the plants to avoid. An excellent resource is a pamphlet available from the American Academy of Dermatology. If the individual is exposed, washing with soap and water within 5 min may prevent an eruption. Protective barrier creams are available that are somewhat beneficial. Quaternium-18 bentonite has been shown to prevent or diminish experimentally produced poison ivy dermatitis. Innumerable attempts have been made to immunize against poison ivy dermatitis by oral administration of the allergen, or subcutaneous injections of oily extracts. To date, no accepted method of immunization is available. Repeated attacks do not confer immunity, although a single severe attack may achieve this by what has been called massive-dose desensitization. When the diagnosis is clear and the eruption severe or extensive, systemic steroidal agents are effective, beginning with 40-60 mg of prednisone in a single oral dose daily, tapered off over a 3-week period. When the eruption is limited in extent and severity, local application of topical corticosteroid creams, lotions, or aerosol sprays is preferred. Time-honored calamine lotion without phenol is helpful and does no harm. Antihistaminic ointments should be avoided because of their sensitization potential. This also applies to the local application of the "caine" topical anesthetics.

OTHER TOXICODENDRON-RELATED DERMATITIS

Lacquer dermatitis is caused by a furniture lacquer made from the Japanese lacquer tree, used on furniture, jewelry, or bric- a-brac. Antique lacquer is harmless, but lacquer less than 1 or 2 years old is highly antigenic. Cashew nutshell oil is extracted from the nutshells of the cashew tree (Anacardium occidentale). This vesicant oil contains cardol, a phenol similar to urushiol in poison ivy. The liquid has many commercial applications, such as the manufacture of brake linings, varnish, synthetic glue, paint, and sealer for concrete. Mango dermatitis is uncommon in natives of mango- growing countries (the Philippines, Guam, Hawaii, Cuba) who have never been exposed to contact with toxicodendron

species. Many persons who have been so exposed, however, whether they had dermatitis from it or not, are sensitized by one or a few episodes of contact with the peel of the mango fruit. The palms carry the allergen, so the eyelids and the male prepuce are often early sites of involvement. Sponging all contaminated or itchy areas meticulously and systematically with equal parts of ether and acetone at the outset will often remove the oleoresin and ameliorate any worsening of the dermatitis, which can be treated with topical or oral steroids as needed. Ginkgo tree dermatitis simulates toxicodendron dermatitis with its severe vesiculation, erythematous papules, and edema. The causative substances are ginkgolic acids from the fruit pulp of the ginkgo tree. Ingestion of the ginkgo fruit may result in perianal dermatitis. Ginkgo biloba given orally for cerebral disturbances is made from a leaf extract so it does not elicit a systemic contact allergy when ingested.

FLOWERS AND HOUSEPLANTS

Among the more common houseplants, the velvetyleafed philodendron, Philodendron crystallinum (and its several variants), known in India as the money plant, is a frequent cause of contact dermatitis. The eruption is often seen on the face, especially the eyelids, carried there by hands that have watered or cared for the plant. English ivy follows philodendron in frequency of cases of occult contact dermatitis. Primrose dermatitis affects the fingers, eyelids, and neck with a punctate or diffuse erythema and edema. It was formerly most frequently encountered in Europe; however, the primrose is now a common houseplant in the US. Primin, a quinone, is the causative oleoresin abounding in the glandular hairs of the plant.

PRIMULA OBCONICA.

The popular cut flower, the Peruvian lily, is the most common cause of allergic contact dermatitis in florists. When handling flowers of the genus Alstroemeria the florist utilizes the thumb, and second and third digits of the dominant hand. Since it is chronic, fissured hyperkeratotic dermatitis results and is

identical to the so-called tulip fingers seen among sensitized tulip workers. Testing is done with the allergen tuliposide A. It does not penetrate nitrile gloves. Chrysanthemums frequently cause dermatitis, with the hands and eyelids of florists most commonly affected. The a-methylene portion of the sesquiterpene lactone molecule is the antigenic site, as it is in the other genera of the Compositae family. A severe inflammatory reaction with bulla formation may be caused by the prairie crocus (Anemone patens L), the floral emblem of the province of Manitoba. Several species of orna mental "bottle brush" from Queensland, Grevillea banksii, G. Robyn Gordon, and G. robusta, may cause allergic contact dermatitis. It is exported to the US and other Western countries. The allergen is a long-chain alkyl resorcinol. A cross-sensitivity to toxicodendron has been demonstrated. Contact dermatitis may be caused by handling many other flowers, such as the geranium, scorpion flower (Phacelia crenu- lata or campanularia), hydrangea, creosote bush (Larvia triden- tata), Heracula, daffodil, foxglove, lilac, lady slipper, magnolia, and tulip and narcissus bulbs. The poinsettia and oleander almost never cause dermatitis, despite their reputation for it, although they are toxic if ingested. Treatment of all these plant dermatitides is the same as that recommended for toxicoden- dron dermatitis. Parthenium hysterophorus, a photosensitizing weed, was accidentally introduced into India in 1956 and has spread over most of the country; it is also spreading in Australia, China, and Argentina. The welldeserved reputation for harmfulness of dieffenbachia, a common, glossyleafed house plant, rests on the high content of calcium oxalate crystals in its sap, which burn the mouth and throat severely if any part of the plant is chewed or swallowed. Severe edema of the oral tissues may result in complete loss of voice; hence its common nickname, "dumb cane." It does not appear to sensitize. The castor bean, the seed of Ricinus communis, contains ricin, a poisonous substance (phytotoxin). Its sap contains an antigen that may cause anaphylactic hypersensitivity and also dermatitis.

FRUIT AND VEGETABLES

Many vegetables may cause contact dermatitis, including asparagus, carrot, celery, cow-parsnip, cucumber, garlic, Indian bean, mushroom, onion, parsley, tomato, and turnip. Onion and celery, among other vegetables, have been incriminated in the production of contact urticaria and even anaphylaxis. Several plants, including celery, fig, lime, and parsley, can cause a phototoxic dermatitis because of the presence of psoralens.

TREES

Trees whose timber and sawdust may produce contact dermatitis include ash, birch, cedar, cocobolo, elm, Kentucky coffee tree, koa, mahogany, mango, maple, mesquite, milo, myrtle, pine, and teak. The latex of fig and rubber trees may also cause dermatitis, usually of the phototoxic type. Melaleuca oil (tea tree oil), which may be applied to the skin to treat a variety of maladies, can cause allergic contact dermatitis, primarily through the allergen D-limonene. The exotic woods, especially cocobolo and rosewood, and tea tree oil are prominent among allergens that may produce erythema multiforme after cutaneous exposure. Toxicodendron, various medicaments, and a variety of other allergens may induce this reaction.

TREE-ASSOCIATED PLANTS

Foresters and lumber workers can be exposed to allergenic plants other than trees. Lichens are a group of plants composed of symbiotic algae and fungi. Foresters and wood choppers exposed to these lichens growing on trees may develop severe allergic contact dermatitis. Exposure to the lichens may also occur from firewood, funeral wreaths, and also fragrances added to aftershave lotions (oak moss and tree moss). Sensitization is produced by D-usnic acid and other lichen acids contained in lichens. The leafy liverwort (Frullania nisquallansis), a forest epiphyte growing on tree trunks, has produced allergic dermatitis in forest workers. The eruption is commonly called cedar poisoning. It resembles

toxicodendron dermatitis; its attacks are more severe during wet weather. The allergen is sesquiterpene lactone.

POLLENS AND SEEDS

The pollens in ragweed are composed of two antigens. The protein fraction causes the respiratory symptoms of asthma and hay fever, and the oil-soluble portion causes contact dermatitis. Ragweed oil dermatitis is a seasonal disturbance seen mainly during the ragweed growing season from spring to fall. Contact with the plant or with wind-blown fragments of the dried plant produces the typical dermatitis. The oil causes swelling and redness of the lids and entire face, and a red blotchy eruption on the forearms that, after several attacks, may become generalized, with lichenification. It closely resembles chronic atopic dermatitis, with lichenification of the face, neck, and major flexures, and severe pruritus. The distribution also mimics that of photodermatitis, the differentiating point being that in ragweed dermatitis there is involvement of the upper eyelids and the retroauricular and submental areas. Chronic cases may continue into the winter; however, signs and symptoms are most severe at the height of the season. Sesquiterpene lactones are the cause. Coexistent sensitization to pyrethrum may account for prolongation of ragweed dermatitis. Men outnumber women in hypersensitivity reactions; farmers outnumber patients of all other occupations.

MARINE PLANTS

Numerous aquatic plants are toxic or produce contact dermatitis. Algae are the worse offenders. Freshwater plants are rarely of concern. Seaweed dermatitis is a type of swimmer's eruption produced by contact with a marine blue-green alga, which has been identified as Lyngbya majuscula Gomont. The onset is within a few minutes of leaving the ocean, with severe itching and burning, followed by dermatitis, blisters, and deep and painful desquamation that affects the areas covered by the bathing suit (in men, especially the scrotum, perineum, and perianal areas; occasionally, in women, the breasts). Patch tests with the alga are neither

necessary nor helpful, since it is a potent irritant. Bathing in fresh water within 10 or 15 min of leaving the ocean may prevent the dermatitis. The Bermuda fire sponge may produce contact erythema multiforme. Trawler fishermen in the Dogger Bank area of the North Sea develop allergic dermatitis after contact with Alcyonidium hir- sutum. This is a seaweedlike animal colony that becomes caught in the fishermen's net and produces erythema, edema, and lichenification on the hands and wrists.

PLANT-ASSOCIATED DERMATITIS

The residua of various insecticides on plants may also produce dermatitis. This is especially true of arsenic- and malathioncontaining sprays. Randox (2-chloro-N, N-diallylacetamide) has been reported as the cause of hemorrhagic bullae on the feet of farmers. Lawn-care companies spray herbicides and fungicides throughout the spring, summer, and fall. Dryene, thiuram, carbamates, and chlorothalonil are potential sensitizers in these workers, whose clothing frequently becomes wetted while spraying.

Barbs, bristles, spines, thorns, spicules, and cactus needles are some of the mechanical accessories of plants that may produce dermatitis. Sabra dermatitis is an occupational dermatitis resembling scabies. It is seen among pickers of the prickly pear cactus plant. It also occurs in persons handling Indian figs in Israel, where the condition is seen from July to November. The penetration of minute, invisible thorns into the skin is the cause. Agave americana is a lowgrowing plant grown for ornamental purposes in many Southwestern communities. Trimming during landscaping can induce an irritant dermatitis caused by calcium oxalate crystals. The stinging nettle is a common weed that bears tiny spines with biologically active substances such as histamine that produce itching and urticaria within minutes of contact.

PLANT DERIVATIVES

Sensitizing substances derived from plants are found in the oleoresin fractions that contain camphors, essential oils, phenols, resins, and terpenes. The chief sensitizers are the essential oils. They may be localized in certain parts of the plant, such as in the peel of citrus fruits, leaves of the eucalyptus tree, and bark of the cinnamon tree. Aromatherapy, an increasingly popular treatment for relief of stress, involves either inhaling or massaging with essential oils; this may cause allergic contact dermatitis in therapists or clients. Exposure to botanical extracts through many cosmetics and homeopathic remedies has resulted in an increasing number of reports of allergic contact sensitivity to individual ingredients, especially tea tree oil. Cinnamon oil (cassia oil) is a common flavoring agent, especially in pastries. Hand dermatitis in pastry bakers is often caused by cinnamon. It is also used as a flavor for lipstick, bitters, alcoholic and nonalcoholic beverages, toothpaste, and chewing gum. Perioral dermatitis may be caused by cinnamon in chewing gum. A 5% cinnamon solution in olive oil is used for patch testing. Eugenol, clove oil, and eucalyptus oil are used by dentists, who may acquire contact dermatitis from them. Anise, peppermint, and spearmint oils may cause sensitization.

Nutmeg, paprika, and cloves are causes of spice allergy. Fragrance-mix is a useful indicator allergen. Lemon oil from lemon peel or lemon wood may cause sensitization in the various handlers of these substances. Citric acid may cause dermatitis in bakers. Lime oil in limescented shaving cream or lotion may cause photoallergy. Myroxylon pereirae contains numerous substances, among which are essential oils similar to the oil of lemon peel. It is known to cross-react with vanilla and cinnamon, among many others. Vanillin is derived from the vanilla plant and frequently produces contact dermatitis, vanillism, in those connected with its production and use. Turpentine frequently acts as an irritant and as an allergic sensitizer (carene). It is contained in paints, paint thinners, varnishes, and waxes.

TESTING FOR PLANT ALLERGENS

The method of testing for plant hypersensitivity is the application of the crushed plant leaf, stem, and petal, and then covering with micropore tape. The plant should be washed thoroughly as infection with fungi from the soil may complicate testing. A test should also be performed on several controls to make sure that the leaf is not an irritant. It must be remembered that some of the plants are photosensitizers. Test sites for these must be done in duplicate, with one set kept covered and the other exposed to artificial light or sunlight for the detection of photosensitivity.

DERMATITIS FROM CLOTHING

A predisposition to contact dermatitis from clothing occurs in persons who perspire freely or who are obese and wear clothing that tends to be tight. Depending on the offending substance, various regions of the body will be affected. Regional location is helpful in identifying the sensitizing substance. The axillary folds are commonly involved; the vaults of the axillae are usually spared. Sites of increased perspiration and sites where evaporation is impeded, such as the intertriginous areas, will tend to leach dyes from fabrics to produce dermatitis. Areas where the material is tight against the skin, such as the waistband or neck, are frequently involved. The thighs are commonly affected when pants contain the offending allergen. Sparing of the hands, face, and undergarment sites is usual, but otherwise these reactions may be scattered and generalized. Secondary changes of lichenification and infection occur frequently because of the chronicity of exposure. Cotton, wool, linen, and silk fabrics were used exclusively before the advent of synthetic fabrics. Most materials are now blended in definite proportions with synthetics to produce superior lasting and esthetic properties. Dermatitis from cotton is virtually nonexistent. In most instances there is no true sensitization to wool. Wool acts as an irritant because of the barbs on its fibers. These barbs may produce severe pruritus at points of contact with the skin, especially in the intertriginous areas. In sensitive-skinned persons, such as those with atopic

dermatitis, the wearing of wool is not advisable because of its mechanical irritative properties. Silk is a sensitizer, but rarely; the nature of the allergen is not known. Many patients believe their detergent is the source of a dermatitis, but this is rarely the case. Numerous synthetic fibers are available for clothing and accessory manufacture, all of which again are remarkably free of sensitizing properties. Polyvinyl resins are the plastics used in such apparel as raincoats, rainhoods, wristbands, suspenders, plastic mittens, and gloves. These again are only infrequently found to be causes of contact dermatitis. The most common causes of clothing dermatitis are the fabric finishers, dyes, and rubber additives. Fabric finishers are used to improve the durability, appearance, and feel of a material. Antiwrinkling and crease-holding chemicals are mostly resins, which are incorporated into the fibers as they are being manufactured or applied to the completed (finished) fabric. Fabrics are treated to make them less vulnerable to the effects of perspiration and ironing. Clothing may be treated with these substances to make it dry rapidly after washing. They are used to make clothing fabrics shrink-resistant, and water- and stain-repellent. When all these uses are taken into consideration, the low incidence of dermatitis from these formaldehyde resin materials is remarkable.

Ethylene urea melamine formaldehyde resin and dimethylol dihydroxyethylene urea formaldehyde resin are the best screening agents. Many also react to formaldehyde and the formaldehyde-releasing preservatives such as quaternium-15. Avoidance of exposure of the skin to formaldehyde resin is most difficult. New clothes should be thoroughly washed twice before wearing the first time. Even with this precaution, however, allergens may still be present in sufficient quantities to continue the dermatitis. Jeans, Spandex, silk, 100% linen, 100% nylon, and 100% cotton that is not wrinkle-resistant or colorfast are best tolerated. T-shirts, sweat shirts, sweat pants, white underclothes suitable for bleaching, and any type of mixed synthetic fibers with cotton fibers that are added to make them drip-dry are most likely to cause problems in these patients. An increasing number of patients allergic to clothing dye are being reported. Synthetic

fabrics such as polyester and acetate liners in women's clothing are prime causes, and affected patients are more commonly women than men. Even infants may be affected, however, with dyes in diapers accounting for five cases reported by Alberta et al. In many cases patients do not react to paraphenylene diamine, but only to the disperse dye allergens. The best screening agents are disperse blue 106 and 124. Suspected fabrics may be soaked in water for 15 min and applied under a patch for 72-96 h. Spandex is a nonrubber (but elastic) polyurethane fiber. It is widely used for garments such as girdles, brassieres, and socks, but is generally safe in the US, as it is free of rubber additives.

SHOE DERMATITIS

Footwear dermatitis may begin on the dorsal surfaces of the toes and may remain localized to that area indefinitely. There is erythema, lichenification, and, in severe cases, weeping and crusting. Secondary infection is frequent. In severe cases an id reaction may be produced on the hands similar to the reaction from fungus infection of the feet. A diagnostic point is the normal appearance of the skin between the toes, which has no contact with the offending substance. In fungus infections the toe webs are usually involved. Another pattern seen is involvement of the sole with sparing of the instep and flexural creases of the toes. Also purpuric reactions to components of black rubber mix may occur. Hyperhidrosis and atopy predispose to the development of shoe allergy. Shoe dermatitis is most frequently caused by the rubber accelerators mercaptobenzothiazole, carbamates, and tetra-methylthiuram disulfide. Potassium dichromate in leather and the adhesives used in synthetic materials (especially p-tertbutylphenol formaldehyde resin) are also common shoe allergens. Diisocyanates are used in making foam rubber padding for athletic shoes and may cause allergy. Other causative agents are felt, cork liners, formaldehyde, dyes, asphalt, dimethyl fumarate and tar. Patch testing with pieces of various shoe parts may be done by soaking them for 15 min in water and applying them to the back for 72-96 h. Once the allergen has been identified, selection of shoes without the offending substance will lead to resolution. This is,

unfortunately, a difficult process, as most shoes are made in areas without mandatory labeling requirements, and plastic, wooden, or fabric shoes which contain fewer allergens are often impractical.

DERMATITIS FROM METALS AND METAL SALTS

Metal dermatitis is most frequently caused by nickel and chro- mates. Usually, with the exception of nickel, the pure metals generally do not cause hypersensitivity; it is only when they are incorporated into salts that they cause reactions. Most objects containing metal or metal salts are combinations of several metals, some of which may have been used to plate the surface, thereby enhancing its attractiveness, durability, or tensile strength. For this reason suspicion of a metal-caused dermatitis should be investigated by doing patch tests to several of the metal salts. Patients have been reported who developed a variety of dermatoses, most often eczematous in type, after placement of an orthopedic implant or an endovascular device. Reed et al and Honari et al have published recent reviews of these two situations. In general, patch testing prior to placement may help guide the specific type of device to be utilized. However, patch testing after placement to evaluate a new eruption is rarely useful. A positive diagnosis of allergy requires at a minimum the appearance of a chronic dermatitis after placement, no other cause, a positive patch test for the suspected metal (or in the case of drug-eluting stents, the drug), and healing after removal. This scenario is exceedingly uncommon; removal of a foreign material rarely results in cure.

BLACK DERMATOGRAPHISM

Black or greenish staining under rings, metal wristbands, bracelets, and clasps is caused by the abrasive effect of cosmetics or other powders containing zinc or titanium oxide on gold jewelry. This skin discoloration is black because of the deposit of metal particles on skin that has been powdered and that has metal, such as gold, silver, or platinum, rubbing on it. Abrasion of the metal results from

the fact that some powders are hard (zinc oxide) and are capable of abrading the metal.

NICKEL

Because we are all constantly exposed to nickel, nickel dermatitis is a frequent occurrence. While still most frequent among women, sensitization is increasing among men. A direct relationship between prevalence of nickel allergy and number of pierced sites has been documented. Nickel produces more cases of allergic contact dermatitis than all other metals combined. Erythematous and eczematous eruptions, sometimes with lichenification, appear beneath earrings, bracelets, rings, wrist watches, clasps, and blue-jeans buttons. The snaps on clothing have been implicated in producing allergy in children; nickel is the most common cause of allergic contact dermatitis in children as well as adults. Several patients with dermatitis on one ear or the preauricular area have been reported to be allergic to their cell phone. The metal portion is often nickel-containing, with this being the implicated allergen. Euro coins have enough nickel in them to elicit allergic responses in nickelsensitive individuals; however, coins are rarely a cause of hand dermatitis. Nickel ranks highly on lists of occupationally induced allergic contact dermatitis.

Nickel dermatitis is seen most frequently on the earlobes. Piercing the earlobes with nickel-plated instruments or wearing nickelplated jewelry readily induces nickel sensitivity. Earlobes should be pierced only with stainless steel instruments, and only stainless steel earrings should be worn until the ears have healed. Exposure to the metal may not be readily adults. Several patients with dermatitis on one ear or the preauricular area have been reported to be allergic to their cell phone. The metal portion is often nickelcontaining, with this being the implicated allergen. Euro coins have enough nickel in them to elicit allergic responses in nickel-sensitive individuals; however, coins are rarely a cause of hand dermatitis. Nickel ranks highly on lists of occupationally induced allergic contact dermatitis. Nickel dermatitis is seen most frequently on the earlobes. Piercing the

earlobes with nickel-plated instruments or wearing nickelplated jewelry readily induces nickel sensitivity. Earlobes should be pierced only with stainless steel instruments, and only stainless steel earrings should be worn until the ears have healed. Exposure to the metal may not be readily apparent most of the time. Even in gold jewelry the clasps and solder may contain nickel. Nickel objects may be plated with chrome and yet cause nickel dermatitis through the leaching of some of the nickel through the small pores of the chromium plating. Nickel oxides in green paints may produce nickel dermatitis. Homeopathic and complementary medicaments may also contain enough nickel to produce a contact allergy. Sweat containing sodium chloride may combine with nickel to form nickel chloride. This affects the degree of nickel dermatitis, it being more severe in persons who perspire profusely. The diagnosis is established by a positive patch-test reaction to nickel sulfate. Nickel may be detected by applying a freshly prepared 1% alcohol solution of dimethylglyoxime and a 10% aqueous solution of ammonia separately in equal amounts to the test object. In the presence of nickel, the cotton swab used to apply the solution will turn orangepink. A positive test always means that nickel is present, but a negative test does not rule out its presence. Sweat, blood, or saline may leach nickel from stainless steel.

Prophylactic measures should include the reduction of perspiration in those sensitive to nickel. Topical corticosteroids applied before exposure to nickel, such as before putting on a wrist band, may be successful. Clasps and other objects are available in plastic material so that some of the exposure to nickel may be decreased. Polyurethane varathane 91 (Flecto) applied in three coats will give protection for several months. Treatment of nickel dermatitis consists of the application of topical corticosteroids. In Europe laws regulating the maximum content of nickel in jewelry are in force; this has led to a marked decrease in sensitization. Efforts to enact a similar standard in the US are under way. Hand eczema and pompholyx in nickel- or cobalt-sensitive patients has rarely been aggravated by orally ingested metals in the diet. In severe, treatment-resistant dermatitis a specific diet low in nickel and cobalt may be tried.

CHROMIUM

The chromates are strongly corrosive and irritating to the skin; they may act as primary irritants or as sensitizers to produce allergic contact dermatitis. Aside from occurrence among employees in chromate works, chrome dermatitis is encountered among tanners, painters, dyers, photographers, polishers, welders, aircraft workers, diesel engine workers, and those involved with the bleaching of crude oils, tallows, and fats. Traces of dichromates in shoe leather and gloves may cause eczema of the feet and hands. Many zippers are chromiumplated, and the nickel underneath the plate may be the causative agent. Chromium metal and stainless steel do not produce contact dermatitis. Zinc chromate paint is a source of dermatitis. Matches, hide glues, chrome alloys, cigarette lighters, and leather hatbands, sandals, or camera cases may cause chrome dermatitis. Anticorrosion solutions used for refrigeration and other recirculation systems often contain chromates that produce dermatitis. Most individuals in the cement industry suffering from cement eczema show positive patch tests to dichromates. Cement eczema is often a primary irritant dermatitis complicated by allergic contact dermatitis to the hexavalent chro- mates. The incidence of cement dermatitis has decreased significantly over the years, which is believed to be because of the addition of ferrous sulfate, delivery of premixed cement to the job site, and improved education. The skin changes are multiform, ranging from a mild follicular dermatitis to widespread nodular and crusted eruptions, all being worse on exposed parts. Often they are slow to clear up, lasting from a few weeks to 6 months after contact has ceased. Heavy exposure of industrial workers to chromates may produce chrome ulcers on the backs of the hands and forearms, usually beginning around a hair follicle, or in the creases of the knuckles or finger webs. The hole begins as a small abrasion that deepens and widens as its edges grow thick, eventually forming a conical indolent ulceration. Chrome ulcers may also arise on and perforate the nasal septum. Arsenic exposure may result in similar ulcers Diagnosis of chrome sensitivity is made by a positive patch test to potassium dichromate in petrolatum. The hexavalent chrome compounds are the

most frequent cause of chrome dermatitis since they penetrate the skin more easily than the trivalent form. Both forms are sensitizers. Even with avoidance of chromate-containing materials, chromate-induced dermatitis is often persistent.

MERCURY

The mercurials may act not only as irritants but also as sensi- tizers. Thimerosal is a mercuric-containing preservative; it is an allergen that is rarely relevant. Allergy to this compound is likely to have been caused by exposure during childhood vaccinations and to tincture of merthiolate antiseptic. In general, these patients tolerate repeated vaccinations well. Most individuals are sensitized to the ethyl mercuric component of thimerosal; however, those who react to the thiosali- cylic acid portion develop photodermatitis to piroxicam. Mercury in amalgam dental fillings has been shown in multiple large studies to cause oral lichoid eruptions. The relationship is especially strong when the oral lesion, often with a painful erosion present, is apposed to a gold or amalgam filling. In many cases where sensitivity is proven by patch testing and fillings are replaced, involution of the oral findings

COBALT

Cobalt is frequently combined with nickel as a contaminant and patients allergic to cobalt are commonly also allergic to nickel. The metals have similar properties but do not produce crossreactions. Cobalt dermatitis may occur in those involved in the manufacture of polyester resins and paints, in the manufacture of hard metal used for cutting and drilling tools, and in the manufacture and use of cement. Cobalt dermatitis may also occur in producers of pottery, ceramics, metal alloys, glass, carbides, and pigments. Individuals may be exposed to cobalt in hair dye, flypaper, and vitamin B12. Blue tattoo pigment contains cobalt oxide. Rarely, cobalt chloride may cause nonimmunologic local release of vasoreactive materials, with a local urticarial response.

GOLD

Gold dermatitis may rarely occur from the wearing of gold jewelry. A predisposing factor in such patients is the presence of dental gold. Oral lichoid eruptions have also been reported with gold, similar to the situation with mercury-containing amalgams. It is not uncommon to see positive reactions to gold when patchtesting patients with facial, eyelid, or widespread dermatitis of unknown cause. Although it is difficult to make a direct clinical correlation with any one piece of jewelry, occasional patients will clear if they stop wearing all gold jewelry. However, in most patients there is a lack of relevance. A number of cases of dermatitis resulting from gold jewelry, especially gold rings, contaminated with radon and its decay products have been reported. This may eventuate in radiation dermatitis and squamous cell carcinoma of the finger. Evidently, the source of contaminated gold for the rings had been reclaimed decayed radon gold seeds.

OTHER METALS

Most other commonly used metals are not important in causing contact dermatitis. Platinum dermatitis may occur from exposure to platinum salts and sprays in industry. Platinum rings, earrings, white gold spectacles, clasps, and other jewelry cause eruptions resembling those caused by nickel. Zinc, aluminum, copper sulfate, titanium, and antimony dermatitis rarely occur; these metals may, however, act as irritants.

CONTACT STOMATITIS

The role of contact allergy in oral symptomatology is significant. Approximately 30% of patients with oral symptoms will have relevant allergens; these are most commonly metals used in dental fillings, food additives (flavorings and antioxidants), and dental products such as acrylic monomers, epoxy resins, and hardeners used in prosthedontics and dental impression materials. Chewing gums and dentifrices may also produce contact stomatitis. Ingredients responsible for this are hexyl- resorcinol, thymol, dichlorophen, oil of cinnamon, and mint.

Clinical signs may be bright erythema of the tongue and buccal mucosa with scattered erosions. Angular cheilitis may also develop. Oral lichenoid lesions may be caused by sensitization to metals in dental fillings or gold caps or crowns.

RUBBER DERMATITIS

Rubber dermatitis generally occurs on the hands from wearing rubber gloves (surgeons, nurses, homemakers). The eruption is usually sharply limited to the gloved area but may spread up the forearms. Rubber dermatitis also develops from exposure to condoms, diaphragms, swim goggles, caps and scuba masks, wet suits, bandages for chronic leg ulcers, respirators, gas masks, rubber sheets, and cosmetic sponges. Shoe dermatitis may be caused by rubber allergy to insoles or sneakers (see above). Natural and synthetic rubbers are used separately or in combination to make the final rubber product. It is the chemicals added in the rubber manufacturing process, most importantly the accelerators and antioxidants, which are the common causes of allergic contact dermatitis. A similar list of additives is present in neoprene, a synthetic rubber. One particular class of additive in neoprene is causing an increasing number of reactions: the dialkyl thioureas. These are not in the standard patch trays and thus may escape detection unless they are applied as a supplemental allergen. Elastic in underwear is chemically transformed by laundry bleach, such as Clorox, into a potent sensitizing substance. The allergen is permanent and cannot be removed by washing. The offending garments must be thrown out and the use of bleaches interdicted.

ACCELERATORS

During the manufacturing process, chemicals are used to hasten the vulcanization of rubber. Among the numerous chemicals available, tetramethylthiuram disulfide, mercaptobenzothiazole, and diphenylguanidine are frequently used. Tetramethylthiuram disulfide and its analogs, known as disulfiram and thiuram, may produce contact dermatitis when moist skin is exposed to the finished rubber product. In one 10-year study of 636 cases of allergy to rubber

additives, thiuram mix was by far the most common sensitizer. Mercaptobenzothiazole is most often the cause in shoe allergy and thiuram in glove allergy.

ANTIOXIDANTS

Antioxidants are used to preserve rubber. Among antioxidants the amine type, such as phenyl-a-naphthylamine, is most effective. Hydroquinone antioxidants may cause depigmentation of the skin, as well as allergic contact dermatitis. A frequent antioxidant sensitizer, propyl p - phenylenediamine, is used in tires, heavy-duty rubber goods, boots, and elastic underwear.

ADHESIVE DERMATITIS

Cements, glues, and gums may cause adhesive dermatitis. Formaldehyde resin adhesives contain free formaldehyde, naphtha, glue, and disinfectants. Synthetic resin adhesives contain plasticizers; hide glues may contain chromates from the tanned leather while other glues incorporate preservatives such as formaldehyde. Dental bonding adhesives may contain acrylic monomers and epoxy resins and hardeners. Pressure-sensitive adhesives contain rubber and acrylates, and anaerobic adhesives primarily acrylates. Vegetable gums, such as gum tragacanth, gum arabic, and karaya, may be used in denture adhesives, hair wave lotions, topical medications, toothpastes, and depilatories, and many cause contact dermatitis. Resins are used in adhesive tapes and in various adhesives such as tincture of benzoin. Turpentine is frequently found in rosin; abietic acid in the rosin is the causative sensitizer. Adhesive tape reactions are frequently irritant in nature. Allergic reactions to adhesive tape itself are caused by the rubber components, accelerators, antioxidants, and various resins or turpentine. Some adhesive tapes contain acrylate polymers rather than rubber adhesives. These acrylates may cause allergic contact dermatitis. Pressure-sensitive adhesives are in widespread use in the tape and label industries. Allergens present in these

adhesives include rosin, rubber accelerators, antioxidants, acrylates, hydroquinones, lanolin, thiourea compounds, and N-dodecylmaleamic compounds.

SYNTHETIC RESIN DERMATITIS

The many varieties of synthetic resins preclude adequate discussion of each. The reactions incurred during the manufacture of these substances are more frequent than those encountered in their finished state.

EPOXY RESINS

The epoxy resins in their liquid (noncured, monomer) form may produce severe dermatitis, especially during the manufacturing process. The fully polymerized or cured product is nonsensitizing. Nonindustrial exposure is usually to epoxy resin glues, nail lacquers, and artificial nails. Epoxy resins are used in the home as glues and paints (bathtub and refrigerator). Artists and sculptors frequently use epoxy resins. Epoxy resins consist of two or more components, the resin and the curing agent. Approximately 90% of allergic reactions are to the resin and 10% to the hardener. There are numerous curing agents such as the amines, phenolic compounds, peroxides, and polyamides. These may be irritants and/or allergens. The resin, based on an acetone and phenol compound known as bisphenol A, in its raw state may cause allergic contact dermatitis. BIS-GMA, a combination of bisphenol A and glycidyl methacrylate, is the main allergen in dental bonding agents. Epoxy resins are used also as stabilizers and plasticizers. Their use in the manufacture of polyvinyl chloride (plastic) film has caused dermatitis from plastic handbags, beads, gloves, and panties.

POLYESTER RESINS

Ordinarily, completely cured or polymerized resins are not sensitizers. The unsaturated polyester resins are dissolved and later copolymerized with vinyl monomers. Such polyester resins are used for polyester plasticizers, polyester fibers (Dacron), and polyester film (Mylar). The unsaturated polyester resins, on the other hand, will produce primary irritation in their fabrication or among

sculptors. The dermatitis occurs typically as an eczematous eruption on the back of the hands, wrists, and forearms. Polyester resins are commonly incorporated into other plastic material as laminates to give them strength; applications include boat hulls, automobile body putty, safety helmets, fuel tanks, lampshades, and skylights.

ACRYLIC MONOMERS

Cyanoacrylates are used widely as adhesives in a variety of home and commercial products. They are generally a rare cause of contact dermatitis. With the advent of skin bonding agents, reports of allergy may increase. Multifunctional acrylic monomers may produce allergic or irritant contact dermatitis. Pentaerythritol triacrylate, trimethylolpropane triacrylate, and hexanediol diacrylate are widely used acrylic monomers. Printers handling multifunctional acrylic monomers in printing inks and acrylic printing plates may present with an ery- thematous, pruritic eruption, mainly of the hands and arms, swelling of the face, and involvement of the eyelids. Orthopedic surgeons experience contact dermatitis from the use of acrylic bone cement (methyl methacrylate monomer) used in mending hip joints. Dentists and dental technicians are exposed when applying this to teeth. The sensitizer passes through rubber and polyvinyl gloves and may additionally cause paresthesias. In patients who are allergic to their acrylate dental prosthesis, coating this with UV lightcured acrylate lacquer may allow it to be worn without adverse effects. Benzoyl peroxide is a popular acne remedy. It is also used for bleaching flour and edible oils, and for curing plastics, such as acrylic dentures. Infrequently, an allergic contact dermatitis may be caused.

COSMETIC DERMATITIS

Cutaneous reactions to cosmetics may be divided into irritant, allergic hypersensitivity, and photosensitivity reactions. More than half of the reactions occur on the face and are due primarily to skincare products, nail cosmetics, shaving preparations, and deodorants. The leading cause of allergic contact

dermatitis associated with cosmetics is from fragrance. A close second is preservatives, such as Bronopol (2-bromo-2- nitropropane-1-3-diol), Kathon CG, quarternium-15, Euxyl K 400, and imidazolidinyl urea. Third is p-phenylenediamine in hair dye. It is recommended that patch testing with the patient's own product, as long as it is applied to the skin as a leave-on product, be part of the evaluation.

FRAGRANCES

Almost all cosmetic preparations, skin-care products, and many medications contain fragrance; even those labeled non- scented often contain a "masking" fragrance that may be a sensitizer. Even "fragrance-free" products have been documented to contain the raw fragrance ingredients, e.g. rose oil in "all-natural" products. Fragrances are the most common cosmetic ingredient causing allergic contact dermatitis. Photodermatitis, irritation, contact urticaria, and dyspigmentation are other types of reactions they may produce. The most common individual allergens identified are cin- namic alcohol, oak moss, cinnamic aldehyde, hydroxy cit- ronellal, musk ambrette, isoeugenol, geraniol, coumarin, lyral, and eugenol. Frequently, unspecified allergens are the cause, as they are not listed on labels and fragrances are combinations of many different ingredients. Myroxylon pereirae (balsam of Peru) will identify approximately half of those often unsuspected cases of allergic dermatitis, and additional testing with the fragrance mixes will identify over 90%. Additionally, a natural fragrance mixture of jasmine absolute, ylang-ylang oil, narcissus absolute, spearmint oil, and sandalwood oil is recommended. New products should be tested for tolerance in those with a history of fragrance sensitivity. Around 1% of the population has fragrance sensitivity. Women still outnumber men, but as the frequency of fragrance contact reactions has increased over the years, men have shown a steeper increase in sensitivity. Ingestion of balsam- related foods, such as tomatoes, citrus fruits, and spices, may cause a flare in some sensitive patients. In particularly difficult- to-treat patients, balsam-restricted diets may be beneficial but are not easy to follow.

HAIR DYES

Permanent hair dyes incorporate p-phenylenediamine (PPDA), a popular but potent sensitizer that may cross-react with many chemicals. In rinses and tints the azo dyes, acid violet 6B, water-soluble nigrosine, and ammonium carbonate may sensitize and cross-react with PPDA. Those engaged in the manufacture of PPDA, furriers, hairdressers, and those in the photographic and rubber vulcanization industries develop eruptions at first on the backs of the hands, wrists, forearms, eyelids, and nose, consisting of an eczematous, erythematous, oozing dermatitis. Lichenification and scaling are seen in the chronic type. In those whose hair has been dyed, sensitivity is manifested by itching, redness, and puffiness of the upper eyelids, tops of the ears, temples, and back of the neck. Beard dermatitis may be due to coloring of the facial hair and eyelid dermatitis from dying eyelashes. PPDA added to temporary henna tattoos to make them darker has resulted in a large number of acute vesicular allergic reactions, some with scarring and hyperpigmentation. Kumkum is a commonly used cosmetic in India, primarily smeared on the forehead of women to denote their marital status; one of many reported allergens in the product is PPDA.

For those sensitive to this type of hair dye, use of semipermanent or temporary dyes might be the solution. In the case of sensitivity to the latter, vegetable dyes such as henna may be tried. Metallic dyes are usually not favored by women but are frequently used by men as "hair color restorers." The metallic hair dyes may contain nickel, cobalt, chromium, or lead. Hair dyes containing FD&C and D&C dyes often do not crossreact with PPDA.

OTHER HAIR PRODUCTS

Hair bleach products incorporate peroxides, persulfates, and ammonia, which may act as primary irritants. Hair bleaches that contain ammonium persulfate, a primary irritant, may produce a local urticarial and a generalized histamine reaction. Several types of permanent wave preparations exist. The

alkaline permanent wave preparations, which use ammonium thioglycolate, are rarely, if ever, sensitizers, and usually cause only hair breakage and irritant reactions. The hot type, or acid perm, is a common sensitizer, the allergen being glyceryl monothioglycolate. Cosmetologists are at risk for development of hand dermatitis. The glyceryl monothioglycolate persists in the hair for at least 3 months after application and may cause a longlasting dermatitis. It readily penetrates rubber and vinyl gloves. A more neutral pH permanent wave solution is less allergenic than the acid perms; however, allergy to cysteamine hydrochloride found in neutral permanent wave products may occur. This allergen does not penetrate household-weight latex gloves and hair waved with it does not produce allergic reactions in sensitized individuals. Also, it is an amine salt and not a thioglycolate, so cross-reactivity is unlikely. Hair straighteners using greases and gums are not sensitiz- ers; however, the perfume incorporated in these preparations can be. Thioglycolates are also used, and hair breakage may occur with these products. Hair sprays may contain shellac, gum arabic, sunscreens, and synthetic resins as sensitizers, and allergic reactions occur infrequently. Lanolin is frequently incorporated into aerosol sprays.

Chemical depilatories containing calcium thioglycolate and the sulfides and sulfhydrates may cause primary irritant dermatitis. Mechanical hair removers are the mercaptans, waxes, and resins. The latter may produce allergic dermatitis. Hair tonics and lotions with tincture of cinchona produce allergic sensitization; tincture of cantharidin and salicylic acid, primary irritation. Resorcin, quinine sulfate, and perfumes such as bay rum are also sensitizers.

NAIL PRODUCTS

Nail lacquers may contain tosylamide/formaldehyde resin and are a frequent cause of eyelid and neck dermatitis. Polishes free of this resin are available. Nail polish removers are solvents such as acetone, which can cause nail brittleness. The acrylic monomers in artificial nails, as well as the ethyl cyanoacrylate glue required to attach the prosthetic nail, may produce allergic sensitivity.

Photoinitiating agents, such as benzophenone, used in photobonded acrylic sculptured nails are other potential allergens.

LIPSTICKS

Various R and C dyes, sunscreens, shellac, flavoring agents, preservative, and lipstick perfumes may cause sensitization reactions. Lipsticks are tested as is. Lip plumpers may cause contact urticaria in those being kissed. Propolis is found in many so called natural products, including lip balms, toothpastes, lotions, shampoos, and other cosmetics. Its main allergens are two types of caffeates.

EYE MAKE-UP

In mascara, eye shadow, and eyeliners, the preservative, shellac, metals, base wax, and perfumes are the components that may produce sensitization, but this occurs rarely. False- positive reactions to some mascaras occur when a closed patch test is used. This is caused by the irritative qualities of the solvents. An open or nonocclusive patch test is recommended. A provocative use test in the antecubital fossae may ultimately be necessary. The rubber sponges used to apply eye make-up also cause eyelid dermatitis.

SUNSCREENS

P-Aminobenzoic acid (PABA) and its derivatives, such as padimate O, padimate A, and glycerol PABA, and dibenzoylmethanes, salicylates, cinnamates, and benzophenones are photosensitizers as well as sensitizers. If allergy to PABA exists, its derivatives should be avoided and there should be an awareness that thiazides, sulfonylurea antidiabetic medication, azo dyes, p-aminosalicylic acid, benzocaine, and p-phenylenediamine all may cause dermatitis from cross-reactions. Oxybenzone is the most common sunscreen allergen.

BLEACHING CREAMS

Hydroquinones are occasional sensitizers. Ammoniated mercury is a sensitizing agent formerly used in bleaching Lanolin. The fatty alcohol lanolin is

rarely a sensitizer on normal skin and most cosmetic and skincare products do not cause dermatitis. It provokes allergic reactions more frequently in therapeutic agents used by atopic patients and in emollient products which may be used postsurgically.

DENTIFRICES AND MOUTHWASHES

Dentifrices and mouthwashes contain sensitizers, such as the essential oils used as flavoring agents, preservatives, formalin, antibiotics, and antiseptics. Beacham et al reported 20 women who developed circumoral dermatitis and cheilitis from tartar- control types of dentifrice.

AXILLARY ANTIPERSPIRANTS

Aluminum salts, such as aluminum chloride and chlorhydroxide, and zinc salts, such as zinc chloride, act as primary irritants, and may rarely produce a folliculitis. Aluminum chlorhydrate is considered to be the least irritating antiperspirant. Zirconium salt preparations, now removed from all antiperspirants, produced a granulomatous reaction. Zirconiumaluminum complexes, however, are commonly used as the active ingredient in topical antiperspirants and may produce granulomas. Quaternary ammonium compounds in some rollon deodorants may produce allergic contact dermatitis.

AXILLARY DEODORANTS AND FEMININE HYGIENE SPRAYS

Fragrances, bacteriostats, and propellants cause the majority of the reactions seen with these products. Deodorants that contain cinnamic aldehyde can induce irritation on axillary skin even when tolerated on healthy skin in other sites.

COSMETIC INTOLERANCE SYNDROME

Occasionally, a patient will complain of intense burning or stinging after applying any cosmetic. Usually there are only subjective symptoms, but objective inflammation may also be present. The underlying cause may be difficult to document, even though thorough patch testing, photopatch testing, and contact

urticaria testing are completed. Endogenous disease, such as seborrheic dermatitis, rosacea, or atopic dermatitis, may complicate the assessment. Avoidance of all cosmetics, with only glycerin being allowed, for 6-12 months is often necessary to calm the reactive state. Adding back cosmetics one at a time, no more frequently than one a week, may then be tolerated.

PRESERVATIVES

Preservatives are added to any preparation that contains water to kill microorganisms and prevent spoilage. Such products include moist materials such as baby wipes, which when used in either infants or adults can produce reactions caused by preservatives. The most important class is formaldehyde and the formaldehyde-releasing compounds, including quaternium-15 (the leading preservative sensitizer in the US), imidazolidinyl urea, diazolidinyl urea, DMDM hydantoin, and 2-bromo-2 nitropropane-1, 3-diol. Kathon CG or methylchloroisothiazolinone/methyl isothia- zolinone (MCI/MI) and Euxyl K 400 (methyldibromoglutar - onitrile and phenoxyethanol in a 1:4 ratio) are other important preservative allergens. In the latter it is the methyldibromo- glutaronitrile component that produces the allergic response. This preservative may produce false-negatives on testing, so repeat open testing is indicated if a specific leave-on product is suspected of causing allergy. Methyldibromoglutaronitrile has been the subject of a European regulation limiting exposure to it. As with similar laws regulating nickel in Europe, allergy to this preservative is also lowering in incidence over time. Tea tree oil is an additive to some natural products that may serve as an antimicrobial. Developing data show it to be a sensitizer as well. Sorbic acid is a rare sensitizer among the preservatives; however, it is a cause of facial flushing and stinging through its action as an inducer of nonimmunologic contact urticaria. Benzalkonium chloride is widely used but a rare sensitizer. Finally, triclosan and benzyl alcohol are weak sensitizers. Thimerosal is discussed above.

FORMALDEHYDE AND FORMALDEHYDE-RELEASING AGENTS

Formaldehyde is used rarely, primarily in shampoos. Because it is quickly diluted and washed away, sensitization through this exposure is rare. Formaldehyde releasers are polymers of formaldehyde that may release small amounts of formaldehyde under certain conditions. Allergy may be to the formaldehyde-releasing preservatives (which act as antibacterial and antifungal agents in their own right) and/or to the released formaldehyde. Cross-reactivity among them is common, so when allergy is proven to one compound and avoidance does not clear the eruption, screening for clinically relevant reactions to the others is indicated. This may be done by repetitive open application testing to the leave-on product, or by extended patch testing.

PARABENS

Allergic contact dermatitis may develop from parabens, which are used in cosmetics, foods, drugs, dentifrices, and suppositories. The paraben esters (methyl, ethyl, propyl, and butyl p-hydroxybenzoates) are used in low concentrations in cosmetics and rarely cause dermatitis. They are found in higher concentration in topical medicaments and may be the cause of allergic reactions. Perpetuation of a dermatitis, despite effective topical medication, suggests the possibility of paraben or corticosteroid sensitivity, or that another sensitizer may be present. Parabens, which are frequently used as bacteriostatic agents, are capable of producing immunologically mediated immediate systemic hypersensitivity reactions. Cross-reactivity to para-phenylenediamine and benzocaine occurs in some individuals.

P-CHLOROMETAXYLENOL (PCMX)

This chlorinated phenol antiseptic is used in many over-the- counter products with the disinfectant properties of p-chlorometacresol. Sensitization occurs primarily through exposure to betamethasonecontaining cream. There is cross-reactivity to p-chloro-metacresol.

VEHICLES

Formulation of topically applied products is complex and additives are blended to make a pleasing base for carriage of the active ingredient to the skin. Various emulsifiers, humectants, stabilizers, surfactants, and surface active agents are used to make esthetically pleasing preparations. These may cause irritation, erythema, and allergy. The surfactant cocamidopropyl betaine produces dermatitis of the head and neck in consumers and the hands in hairdressers, often due to its presence in shampoos. Propolis and lanolin are discussed within the cosmetic portion above.

PROPYLENE GLYCOL

Propylene glycol is widely used as a vehicle for topical medications, cosmetics (especially antiperspirants), and various emollient lotions. It is used in the manufacture of automobile brake fluid and alkyd resins, as a lubricant for food machinery, and as an additive for food colors and flavoring agents. Propylene glycol must be considered as a sensitizer able to produce contact dermatitis, and it can cause a flare of the contact dermatitis when ingested. It is tested as a 4% aqueous solution, but irritant reactions or falsenegatives are common. A use test of the implicated propylene glycol-containing products may be required.

ETHYLENEDIAMINE

Ethylenediamine is used as a stabilizer in medicated creams. It may cause contact dermatitis and cross-react with internally taken aminophylline, which consists of theophylline and ethylenediamine. Hydroxyzine is a piperazine derivative that is structurally based on a dimer of ethylenediamine, to which patients sensitive to the stabilizer may develop a generalized itchy, red eruption that recurs each time hydroxyzine is taken orally.

TOPICAL DRUG CONTACT DERMATITIS

Drugs, in addition to their pharmacologic and possible toxic action, also possess sensitizing properties. Sensitization may occur not only from topical application but also from inges- tion, injection or inhalation. Some, such as the antihistamines, including topical doxepin, sensitize much more frequently when applied topically than when taken orally. With the advent of transdermal patches for delivery of medications such as nitroglycerin, hormones, nicotine, clonidine, fentanyl, lidocaine, and scopolamine, reports of sensitization are increasing. Clonidine induces the highest rate of allergic reactions. At times erythema multiforme-like reactions may occur with transdermally applied drugs. Some drugs may produce sensitization of the skin when applied topically; if the medication is taken later internally, an acute flare at the site of the contact dermatitis may result. This so-called anamnestic (recalled) eruption or systemic contact dermatitis can occur with antihistamines, sulfonamides, and penicillin. The same is true of the local anesthetic ointments containing "caine" medications. Usually, if sensitization occurs when using transdermal patches, the drugs do not cause systemic contact dermatitis when taken orally. Although it is impossible to mention all topical medications that cause irritation or allergic contact dermatitis, some are important enough to be dealt with individually.

LOCAL ANESTHETICS

Physicians and dentists may develop allergic contact dermatitis from local anesthetics. In addition, the continued use of these local anesthetics as antipruritic ointments and lotions causes sensitization of the skin. Benzocaine is a frequently used topical antipruritic and is the most common topical sen- sitizer of this group. Itchy dermatitis of the anogenital area may be due to a topically applied anesthetic. Local anesthetics may be divided into two groups. The first includes the p-aminobenzoic acid esters, such as benzocaine, butethamine, chloroprocaine, procaine (Novacaine), and tetracaine (Pantocaine). The second, which sensitizes much less frequently, includes the amides, such as dibucaine (Nupercainal),

lidocaine (Lido-Mantle, EMLA, Lidoderm patch, LMX, Xylocaine), mepivacaine (Carbocaine), and prilo- caine (Citanest). In addition, the preservative methylparaben, frequently found in these prepared solutions, may cause hypersensitivity reactions that can easily be misattributed to the local anesthetics. It should be kept in mind that numerous crossreactions are seen in benzocaine-sensitive individuals. These are discussed in the section on sunscreens and preservatives. Lidocaine can induce contact urticaria as well.

ANTIMICROBIALS

Physicians, dentists, nurses, and other medical personnel, as well as patients, especially those suffering from chronic leg ulcers, may develop contact dermatitis from various antibiotics. Neomycin and bacitracin are only behind nickel, fragrances (and the related Myroxylon pereirae), and quaternium-15 as the most frequent sensitizers in the US. As a topical antibiotic, neomycin sulfate has been incorporated into innumerable ointments, creams, and lotions. It is present in such preparations as underarm deodorants, otic and ophthalmologic preparations, and antibiotic creams and ointments available without prescription. The signs of neomycin sensitivity may be those of a typical contact dermatitis but are often those of a recalcitrant skin eruption that has become lichenified and even hyperkeratotic. This may be because many topical agents contain several types of antibiotic but also often have corticosteroids present. This picture may be seen in persistent external otitis, lichen simplex chronicus of the nuchal area, or dermatophytosis between the toes. A late-appearing reaction on patch testing is not uncommon, so an assessment at day 7 is recommended. There has been a dramatic rise in allergy to bacitracin. Its use after minor surgical procedures may account for this. After clean surgical procedures white petrolatum is as effective in aiding wound healing as antibiotic ointment, allows no more infection, and of course does not carry the allergenic potential. Petrolatum should be used after clean cutaneous surgery; antibiotic ointments are not necessary and contribute to the overall increasing problem of allergy to these medications. There is a high rate of

coreaction (not cross-reaction) with neomycin because of simultaneous exposures. Contact urticaria and anaphylaxis are reported more often with bacitracin than with other antibiotics. Mafenide acetate, the topical antimicrobial found in Sulfamylon, a burn remedy, may cause allergic contact dermatitis, as can metronidazole.

ANTIFUNGAL AGENTS

Allergic contact dermatitis to imidazole and other antifungal agents may occur. There is a high crossreactivity rate between miconazole, isoconazole, clotrimazole, and oxiconazole because of their common chemical structure.

PHENOTHIAZINE DRUGS

Handling injectable solutions and tablets may produce dermatitis in those sensitized to chlorpromazine and other phenothiazine derivatives. The reactions may be photoallergic or nonphotoallergic.

CORTICOSTEROIDS

Numerous reports of large series of patients who have developed allergy to these commonly used preparations emphasize the need for a high index of suspicion when treating patients with chronic dermatitis who fail to improve, or who worsen, when topical steroidal agents are used. Once sensitized to one type of corticosteroid, cross-sensitization may occur. The corticosteroids have been separated into four structural classes:

Class A is the hydrocortisone, tixocortol pivalate group.

Class B is the triamcinolone acetonide, budesonide group.

Class C is the betamethasone group.

Class D is the hydrocortisone-17-butyrate group.

There are frequent cross-reactions between classes B and D. Tixocortol pivalate and budesonide have been found to be the best screening agents, finding

93% of steroid allergies. In the absence of having these materials, patch testing to the implicated product may be useful. An empiric trial of desoximeta- sone (Topicort) or mometasone (Elocon) in the absence of patch testing will give the best chance of selecting a topical steroid with an extremely low risk of sensitization.

OCCUPATIONAL CONTACT DERMATITIS

Workers in various occupations are prone to contact dermatitis from primary irritants and allergic contactants. In certain occupations it is a common occurrence. Irritant contact dermatitis is more frequent in the workplace, but it tends to be less severe and less chronic than allergic contact dermatitis. Occupational skin disease has declined over the past 30 years but still constitutes approximately 10% of all occupational disease cases. Agriculture, forestry, and fishing have the highest incidence of occupational skin disease, with the manufacturing and healthcare sectors contributing many cases as well. Irritant contact dermatitis is commonly present in wet-work jobs, and allergy occurs in hairdressers, machinists, and many others with unique exposures to multiple sensitizing chemicals. The hands are the parts most affected, being involved in 60% of allergic reactions and 80% of irritant dermatitis. Epoxy resin is an allergen overrepresented when evaluating occupa- tional patients. The allergens most frequently encountered in occupational cases are carba mix, thiuram mix, epoxy resin, formaldehyde, and nickel.

MANAGEMENT

Occupational contact dermatitis is managed by eliminating contact of the skin with irritating and sensitizing substances. The work environment should be carefully controlled, with use of all available protective devices to prevent acci- dental and even planned exposures. Personal protective measures, such as frequent clothing changes, cleansing showers, protective clothing, and protective barrier creams should be used as appropriate. Handcleansing procedures should be thoroughly surveyed, with particular attention paid to the soaps available and also

what solvents may be used. Treatment of the dermatitis follows closely that recommended for toxicodendron dermatitis. Topical corticosteroid preparations are especially helpful in the acute phase. For dry, fissured hands, soaking them in water for 20 min at night followed immediately upon removing (without drying them) with triamcinolone 0.1% ointment will help hydrate and heal them. Topical tacrolimus ointment and pimecrolimus cream may assist in maintenance therapy. When rubber and poly- vinyl gloves cannot be used against irritant and allergenic substances, skin protective creams may offer a solution, although they are often impractical. A wide variety is available, but two main types are used. One is for "wet work"-to protect against acids, alkalis, waterbase paints, coolants, and cutting oils with water; and the other type is for "dry work"- to protect against oils, greases, cutting oils, adhesive, resins, glues, and wood preservatives. Unfortunately, despite the best efforts at treatment and prevention, the prognosis for occupational skin disease is guarded. One-third to one-quarter heal, and another one-third to one- half improve, with the remainder the same or worse. A change or discontinuance of the job does not guarantee relief, as many individuals continue to have persistent postoccupational dermatitis. The importance of thorough patient education cannot be overemphasized. Atopics, males with chromate allergy, females with nickel allergy, those with a delay in diagnosis before institution of treatment, and construction industry workers fare the worst, while irritation from metalworking fluids, reactions to urushiols in foresters, and allergic contact dermatitis to acrylic monomers or amine-curing agents is usually shortlived.

CONTACT URTICARIA

Contact urticaria may be defined as a wheal and flare reaction occurring when a substance is applied to the intact skin. Urticaria is only one of a broad spectrum of immediate reactions, including pruritus, dermatitis, local or general urticaria, bronchial asthma, orolaryngeal edema, rhinoconjunctivitis, gastrointestinal distress, headache, or an anaphylactic reaction. Any combination of these is subsumed under the expression "syndrome of immediate reactions". It

may be nonimmunologic (no prior sensitization), immunologic, or of unknown mechanism. The nonimmunologic type is the most common, and may be caused by direct release of vasoactive substances from mast cells. The allergic type tends to be the most severe, as anaphylaxis is possible. The third type has features of both.

NONIMMUNOLOGIC MECHANISM

This type of reaction occurs most frequently and may produce contact urticaria in almost all exposed individuals. Examples of this type of reaction are seen with nettle rash (plants), dimethyl sulfoxide (DMSO), sorbic acid, benzoic acid, cinnamic aldehyde, cobalt chloride, and Trafuril.

IMMUNOLOGIC MECHANISM

This reaction is of the immediate (IgE-mediated) hypersensi- tivity type. Latex, potatoes, phenylmercuric propionate, and many other allergens have been reported to cause this.

UNCERTAIN MECHANISM

This type of reaction occurs with those agents that produce contact urticaria and a generalized histamine type of reaction but lack a direct or immunologic basis for the reaction. Substances causing contact urticaria. Many different substances can elicit such a reaction. It is seen in homemakers and food handlers who handle raw vegetables, raw meats and fish, shellfish, and other foods. Raw potatoes have been shown to cause not only contact urticaria but also asthma at the same time. It has been seen in hairdressers who handle bleaches and hair dyes containing ammonium persulfate, in whom the contact urticaria is accompanied by swelling and erythema of the face, followed by unconsciousness. Caterpillars, moths, and hedgehogs may cause contact urticaria just by touching the skin. Additional substances inducing this reaction are oatmeal, flour, meat, turkey skin, calf liver, banana, lemon, monoamylamine, benzophenone, nail polish, tetanus antitoxin, streptomycin, cetyl alcohol, stearyl alcohol, estrogenic cream, cinnamic aldehyde, sorbic acid, benzoic acid, castor bean, lindane, carrots, spices, wool, silk, dog and

cat saliva, dog hairs, horse serum, ammonia, sulfur dioxide, formaldehyde, acrylic monomers, exotic woods, wheat, cod liver oil, and aspirin. Bacitracin ointment may cause anaphylactic reactions when applied topically, especially to chronic leg ulcers; however, it may rarely occur after application to acute wounds. Universal precautions not only led to a marked increase in delayedtype hypersensitivity reaction to rubber additives, but also to a large number of reports of contact urticaria and anaphylaxis to latex. Most of these reactions occur in health professionals. Reactions are characterized by itching and swelling of the hands within a few minutes of donning the gloves, and will usually resolve within an hour after removing them. In patients with continued exposures the eruption may eventually appear as chronic eczema. Glove powder may aerosolize the allergen and produce more generalized reactions. While these reactions may occur on the job, many cases present as death or near-death events when sensitized individuals undergo operations or other procedures, especially when there is mucosal exposure (dental care, rectal examination, childbirth). In addition to healthcare workers, who have a reported incidence of between 3% and 10%, atopics and spina bifida patients are other risk groups for the development of type I allergy to latex protein. The sensitized individual should also be aware that up to 50% of them will have a concomitant fruit allergy to foods such as banana, avocado, kiwi, chestnut, and passion fruit.

TESTING

The usual closed patch tests do not show sensitivity reactions. Instead, open patch tests are performed for eliciting immediatetype hypersensitivity. The substance is applied to a 1 cm2 area on the forearm and observed for 20-30 min for erythema that evolves into a wheal and flare response. When foods are tested, a small piece of the actual food is placed on the skin. Rubber glove testing can be done by applying one finger of a latex glove to a moistened hand for 15 min. If no reaction is observed, the entire glove is worn for another 15-20 min. Radioallergosorbent testing (RAST) detects 75% of latexallergic individuals.

There is no standard allergen available for prick testing. Prick, scratch, or intradermal testing is resorted to only when there are problems of interpretation of the open patch tests. These tests have produced anaphylactic reactions and should only be attempted when support for this complication is available.

MANAGEMENT

Avoidance of the offending substance is best, but if this is not possible, antihistamines are of benefit. If generalized urticaria or asthmatic reactions occur, then systemic glucocorticoids are best. For anaphylaxis, epinephrine and supportive measures are needed.

DRUG REACTIONS EPIDEMIOLOGY

Adverse drug reactions (ADRs) are a common cause of dermatologic consultation. In a large French study, about 1 in 200 inpatients on medical services developed a drug eruption, as compared to 1 in 10 000 on surgical services. In the US, similar studies have shown a reaction rate of 2-3 in 100 for medical inpatients. In only about 55% of patients who were carefully evaluated was it possible to attribute a specific medication definitely as the cause of the eruption. Simple exanthems (7595%) and urticaria (5-6%) account for the vast majority of drug eruptions. The risk for development of a drug eruption is related to the following factors: age, gender, dose, and the nature of the medication itself. Females are 1.3-1.5 times more likely to develop drug eruptions, except in children under the age of 3 where boys are more likely to be affected. Not all drugs cause reactions at the same rate. Aminopenicillins cause drug eruptions in between 1.2% and 8% of exposures, and the combination of trimethoprim-sulfamethoxazole at a rate of 2.8-3.7%. About 20% of emergency room (ER) visits for adverse events due to medications were caused by antibiotics, largely penicillins and cephalosporins. This is estimated to have accounted for more than 28 000 visits annually in the US. Up to 20 ER visits occurred per 10 000 prescriptions written for certain antibiotics. Nonsteroidal anti-inflammatory drugs (NSAIDs) have a reaction rate of about 1 in

200. In contrast, reaction rates for digoxin, lidocaine, prednisone, codeine, and acetaminophen are less than 1 in 1000. In addition, the immune status and genetic make-up of the patient strongly determine the risk of developing certain drug eruptions. For example, patients with human immunodeficiency virus (HIV) infection and Epstein-Barr virus (EBV) infection have dramatically increased rates of exanthematous reactions to certain antibiotics. Hypersensitivity syndromes from multiple drug classes have been associated with reactivation of latent viral infections, primarily human herpes virus (HHV)-6 and 7, but also EBV and cytomegalovirus. In addition, the status of the immune system, as measured by helper T-cell count in the case of HIV, defines a window of immune dysfunction in which this enhanced risk for ADRs occurs. Certain hypersensitivity syndromes are closely associated with genetic differences in the ability of the patient to metabolize a specific medication or a toxic metabolite of the medication. In addition, HLA type, in a race-specific manner, may increase risk for drug reactions for specific medications. Therefore, drug eruptions are not simply drug "allergy," but result from variations in drug metabolism, immune status, coexistent viral disease, the patient's racial background, the patient's HLA status, and the inherent chemical structure (allergenicity) and dosage of the medication itself (see below).

EVALUATION

Four basic rules should always be applied in evaluating the patient with a suspected drug reaction. First, the patient is probably on unnecessary medications, and all of these should be stopped. Pare down the medication list to the bare essentials. Second, the patient must be asked about non-prescription medications and pharmaceuticals delivered by other means (eye drops, suppositories, implants, injections, patches, and recreational drugs). Third, no matter how atypical the patient's cutaneous reaction, always consider medication as a possible cause. In patients with unusual reactions, searching the medical literature and calling the manufacturer for prior reports may be very useful. • Fourth, the timing of drug administration must correlate with the appearance of the eruption. A drug chart

lists all the drugs given to the patient in the left column, with the dates along the lower axis, and the course of the drug eruption at the top. Lines extend from left to right for the dates of administration of each medication. These are directly below the course of the eruption. This graphic representation of the timing of medication administration and eruption is a very handy tool in assigning plausibility to a certain medication causing an eruption. The nurses' notes and patient history are most useful in determining exactly when the eruption first appeared. An important step in evaluating a patient with a potential drug reaction is to diagnose the cutaneous eruption by clinical pattern (e.g. urticaria, exanthem, vasculitis, hypersensitivity syndrome, etc.). In determining whether the patient's current eruption could be related to a specific medication, two basic questions should be asked. Which of this patient's medications cause this pattern of reaction? How commonly does this medication cause this reaction pattern? Bigby reviewed how to use this information to make clinical decisions about stopping possible reaction-inducing medications. A regularly updated manual (such as Litt) or similar databases on the web are strongly recommended as ready reference sources for this information. An algorithm by which the likelihood can be evaluated of a certain medication causing a particular reaction has been developed. This algorithm, summarized below, can be used as a framework for the evaluation of a given patient: Previous general experience with the drug: Has the suspected medication been reported to cause the reaction the patient is experiencing? If so, how commonly? Also ask the patient if he/she has had a previous reaction to any medications, as the current eruption may represent a cross-reaction from a prior exposure. Alternative etiologic candidates: What are other possible causes of the patient's eruption? An exanthem, for instance, could be related to an associated viral illness, not the medication. Timing of events: When did the eruption appear relative to the administration of the suspected medication? A detailed history from the patient and a careful review of the patient record, including the nursing notes, are useful to establish the chronologic sequence of all drug therapy. A drug chart as described above is very useful. Drug levels and evidence of overdose: Certain

reactions are known to be related to rate of administration (vancomycin red man syndrome) or cumulative dose (lichenoid reactions to gold). Response to discontinuation (dechallenge): Does the eruption clear when the suspected medication is stopped? Because certain eruptions may clear in the face of continuation, this is a useful, but not irrefutable criterion to ascribe a specific reaction to a medication. Rechallenge: If the offending medication reproduces the reaction on readministration, this is strong evidence that the medication did indeed cause the reaction. Reactions associated with an increase in dosage may also be considered in this category. In certain reaction patterns (e.g. exanthems), even a fraction of the original dose may reproduce the reaction. It may be impossible to rechallenge if the reaction was severe. In addition to the clinical evaluations noted above, complete evaluation may include special testing for confirmation. Skin testing is most useful in evaluating type I (immediate) hyper- sensitivity. It is most frequently used in evaluating adverse reactions to penicillin, local anesthetics, insulin, and vaccines. RAST has a 20% false-negative rate in penicillin type I allergy, so it must be followed by skin testing. In their current form, RAST tests cannot replace skin testing. Intradermal, prick skin, and patch testing are also reported to be beneficial in some cases of morbilliform reactions or fixed drug reaction. The patient's metabolism of certain drugs in lymphocytotoxicity assays may be associated with an adverse reaction. Such testing is commercially available, but is expensive and time- consuming, and its value is limited to certain situations such as anticonvulsant or sulfonamide hypersensitivity reactions. The patient should be given concrete advice about his/her reaction. What was the probability that the patient's reaction was caused by the medication? Can the patient take the medication again, and if so, what may occur? What cross-reactions are known? What other medications must the patient avoid? Unusual reactions should be reported to regulatory agencies and the manufacturer.

PATHOGENESIS

T - cells, specifically Th1 cells, are felt to be important inducers of ADRs. These T cells act in two ways to induce reactions. They can directly secrete biologically active molecules, resulting in direct tissue effects (epidermal necrosis, for example), or they can act by secreting chemokines that recruit the effector cells (eosinophils or neutrophils, for example). In biopsies from ADRs, the cytokines produced by helper T - cells in the skin parallel the reaction pattern observed. For example, T - cells in the dermis in acute generalized exanthematous pustu- losis (AGEP) secrete interleukin (IL)-8, a neutrophilattracting chemokine. In drug rash with eosinophils and systemic symptoms (DRESS), they secrete IL-5 and eotaxin, recruiting eosinophils. As a consequence of helper T-cell activation, memory T cells are produced, resulting in recurrence of the eruption upon rechallenge. Since Th1 cells are mediators of these eruptions, interferon (IFN)-y release assays using peripheral blood lymphocytes are being evaluated for confirming the inciting medication in ADRs. The sensitivity appears to be drug classdependent, and specifically of low sensitivity for ADRs induced by anticonvulsants, antibiotics, and cardiovascular medications. The medications that induce ADRs can create immune- mediated reactions by several mechanisms. Large molecules, such as rat- or mouse-derived antibodies, can be immunogenic. Most medications, however, are too small to be recognized as antigens by immunologically active cells. They must bind to a larger molecule, usually a protein, to form an immu- nogenic product. The medication is the hapten, and the immunologically active molecule is a medication-protein complex, or haptencarrier complex. Some medications, such as penicillin, are active enough to bind directly to proteins. Most, however, need to be metabolized to more active or more immunogenic forms in order to bind to proteins and cause an immunologic reaction. The drug metabolites can also be toxic to cells, causing direct cell damage. This metabolism occurs in the cytochrome P450 system in the liver, and perhaps in lower amounts in other organs. These active immunogenic molecules are inactivated through metabolism. This model of immune-mediated ADR explains why the drug itself, the

metabolism and breakdown of the medication by the patient, and the patient's immune status all determine the likelihood of developing an ADR. There has also been a proposed model for ADRs in which the drug or a metabolite binds directly to T cells or Langerhans cells in close opposition to sentinel T cells in the skin. This direct binding could activate the T cell-Langerhans cell interactive unit, resulting in the production of biologically active molecules. This would explain how some drug eruptions occur soon after exposure or with the first exposure to a medication. It could also explain a dose-dependent effect in drug eruptions. Also, a systemic viral infection would have already activated the immune cells in the skin, reducing their threshold for activation by drug binding. This could also explain why many drug eruptions occur only on the skin, apparently sparing other organs. The skin may uniquely have T cells that are sensitive to activation corresponding to a "sentinel" activity appropriate for cells residing on a surface that interacts with the environment. Since the avidity with which drugs directly bind to T cells would vary considerably, this could account for the wide variation in the rate of exanthems from different medications (from 30% for gemifloxacin to <1% for acetaminophen). Once the T cell is activated, it chooses among one of four programs (or some combination) to create the specific reaction pattern the dermatologist observes. Since it might be possible for several different programs to be chosen, there could be a significant pleomorphism in the clinical and histological pattern observed with any ADR. The four options are as follows: T cells stimulate IFN-y production and a Th1 response, simulating contact dermatitis. This type of reaction could be "bullous" but without extensive epidermal necrosis. T cells could be activated to function in a Th2 manner and stimulate eosinophil ingress through Th2 cytokines (morbilliform and urticarial drug eruptions). T cells could activate cytotoxic (CD8+) T cells which would secrete perforin/granzyme B and Fas ligand, resulting in keratinocyte apoptosis. This could explain bullous reaction, the observation that occasional necrotic keratinocytes are seen in patients with exanthems, and the rare eruption that begins as an exanthem then progresses to a bullous eruption. Drug eruptions containing activated CD8+ T cells are more

dangerous, since CD8+ cells attack all major histocompatibility complex (MHC) class I-expressing cells (including keratinocytes), resulting in more severe reactions. T cells, via granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-8 local production, call in neutrophils, resulting in pustular exanthems and AGEP. Dermal CD4+CD25+Foxp3 regulatory T cells (T-regs) are reduced in severe bullous drug eruptions (TEN). Circulating T-regs expressing skin-homing molecules are increased in early drug-induced hypersensitivity syndromes. They are immunologically active early on in the course of the eruption, enter the skin, and can effectively suppress the immune response. However, they become functionally deficient later, perhaps explaining the occasional development of autoimmune phenomena months following druginduced hypersen- sitivity syndromes (DIHS), and the tendency of DIHS reactions to relapse, recur, or fail to resolve. In addition, peripheral blood mononuclear cells are stimulated by the incriminated drug (in a lymphocyte transformation test [LT1]) for only the first week in TEN and exanthems. However, in DIHS, the LTT test is negative until 5-6 weeks following the eruption and remains positive for 1 year or more. This supports the observation that DIHS reactions are long-lived. In addition, the LTT is essentially only useful in diagnosing DIHS, since it is rarely performed during the first week of an ADR.

CLINICAL MORPHOLOGY

Cutaneous drug reactions will initially be discussed by their morphologic pattern. In addition to the cutaneous eruption, some reactions may be associated with other systemic symptoms or findings. The modifier "simple" is used to describe reactions without systemic symptoms or internal organ involvement. "Complex" reactions are those with systemic findings. Complex reactions are also called DIHS, since the ancillary features of complex reactions are often a characteristic syndrome of findings (e.g. an infectious mononucleosis-like picture with anticonvulsant hypersensitivity reactions). DIHS or complex reaction is synonymous with DRESS. Drug reactions may cause cutaneous lesions and

findings identical to a known disease or disorder. These may be of similar or disparate pathogenesis. For example, true serum sickness caused by the injection of foreign proteins, such as antithymocyte globulin, is associated with circulating immune complexes. Medications, notably cefaclor, induce a serum sickness-like illness, clinically extremely similar to, but not associated with, circulating immune complexes. The suffix "-like" is used to describe these syndromes with different or unknown pathogenesis but similar clinical features.

EXANTHEMS (MORBILLIFORM OR MACULOPAPULAR REACTIONS)

Exanthems are the most common form of adverse cutaneous drug eruption. They are characterized by erythema, often with small papules throughout. They tend to occur within the first 2 weeks of treatment but may appear later, or even up to 10 days after the medication has been stopped. Lesions tend to appear first proximally, especially in the groin and axilla, generalizing within 1 or 2 days. The face may be spared. Pruritus is usually prominent, helping to distinguish a drug eruption from a viral exanthem. Antibiotics, especially semisynthetic penicillins and trimethoprim-sulfamethoxazole, are the most common causes of this reaction pattern. Ampicillin- amoxicillin given during EBV causes an exanthem in 29-69% of adults and 100% of children. Trimethoprim-sulfamethoxazole given to AIDS patients causes exanthems in a large proportion of patients (about 40%). Certain quinolones (gemfloxacin) cause exanthems at a high rate (4% overall and 30% in young women). Morbilliform eruptions may rarely be restricted to a previously sunburned site, the so-called "UV recall-like" phenomenon. It occurs during antibiotic therapy from various antibiotics. The sunburn may have occurred 1-7 months before the drug eruption. This pattern of eruption must be distinguished from a true UV recall caused by antimetabolites and true radiation recall (see adverse reactions to chemotherapy below). In the case of simple exanthems, treatment is supportive. The eruption will clear within 2 weeks of stopping the offending medication, and may clear even if it is continued. Topical steroids and antihistamines may benefit and allow the course of therapy to be completed.

Rechallenge usually results in the reappearance of the eruption, except in the setting of HIV. In many HIV-infected patients with simple reactions to trimethoprim-sulfamethoxazole, re-exposure by slow introduction or fulldose re-exposure may be tolerated. Uncommonly in HIV infection, however, and rarely in persons with normal immune function, rechallenge may result in a more severe blistering reaction. The use of patch and intradermal testing for the confirmation of the incriminated drug in morbilliform exanthems is not standardized. Only between 2% and 10% of patients who experience the eruption on rechallenge will have a positive patch or intradermal test, making such testing not very useful clinically. Cutaneous findings identical to simple exanthems may occur as part of DIHS or DRESS. As opposed to simple exanthems, in complex exanthems the inciting agent must be stopped immediately and rechallenge should rarely be undertaken. Drug-induced hypersensitivity syndrome (DIHS or DHS) or drug reaction with eosinophilia and systemic symptoms (DRESS). Hypersensitivity syndromes are discussed by the class of medication that causes them. Each class of medication appears to cause a constellation of features characteristic of that medication class, although all cases of DIHS or DRESS share the characteristic features of fever, rash, and internal organ involvement. The characteristic (and according to some authors) diagnostic features of DRESS include: Rash developing late (more than 3 weeks) after the inciting medication is started. It often occurs with the first exposure to the medication. Long-lasting symptoms (>2 weeks) after the discontinuation of the causative drug.

Fever (over 38°C).

Multiorgan involvement.

Eosinophilia (>1500 absolute eosinophilia).

Lymphocyte activation (lymphocytosis, atypical lymphocytosis, lymphadenopathy). Frequent reactivation of herpesviruses HHV-6, HHV-7, EBV, and cytomegalovirus. The vast majority of DRESS cases are caused by a limited

number of medications, although more than 200 medications have been incriminated. Only 7 medications/classes of medication are implicated: anticonvulsants (phenobarbital, lamotrigine, and phenytoin) long-acting sulfonamides (sulfamethoxazole, sulfadiazine, and sulfasalazine but NOT related medications-sulfonylureas, thiazine diuretics, furosemide, and acetazolamide):

allopurinol

nevirapine

abacavir

dapsone

minocycline.

Vancomycin has also recently been recognized as a cause. The skin eruption accompanying DRESS (DIHS) is typically morbilliform and can vary from faint and mild to severe with exfoliative erythroderma. Facial edema often accompanies the skin eruption, and the eruption may evolve to demonstrate superficial pustules (especially on the face). Some patients with Stevens-Johnson syndrome (SJS)/TEN may have some of the features of DRESS, specifically fever, eosinophilia, and internal organ involvement. How to classify these cases is controversial, but from a pragmatic point of view, the management is that of SJS/TEN and they are best given that diagnosis. The relative frequency of internal organ involvement and other features of DRESS differs depending on the medication which causes the reaction. The variants of DRESS/DIHS are outlined below. The internal organ involvement described in DRESS can be divided into two types: organ dysfunction occurring during or immediately associated with the acute episode; and late sequelae, possibly with an autoimmune basis. The first category includes colitis/intestinal bleeding, encephalitis/aseptic meningitis, hepatitis, interstitial nephritis, interstitial pneumonitis/ respiratory distress syndrome, sialadenitis, and myocarditis. Late sequelae include syndrome of inappropriate secretion of antidiuretic hormone (ADH), thyroiditis/Graves' disease, and diabetes mellitus.

Systemic lupus erythematosus (SLE) can rarely occur. In one series, 5% of patients with DRESS died, usually due to complications of liver or renal involvement. The pathogenesis of DRESS has been studied extensively. Three factors appear to play a role, to various degrees depending on the medication class inducing the DRESS. These are: Certain HLA types put individuals from specific genetic backgrounds at risk of developing DRESS from specific medications. Genetic or acquired inadequate metabolism of toxic or immunogenic breakdown products of certain classes of medication increases the risk for DRESS. Reactivation of herpes viruses (especially HHV-6, but also cytomegalovirus, EBV, and HHV-7) is associated with the development of DRESS. HHV-6 may reactivate during the transient hypogammaglobulinemia that often accompanies DRESS. The mononucleosis-like syndrome accompanying DRESS could be analogous to the mononucleosis-like syndrome accompanying primary HHV-6 infection. In severe DRESS cases, HHV-6 can also be found in the liver and cerebrospinal fluid associated with hepatitis and encephalitis. Certain drugs known to induce DRESS, e.g. sodium valproate, directly induce HHV-6 replication. In one series all fatal cases of DRESS were associated with HHV-6 reactivation. During the acute phase of DRESS, regulatory T cells (T-regs) are expanded and functionally more robust. T-regs become functionally deficient as DRESS resolves, perhaps allowing for the development of autoimmune disease.

ANTICONVULSANT HYPERSENSITIVITY SYNDROME

Anticonvulsant hypersensitivity syndrome can be seen with phenytoin, phenobarbital, carbamazepine, lamotrigine, zonisa- mide, and other anticonvulsants, so the general term "anticon- vulsant hypersensitivity syndrome" is preferred to the original descriptive term "dilantin hypersensitivity syndrome." The incidence of this condition has been estimated at between 1 in 1000 and 1 in 10 000 patients treated with these medications, but is ten times that rate for lamotrigine. Carbamazepine is currently the most common anticonvulsant causing DRESS, because it is also used to treat neuropathic pain, bipolar disorder, and

schizophrenia. Medication dosage does not determine risk for this syndrome. HHV-6 and 7 reactivation are observed in about 30% of anticonvulsant hypersensitivity syndrome patients, much more commonly in carbamazepine-induced cases. The DRESS begins on average 30-40 days after starting the anticonvulsant. Low-grade fever and pharyngitis may precede the eruption by a few days. The skin eruption is typically morbilliform initially, and associated with marked facial and neck edema. The eruption begins on the trunk and face, spreading centrifugally. As the eruption becomes more severe, it may evolve to confluent plaques with purpura. The intense dermal edema accompanying the eruption may lead to bulla formation. Commonly associated findings include fever (in more than 50%), adenopathy (in about 20% of cases), and elevated liver function tests (in between two-thirds and three-quarters of cases). Atypical lymphocytosis can occur, completing a mononucleosislike picture. Lung and renal involvement is uncommon. Lamotrigine DRESS is somewhat different than that induced by the other anticonvulsants. It has eosinophilia in only 19% of cases, lymphadenopathy in only 12%, and multiorgan involvement in only 45%-lower rates than seen with the other anticonvulsants. Lamotrigine DRESS occurs within 4 weeks in most patients, but may not occur for up to 6 months in 10% of cases. Coadministration of valproate increases the risk of lamotrigine DRESS. Slow introduction reduces the risk for lamotrigine DRESS. In anticonvulsant hypersensitivity syndrome, as the eruption evolves, it is typical for widespread pinpoint pustules to appear on the face, trunk, and extremities, especially in dark-skinned patients. The syndrome may continue to progress, even after the inciting medication has been stopped. The associated hepatitis can be life-threatening. Because many of the anticonvulsants are metabolized through the same pathway, cross-reactions are frequent, making selection of an alternative agent quite difficult. The rate of cross-reactivity between phenytoin, phenobarbital, and carbamazepine is 70%. In vitro tests are commercially available and may aid in selecting an agent to which the patient will not crossreact. Valproate is a safe alternative. The management of anticonvulsant hypersensitivity syndrome begins

with considering it in the appropriate setting and ruling out other possible explanations for the patient's findings. The offending medication must be immediately discontinued. Because cross-reactivity among these drugs is high, the therapeutic benefit of a medication from this class must be carefully reconsidered. If the treatment is for depression, prophylaxis after closed head injury, or atypical pain syndromes, medication from another class can often be substituted. Treatment is initially supportive until the extent and severity of the syndrome are assessed. Some patients clear if the medication is simply discontinued. If there is liver or renal involvement, or if the patient appears ill or requires hospitali- zation, and there is no contraindication, systemic steroids are given. The usually starting dose is between 1 and 1.5 mg/kg/ day. N-acetylcysteine may be added if hepatitis is present. Steroid therapy is continued at doses required for control then gradually tapered. It may require months to wean the patient off steroids successfully. If steroids are tapered too rapidly, the syndrome may recur. Intravenous immunoglobulin (IVIG) and other immunosuppressives, such as azathioprine or cyclosporine, have been successfully used in steroid-refractory cases.

ALLOPURINOL HYPERSENSITIVITY SYNDROME

Allopurinol hypersensitivity syndrome typically occurs in persons with preexisting renal failure. Often, affected patients are treated unnecessarily for asymptomatic hyperuricemia, with clear indications for therapy present in only about one- third of patients suffering this syndrome. They are often given a dose not adjusted for their coexisting renal disease. They are frequently on a thiazide diuretic. Weeks to many months (average 7 weeks) after the allopurinol is begun, the patient develops a morbilliform eruption (50% of cases) that often evolves to an exfoliative erythroderma (20%). Bullae as a consequence of severe dermal edema may occur, especially on the palms and soles. Occasional oral ulcers may occur. Associated with the dermatitis are fever, eosinophilia, sometimes hepatitis (70% of cases), and typically worsening of renal function (40-80% of cases, the higher percentage in those with pre-existing renal disease). Lung involvement and

adenopathy are uncommon. About 25% of patients die as a consequence of this syndrome, often from cardiovascular complications of the syndrome. Pancreatitis and subsequent insulin-dependent diabetes may occur as a complication. Dialysis does not appear to accelerate the resolution of the eruption, suggesting that if a drug metabolite is responsible, it is not dialyzable. It has been suggested that adjusting the allopurinol dose to compensate for the patient's impaired renal function might reduce the risk of developing this reaction. There is a strong association between HLA-B-5801 and the development of allopurinol hypersensitivity syndrome in the Han Chinese, but not in other races. HHV-6 reactivation may be associated. This syndrome may be steroidresponsive, but is extremely slow to resolve, frequently lasting for months after allopurinol has been stopped. Very gradual tapering of systemic steroids with monitoring of eosinophil count and renal function is essential. Too rapid tapering may lead to relapse of the syndrome.

SULFONAMIDE HYPERSENSITIVITY SYNDROME

Fewer than 0.1% of treatment courses with sulfonamides are complicated by a hypersensitivity syndrome. Sulfonamide hypersensitivity syndrome is similar to that seen with the anti- convulsants, including the characteristic facial and periorbital edema. It typically begins 3 weeks after starting the medication, but may occur as soon as 1 week after. The skin eruption is usually morbilliform or an erythroderma. Patients with this syndrome are often slow acetylators unable to detoxify the toxic and immunogenic metabolites generated during the metabolism of the sulfonamides. Patients with sulfonamide hypersensitivity syndrome may develop antibodies that recognize microsomal proteins to which the reactive metabolite of the sulfonamides binds. Hepatitis, nephropathy, pneumonitis, pericarditis, myocarditis, pancreatitis, and pleural effusion can all occur as a part of the syndrome. The hepatitis can be life-threatening. Sulfonamide hypersensitivity syndrome is treated with topical treatments appropriate for the skin eruption, and

systemic steroids for systemic complications. Zonisamide, a sulfonamide anticonvulsant, cross-reacts with sulfonamides but not other anticonvulsants.

MINOCYCLINE HYPERSENSITIVITY SYNDROME

Minocycline hypersensitivity syndrome occurs in young adults, usually in the context of acne therapy. Females are favored, as are those of Afro-Caribbean ancestry. Deficiency of glutathione S-transferases is common in affected individuals, and is more common in persons of Afro-Caribbean descent. In patients with minocycline hypersensitivity syndrome, minocycline may be detected in the blood up to 17 months after discontinuation of the medication, suggesting that slow metabolism and persistent levels of medication may play a role. The syndrome begins usually 2-4 weeks after starting the minocycline. Fever, a skin eruption, and adenopathy occur in more than 80% of cases. Headache and cough are common complaints. The eruption can be morbilliform, erythrodermic, or pustular. Facial edema is common. Liver involvement occurs in 75% of cases, and renal disease in 17%. Minocycline hypersensitivity is particularly associated with interstitial pneumonia with eosinophilia. This may progress to respiratory distress syndrome. It can be life-threatening, but most patients survive. Myocarditis has also been reported. Treatment is systemic steroids.

DAPSONE HYPERSENSITIVITY SYNDROME

Dapsone hypersensitivity syndrome occurs in <1% of patients given this medication. It usually begins 4 weeks or more after starting the drug. Hemolytic anemia and methemoglobinemia may be present. A morbilliform eruption that heals with de- squamation is most characteristic. Icterus and lymphadenopa- thy occur in 80% of patients. Eosinophilia is typically NOT present. Liver involvement is a mixture of hepatocellular and cholestatic. The bilirubin is elevated in 85%, partly attributable to the hemolysis. Liver involvement may be fatal. Hypoalbuminemia is characteristic. Bullous drug reactions (Stevens-Johnson syndrome [SJS] and toxic epidermal necrolysis [TEN]. Skin blistering may

complicate drug reactions in many ways. Medications may induce known autoimmune bullous diseases such as pemphigus (penicillamine) or linear IgA disease (vancomycin). Acute generalized exanthematous pustulosis may be so extensive as to cause a positive Nikolsky sign, and have a background of purpura and targetoid lesions, simulating SJS/TEN. Pseudoporphyria and other photodermatoses from drugs may form bullae. Cytokines may produce widespread bullous eruptions, perhaps through physiologic mechanisms. The term bullous drug reaction, however, most commonly refers to a drug reaction in the erythema multiforme group. These are fortunately uncommon reactions to medications, with an incidence of 0.4-1.2 per million person-years for TEN and 1.2-6.0 per million person-years for SJS. These drug- induced forms of erythema multiforme are usually more extensive than herpes-associated erythema multiforme or mycoplasma-associated SJS, but at times the distinction may be difficult. The more severe the reaction, the more likely it is to be drug-induced (50% of cases of SJS and 80% of cases of TEN). The exact definitions of SJS and TEN remain arbitrary as a result of overlap in some cases. The following definitions are useful to classify cases: SJS has less than 10% body surface area (BSA) involved, cases with 10-30% are SJS-TEN overlap cases, and more than 30% BSA erosion is called TEN. SJS and TEN are considered by some as parts of a disease spectrum based on the following: They are most commonly induced by the same medications. Patients initially presenting with SJS may progress to extensive skin loss resembling TEN. The histologic findings are indistinguishable. Both are increased by the same magnitude in HIV infection. However, recently, genetic evaluations of Caucasians with SJS and TEN showed distinct genetic predispositions for these conditions, allowing for consideration of them as distinct disorders. The cause of SJS/TEN is not established. In Taiwan car-bamazepine causes up to one-third of cases, but only 5% of cases in Europe. In Han Chinese the HLA haplotype HLA- B*1502 is present in the vast majority of cases of carbamazepine- induced SJS/TEN patients and is present in about 10% of the Han Chinese population in general. This HLA association is NOT found, however, in patients with carbamazepine-induced

SJS/TEN of other ethnicities, suggesting that this marker for risk is specific for Asians. HLA typing should be performed in all Asians before starting carbamazepine, since the prevalence of HLA-B*1502 is 5-10% in Asians in the USA and Asia. HHV-6 reactivation may also be seen in SJS/TEN patients. More than 100 medications have been reported to cause SJS and TEN. In adults, common inciting medications are trimethoprim-sulfamethoxazole (1-3 in 100 000), Fansidar-R, sulfadoxine plus pyrimethamine (10 in 100 000), nevirapine, lamotrigine (1 in 1000 adults and 3 in 1000 children), and carbamazepine (14 in 100 000). Antibiotics (especially long- acting sulfa drugs and penicillins), other anticonvulsants, anti-inflammatories (NSAIDs), and allopurinol are also frequent causes. Currently, in Europe, allopurinol is the most common cause of SJS and TEN. In children SJS/TEN is most commonly caused by sulfonamides and other antibiotics, antiepileptics, and acetaminophen. SJS/TEN from trimethoprim-sulfamethoxazole is significantly more common in the spring. If the inciting drug has a short half-life, and the drug is promptly stopped, the mortality is reduced from 26% to 5%. This suggests that the use of agents with short half-lives and the prompt discontinuation of the medication when the first signs of an adverse reaction appear may be very important ways to reduce the mortality from TEN. Fever and influenza-like symptoms often precede the eruption by a few days. Skin lesions appear on the face and trunk and rapidly spread (usually within 4 days) to their maximum extent. Initial lesions are macular and may remain so, followed by desquamation, or may form atypical targets with purpuric centers that coalesce, form bullae, then slough. Patients with purpuric atypical targets may evolve more slowly, and usually the skin lesions are clinically inflammatory. In SJS, virtually always, two or more mucosal surfaces are also eroded, the oral mucosa and conjunctiva being most frequently affected. There may be photophobia, difficulty with swallowing, rectal erosions, painful urination, and cough, indicative of ocular, alimentary, urinary, and respiratory tract involvement, respectively. Over time more than 10% of the skin surface may be sloughed, leading to SJS/TEN overlap; if more than 30% of the skin is lost, a case is classified as TEN. In other patients,

macular erythema is present in a local or widespread distribution over the trunk. Mucosal involvement may not be found. The epidermis in the areas of macular erythema rapidly becomes detached from the dermis, leading to extensive skin loss, often much more rapidly than occurs in the patients with atypical targets and extensive mucosal involvement. "Pure TEN" is a conceptual way of thinking of such patients. Rarely, SJS/TEN patients may present with lesions predominantly in sun-exposed areas, with a clear history of a recent significant sun exposure. This suggests that, in rare cases, SJS/TEN may be photoinduced or photo-exacerbated. Patients with SJS/ TEN may have internal involvement very similar to patients with DRESS/DIHS induced by the same medication (see above). These most commonly include eosinophilia, hepatitis, and worsening renal function. A skin biopsy is usually performed. Frozensection analysis may lead to a rapid diagnosis. This is to exclude other diseases (such as staphylococcal scalded skin syndrome, pemphigus, graft versus host disease (GVHD), etc.) and to confirm the diagnosis. Independent of the extent of the slough, the clinical morphology (atypical targets as opposed to simple erythema), or the clinical diagnosis (SJS or TEN), the histology is similar. There is a lymphocytic infiltrate at the dermoepidermal junction with necrosis of keratinocytes that at times may be full-thickness. The infiltrate may be marked or very scant. Paraneoplastic pemphigus also shows changes of erythema multiforme and may be excluded with direct immunofluorescence. Patients with GVHD may also demonstrate a TEN-like picture with identical histology. Management of these patients is similar to those with an extensive burn. They suffer fluid and electrolyte imbalances, bacteremia from loss of the protective skin barrier, hypercatabolism, and sometimes acute respiratory distress syndrome. Their metabolic and fluid requirements are less than in burn victims, however. Survival is improved if patients are cared for in a specialized "burn unit," or on a special dermatology unit with skill in managing these patients. Hospital dermatologists have greatly improved the care of such patients. Nutritional support is critical. Patients who are very ill or with more than 30-50% loss of epidermis should be transferred for such care. In addition to extent

of skin loss, age, known malignancy, tachycardia, renal failure, hypergly- cemia, and low bicarbonate are all risk factors for having a higher mortality with SJS/TEN. The SCORTEN gives one point for each of these findings. The SCORTEN total predicts mortality, with a 3.2% mortality for 0-1 points, and a 90% mortality for 5 or more points. However, respiratory tract involvement, not included in the SCORTEN, is also a bad prognostic sign. About one-quarter of TEN patients have bronchial involvement. In TEN, epithelial detachment of the respiratory mucosae and associated acute respiratory distress syndrome are associated with a mortality of 70%. Pre-existing diabetes mellitus and concurrent tuberculosis may also increase mortality. The use of systemic agents to treat SJS/TEN is very controversial due to the rarity of these cases and the lack of controlled interventional trials. One important point appears to be that, whatever therapy is considered, it should be given early and in adequate doses. Low doses are associated with either lack of efficacy or medication complications without benefit. IVIG is now frequently used to manage the more severe adult and pediatric patients with bullous drug eruptions (TEN). A dose of 1 g/kg/day for the first 4 days following admission is effective. It is best used when detachment has not become extensive, as total BSA of skin loss is an important predictor of mortality. Keratinocyte death in SJS and TEN is proposed to occur via two potential mechanisms, and the relative importance of each of these mechanisms in SJS and TEN is not known. Activated cytotoxic T cells and natural killer (NK) cells produce granulysin, perforin, and granzyme B, all of which can induce keratinocyte necrosis. In addition, keratinocyte necrosis can be induced by the binding of soluble Fas ligand (sFasL) to Fas (also known as the death receptor or CD95). Soluble Fas ligand is elevated in the blood of patients with TEN, and its level correlates with BSA involvement. In addition, the peripheral blood mononuclear cells of patients with TEN secrete Fas ligand upon exposure to the incriminated drug. The sera of patients with TEN induce necrosis of cultured keratinocytes, and a monoclonal antibody to Fas ligand in a dose-dependent fashion inhibits keratinocyte necrosis exposed to TEN patient sera. This strongly

supports Fas expression by keratinocytes, and Fas ligand production by immune cells, as the mechanisms by which TEN is mediated. The proposed mechanism of action of IVIG in TEN is by IVIG blocking the binding of sFasl to Fas, stopping keratinocyte apoptosis. Fever and influenzalike symptoms often precede the eruption by a few days. Skin lesions appear on the face and trunk and rapidly spread (usually within 4 days) to their maximum extent. Initial lesions are macular and may remain so, followed by desquamation, or may form atypical targets with purpuric centers that coalesce, form bullae, then slough. Patients with purpuric atypical targets may evolve more slowly, and usually the skin lesions are clinically inflammatory. In SJS, virtually always, two or more mucosal surfaces are also eroded, the oral mucosa and conjunctiva being most frequently affected. There may be photophobia, difficulty with swallowing, rectal erosions, painful urination, and cough, indicative of ocular, alimentary, urinary, and respiratory tract involvement, respectively. Over time more than 10% of the skin surface may be sloughed, leading to SJS/TEN overlap; if more than 30% of the skin is lost, a case is classified as TEN. In other patients, macular erythema is present in a local or widespread distribution over the trunk. Mucosal involvement may not be found. The epidermis in the areas of macular erythema rapidly becomes detached from the dermis, leading to extensive skin loss, often much more rapidly than occurs in the patients with atypical targets and extensive mucosal involvement. "Pure TEN" is a conceptual way of thinking of such patients. Rarely, SJS/TEN patients may present with lesions predominantly in sun-exposed areas, with a clear history of a recent significant sun exposure. This suggests that, in rare cases, SJS/TEN may be photo-induced or photo-exacerbated. Patients with SJS/ TEN may have internal involvement very similar to patients with DRESS/DIHS induced by the same medication (see above). These most commonly include eosinophilia, hepatitis, and worsening renal function. A skin biopsy is usually performed. Frozen-section analysis may lead to a rapid diagnosis. This is to exclude other diseases (such as staphylococcal scalded skin syndrome, pemphigus, graft versus host disease (GVHD), etc.) and to confirm the diagnosis. Independent of the extent of the

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skin loss has occurred, immunosuppressives only add to the morbidity and perhaps mortality of the disorder. In children with SJS, this adverse effect has been documented, probably since their mortality is low and immunosuppressives only add risk for infection. Because SJS and TEN evolve rapidly (average 4 days to maximum extent), very early treatment would be required to observe benefit. Patients have developed TEN while undergoing systemic corticosteroid therapy in moderate to high doses (40-60 mg of prednisone equivalent daily), suggesting that this level of immunosuppression is insufficient to alter the evolution of SJS or TEN. If immunosuppressive treatment is considered, it should be used as soon as possible, given as a short trial to see if the process may be arrested, and then tapered rapidly to avoid the risk of immunosuppression in a patient with substantial loss of skin. High-dose corticosteroids given intravenously with reported success have included 100 mg of dexamethasone per day for 3 or 4 days and methylprednisolone, 30 mg/kg/day for 3 days. Cyclosporine in doses of 3-5 mg/kg/day for 8-24 days, with or without an initial burst of systemic steroids, has also been reported to stop SJS and TEN abruptly. Anecdotally, both etanercept, 25 mg twice, and infliximab, 5 mg/kg intravenously once, have led to rapid termination of skin sloughing. Systemic and topical steroid therapy for ocular involvement also appears to improve outcomes. In patients with SJS/TEN who also have systemic involvement as seen in DIHS (considered by some as SJS/TEN representing the cutaneous eruption of DIHS), systemic steroids should be considered. For patients who survive, the average time for epidermal regrowth is 3 weeks. The most common sequelae are ocular scarring and vision loss. The only predictor of eventual visual complications is the severity of ocular involvement during the acute phase. A sicca-like syndrome with dry eyes may also result, even in patients who never had clinical ocular involvement during the acute episode. Other complications include cutaneous scarring, eruptive melanocytic lesions, and nail abnormalities. Transient, widespread verrucous hyperplasia resembling confluent seborrheic keratoses has also been reported.

RADIATION-INDUCED ERYTHEMA MULTIFORME

If phenytoin is given prophylactically in neurosurgical patients who are receiving whole-brain radiation therapy and systemic steroids, an unusual reaction occurs. As the dose of steroids is being reduced, erythema and edema initially appear on the head in the radiation ports. This evolves over 1 or 2 days to lesions with the clinical appearance and histology of SJS or even TEN. The eruption spreads caudad and mucosal involvement may occur. A similar syndrome has been reported with the use of amifostine during radiation for head and neck cancers. This syndrome can rarely be seen with radiation therapy alone. If amifostine is used to reduce head and neck radiation-associated acute and chronic xerostomia, there is a significant risk of SJS/TEN.

HIV DISEASE AND DRUG REACTIONS

HIV-infected patients, especially those with helper T-cell counts between 25 and 200, are at increased risk for the development of adverse reactions to medications. Morbilliform reactions to trimethoprimsulfamethoxazole occur in 45% or more of AIDS patients being treated for Pneumocystis jirovecii (formerly carinii) pneumonia. In twothirds of patients without life-threatening reactions, trimethoprimsulfamethoxazole treatment can be continued with simple conservative support, and the eruption may resolve. Associated hepatitis or neutropenia may require discontinuation of the drug. A similar increased rate of reaction to amoxicillinclavulanate in HIV is also seen. If the dermatitis is treatment-limiting but the eruption is not life-threatening, lowdose rechallenge / desensitization may be attempted. It is successful in 65-85% of patients in the short term, and in more than 50% in the long term. In fact, initial introduction of trimethoprimsulfamethoxazole for prophylaxis by dose escalation reduces the rate of adverse reactions as well. However, rechallenge at full dose may have the same rate of recurrent eruptions as does introduction by dose escalation. Although low-dose rechal- lenge is usually safe, severe, acute reactions including marked hypotension may occur. Although most adverse reactions occur in the first few

days of rechallenge, adverse reactions may appear months after restarting trimethoprim- sulfamethoxazole, and may be atypical in appearance. The mechanism of this increased adverse reaction to trimethoprimsulfamethoxazole is unknown. Severe bullous reactions, SJS, and TEN are between 100 and 1000 times more common per drug exposure in patients with AIDS. These reactions are usually caused by sulfa drugs, especially long-acting ones, but may be caused by many agents. Nevirapine, a non-nucleoside reverse transcriptase inhibitor, has been associated with a high rate of severe drug eruptions including SJS/TEN. Most of these adverse reactions are cutaneous and occur in the first 6 weeks of treatment. This high rate of reaction can be reduced by starting with a lower lead-in dose, and by concomitant treatment with prednisone during the induction period. Nevirapine hypersensitivity syndrome presents with fever, hepatitis, or rash. Over 1% of patients will develop SJS/TEN. HLA-DRB1*0101 patients are at increased risk for cutaneous reactions to nevirapine if not associated with hepatotoxicity. Hepatitis, but not cutaneous reactions, is seen more commonly in patients with CD4 counts above 200250. Fixed drug eruptions are also frequently seen in patients with HIV infection. Abacavir is associated with a potentially life-threatening adverse reaction in 8% of patients. The syndrome includes fever, rash, gastrointestinal, or respiratory symptoms. It usually occurs in the first 6 weeks of treatment, but can happen within hours of the first dose. Rechallenge in these patients may lead to life-threatening hypotension and death. Abacavir hypersensitivity is increased in patients who are HLA-B*5701 positive, and screening of patients for this HLA type and not exposing patients with this HLA type to abacavir have decreased the number of cases of abacavir hypersensitivity syndrome. Adverse drug reactions to abacavir can also occur in HLA-B*5701-negative patients. Aciclovir, nucleoside and non-nucleoside reverse transcriptase inhibitors (except nevirapine), and protease inhibitors are uncommon causes of ADRs. Many reactions attributed to these agents may actually be coexistent HIV-associated pruritic disorders, especially folliculitis, which are very common in patients with AIDS.

FIXED DRUG REACTIONS

Fixed drug reactions (FDE) are common. Fixed drug eruptions are so named because they recur at the same site with each exposure to the medication. The time from ingestion of the offending agent to the appearance of symptoms is between 30 minutes and 8 hours, averaging 2 hours. In most patients, six or fewer lesions occur, and frequently only one. Uncommonly, fixed eruptions may be multifocal with numerous lesions. They may present anywhere on the body, but half occur on the oral and genital mucosa. Fixed eruptions represent 2% of all genital ulcers evaluated at clinics for sexually transmitted diseases, and are not infrequent in young boys. In males lesions are usually unifocal and can affect the glans or shaft of the penis. FDE of the vulva is often symmetrical, presenting as an erosive vulvitis, with lesions on the labia minora and majora and extending on to the perineum. Other unusual variants of FDE include eczematous, urticarial, papular, purpuric, linear, giant, and psoriasiform. At times, some lesions of FDE will not reactivate with exposure due to a presumed "refractory period" which may last from weeks to months. Clinically, an FDE begins as a red patch that soon evolves to an iris or target lesion similar to erythema multiforme, and may eventually blister and erode. Lesions of the genital and oral mucosa usually present as erosions. Most lesions are 1 to several cm in diameter, but larger plaques may occur, resembling cellulitis. Characteristically, prolonged or permanent postinflammatory hyperpigmentation results, although a nonpigmenting variant of an FDE is recognized. With repeated or continued ingestion of the offending medication, new lesions may be added, sometimes eventuating in a clinical picture similar to SJS. Histologically, an interface dermatitis occurs with subepidermal vesicle formation, necrosis of keratinocytes, and a mixed superficial and deep infiltrate of neutrophils, eosinophils, and mononuclear cells. Pigment incontinence is usually marked, correlating with the pigmentation resulting from FDEs. As biopsies are generally performed during the acute stage of a recurrence, the stratum corneum is normal. Papillary dermal fibrosis and deep perivas- cular pigment incontinence are commonly present from prior episodes. This contrast between a

normal stratum corneum (suggesting an acute process) and chronic dermal changes is virtually pathognomonic of FDE. Medications inducing FDEs are usually those taken intermittently. Many of the NSAIDs, especially pyrazolone derivatives, paracetamol, naproxen, oxicams, and mefenamic acid, cause FDE, with a special predilection for the lips. Sulfonamides, trimethoprim, or the combination are now responsible for the majority of genital FDEs. Barbiturates, tetracyclines, phenolphthalein (in laxatives), acetaminophen, cetirizine, celecoxib, dextromethorphan, hydroxyzine, quinine, lamotrigine, phenylpropanolamine, erythromycin, and Chinese and Japanese herbs are other possible causes. The risk of developing an FDE has been linked to HLA-B22. Patch tests with various concentrations of the offending medication can reproduce the lesion on affected but not unaffected skin. Tape-stripping the skin before applying the suspected medication in various vehicles may increase the likelihood of a positive patch test. This technique appears to be most useful in pyrazolone derivativerelated reactions that are reproduced in 85% or more of cases. Occasionally, FDEs do not result in long-lasting hyperpig- mentation. The so-called nonpigmenting FDE is distinctive, and has two variants. One is the pseudo-cellulitis or scarlati- niform type which is characterized by large, tender, erythematous plaques that resolve completely within weeks, only to recur on reingestion of the offending drug. Pseudoephedrine hydrochloride is by far the most common culprit. The second variant is the baboon syndrome, also called symmetrical drug-related intertriginous and flexural exanthema (SDRIFE). SDRIFE preferentially affects the buttocks, groin, and axilla with erythematous, fixed plaques. Histologically, a giant cell lichenoid dermatitis can be seen in this setting. The diagnosis of FDE is often straightforward and is elucidated by the history. However, confirmation with provocation tests can be performed. Due to the "refractory period," provocation tests need to be delayed at least 2 weeks from the last eruption. If an oral provocation test is considered, the initial challenge should be 10% of the standard dose, and patients with widespread lesions (SJS/TEN-like) should not be challenged. Patch testing using a drug concentration of 10-20% in petrolatum or water applied to a previously reacted site

is the recommended approach. In most patients the treatment is simply to stop the medication. Desensitization can be successful. Lesions of an FDE contain intraepidermal CD8+ T cells with the phenotypic markers of effector memory T cells. These epidermal-resident T cells produce IFN-y. Such cells are found in resolved lesions of HSV, suggesting they are a defense mechanism preventing viral reactivation in the epidermis. Once the medication is stopped, the abundant CD4+ Fox P3+ T cells (T-regs) in lesions of FDE are felt to downregulate the eruption. In SJS/TEN patients, such T-regs are found in much fewer numbers than in FDE, explaining the progression of SJS/TEN despite stopping of the medication. Resident mast cells in lesions of FDE may be the cells initially activated with drug exposure, explaining the rapid onset of the lesion.

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

Acute generalized exanthematous pustulosis (AGEP), also known as toxic pustuloderma and pustular drug eruption, is an uncommon reaction with an incidence of 1-5 cases per million per year. The average age in Europe is in the fifties, and about one decade younger in Israel and Taiwan. Children can be affected. Women have been slightly more commonly affected until recently, when a strong female predominance has been identified. Drugs are the most common cause of this reaction pattern, but it has also been reported following mercury exposure. AGEP following viral and bacterial infections has been reported, but a causal association has not been validated. Similarly, Loxoceles bites have been followed by AGEP, but these patients in some cases have also received antibiotics. Recent reports of "acute localized exanthematous pustulosis" (ALEP) appear to be acneiform eruptions which occur acutely following antibiotic exposure. Their relationship to AGEP is unclear. The eruption is of sudden onset, within 1 day in many cases associated with antibiotics, and averaging 11 days in other cases. The rash is accompanied by fever in most cases. Facial edema may be present. Initially, there is a scarlatiniform erythema. The eruption evolves and disseminates rapidly, consisting usually of more than 100 nonfollicular pustules less than 5 mm in

diameter. The Nikolsky sign may be positive. Mucous membrane involvement is common, but usually only affects one surface and is non-erosive. Laboratory abnormalities typically include a leukocytosis with neutrophilia (90%), and at times an eosinophilia (30%). Typically, the entire self-limited episode lasts up to 15 days. Characteristically, widespread superficial desquamation occurs as the eruption clears. The reported mortality is 5%. AGEP can recur with a second exposure to the medication. In over 90% of cases, drugs are the cause of AGEP. Commonly implicated medications include ampicillin/amoxicillin, pristi- namycin, quinolones, hydroxychloroquine, sulfonamide antibiotics, terbinafine, imatinib, and diltiazem. Corticosteroids, macrolides, oxicam, NSAIDs, pseudoephedrine, terazosin, omeprazole, sennoside, and antiepileptics have also caused AGEP. In some cases contact sensitivity has been implicated as a cause, with corticosteroids, mercury, bufexamac, and lacquer chicken the triggering agents. Recently radiocontrast material has been shown to cause AGEP. In 5% of cases, no trigger can be identified. In the classic case, the diagnosis is straightforward, with the characteristic sudden and rapid onset, widespread pustulation, and selflimited course. The facial edema and pustulation can simulate DRESS/DIHS from anticonvulsants. In anticonvulsant hypersensitivity syndrome, eosinophilia, lymphadenopathy, atypical lymphocytosis, and liver dysfunction are often found. Recently, cases of AGEP have been reported with a prolonged course, widespread erosive mucosal lesions, and systemic involvement identical to DRESS/DIHS, suggesting that AGEP can be the eruption seen in anticonvulsant hyper- sensitivity syndrome. In about 1% or less of AGEP cases, skin lesions similar to SJS/TEN are seen. These include purpuric atypical targets and widespread skin loss. Biopsies may show AGEP with or without additional features of SJS/TEN. These cases are termed AGEP/TEN overlap. Pustular psoriasis, especially pustular psoriasis of pregnancy, can be difficult to differentiate from AGEP. If there are no characteristic lesions of psoriasis elsewhere, and no prior personal or family history of psoriasis, distinguishing these two entities may be impossible, and the patient may need to be followed for a final diagnosis to be made. Amicrobial

pustulosis in the setting of a connective tissue disease can also resemble AGEP, but lesions are usually localized to the flexors and the course is more chronic. Histologically, early lesions show marked papillary edema, neutrophil clusters in the dermal papillae, and perivascular eosinophils. There may be an associated leukocytoclastic vas- culitis. Well-developed lesions show intraepidermal or subcorneal spongiform pustules. If there is a background of erythema multiforme clinically, the histologic features of erythema multiforme may be superimposed. The presence of eosinophils and the marked papillary edema help to distinguish this eruption from pustular psoriasis. However, pustular psoriasis of pregnancy is often associated with tissue eosinophilia. Patch testing with the suspected agent may reproduce a pustular eruption on an erythematous base at 48 h in about 50% of cases. Patch testing rarely will result in a recrudescence of AGEP. AGEP is mediated by T cells, which produce high levels of IL-8, IFN-y, IL-4 and 5, and GM-CSF. IL-8 is also produced by keratinocytes in lesions of AGEP. Most patients with AGEP can be managed with topical steroids and antihistamines. In many cases, systemic steroids are also given. In severe cases infliximab and etanercept have rapidly stopped the pustulation and appeared to have hastened the resolution of the eruption. This approach has also been used in AGEP/TEN cases with success. Cyclosporine, as used for pustular psoriasis, has been used effectively in an AGEP case that relapsed as systemic steroids were tapered.

DRUGINDUCED PSEUDOLYMPHOMA

At times, exposure to medication may result in cutaneous inflammatory patterns that resemble lymphoma. These pseudolymphomatous drug eruptions may resemble either T-cell or B-cell lymphomas. The most common drug-induced pseudolymphoma is one resembling cutaneous T-cell lymphoma (CTCL) clinically and histologically. The most frequent setting in which they occur is that of a drug-induced hypersensitivity syndrome (DRESS/DIHS) as described above, in which, uncommonly, the histology may resemble cutaneous T-cell lymphoma. More rarely, medications may induce plaques or nodules, usually in elderly white men

after many months of treatment. Lymphadenopathy and circulating Sezary cells may also be present. CD30-positive cells may be present in the infiltrate. Usually, other features such as kerati- nocyte necrosis and dermal edema help to distinguish these reactions from true lymphoma. Importantly, T-cell receptor gene rearrangements in the skin and blood may be positive (or show pseudoclones) in these drug-induced cases, representing a potential pitfall for the unwary physician. Pseudolymphoma resolves with discontinuation of the medication. The medication groups primarily responsible are anticonvulsants, sulfa drugs (including thiazide diuretics), dapsone, and antidepressants. Vaccinations and herbal supplements can also induce pseudolymphoma.

URTICARIA/ANGIOEDEMA

Medications may induce urticaria by immunologic and non- immunologic mechanisms. In either case, clinically the lesions are pruritic wheals or angioedema. Urticaria may be part of a more severe anaphylactic reaction with broncho- spasm, laryngospasm, or hypotension. Immediate hypersensitivity skin testing and sometimes RAST is useful in evaluating risk for these patterns of reaction. Aspirin and the NSAIDs are the most common causes of nonimmunologic urticarial reactions. They alter prostaglandin metabolism, enhancing degranulation of mast cells. They may therefore also exacerbate chronic urticaria of other causes. The nonacetylated salicylates (trilisate and salsalate) do not cross- react with aspirin in patients experiencing bronchospasm and may be safe alternatives. Some patients have urticaria to only one medication in this family, without cross-reaction with other NSAIDs, suggesting that specific IgE-mediated mechanisms may also be possible in NSAID-induced urticaria. Other agents causing nonimmunologic urticaria include radiocontrast material, opiates, tubocurarine, and polymyxin B. Pretesting does not exclude the possibility of anaphylactoid reaction to radiocontrast material. The use of low-osmolarity radiocontrast material and pretreatment with antihistamines, systemic steroids, and in those with a history of asthma, theophylline, may reduce the likelihood of

reaction to radiocon- trast material. Immunologic urticaria is most commonly associated with penicillin and related P-lactam antibiotics. It is associated with IgE antibodies to penicillin or its metabolites. Skin testing with penicillin and its major and minor determinants is useful in evaluating patients with a history of urticaria associated with penicillin exposure. If the patient is skin testpositive, an alternative antibiotic must be considered, or the patient should be given penicillin in a desensitization protocol. Most patients with a history of penicillin "allergy" are skin testnegative. These patients can be treated with penicillin with a low likelihood of a severe adverse event. If a semisynthetic penicillin is associated with the initial reaction, the patient may be skin test-negative to the standard penicillin-derived reagents and still suffer anaphylaxis. This may be caused by IgE antibodies directed against the acyl side chain, in the case of amoxicillin. Patients with penicillin allergy have an increased rate of reaction to cephalosporins. In the case of cefaclor, half of anaphy- lactic reactions occur in patients with a history of penicillin allergy. Third-generation cephalosporins are much less likely to induce a reaction in a penicillin-allergic patient than are firstor second-generation ones. Bupropion is commonly used for depression and smoking cessation. It can induce urticaria, which may be associated with hepatitis and a serum sickness-like syndrome. Two anti- histamines, cetirizine and hydroxyzine, may induce urticaria, an apparent paradox which may lead to confusion in the clinical setting. Angioedema is a known complication of the use of angiotensinconverting enzyme (ACE) inhibitors and angiotensin II antagonists. Black persons are at nearly five times greater risk than white persons. Lisinopril and enalapril produce angioedema more commonly than captopril. Angioedema typically occurs within a week of starting therapy, but may begin after months of treatment. The episodes may be severe, requiring hospitalization in up to 45% of patients, intensive care in up to 27%, and intubation in up to 18%. One- quarter of patients affected give a history of previous angioedema. Captopril enhances the flare reaction around wheals. The angioedema appears to be dose-dependent, as it may resolve with decreased dose. All these factors suggest that the angioedema may represent a consequence of a

normal pharmacologic effect of the ACE inhibitors. The blocking of kininase II by ACE inhibitors may increase tissue kinin levels, enhancing urticarial reactions and angioedema. Although this is dose-dependent, ACE inhibitor users with one episode of angioedema have a ten-fold risk of a second episode, and the recurrent episodes may be more severe. The treatment of urticaria is discussed in Chapter 7.

RED MAN SYNDROME

The intravenous infusion of vancomycin is frequently complicated, especially if the infusion is rapid, by a characteristic reaction called "red man syndrome." At any time during the infusion, a macular eruption appears initially on the back of the neck, sometimes spreading to the upper trunk, face, and arms. Angioedema has been described. There is associated pruritus and "heat," as well as hypotension. The hypotension may be severe enough to cause cardiac arrest. Oral vanco- mycin has caused a similar reaction in a child. Children with systemic juvenile idiopathic arthritis (JIA) may suffer potentially fatal macrophage activation syndrome (MAS) during or after a red man reaction from vancomycin. The red man reaction is caused by elevated blood histamine. Red man syndrome can be prevented in most patients by reducing the rate of infusion of the antibiotic, or by pretreatment with H and H2 antihistamines. While typically reported with vancomycin, similar "anaphylactoid" reactions have been seen with ciprofloxacin, amphotericin B, rifampin, infliximab, and teicoplanin.

PHOTOSENSITIVITY REACTIONS (PHOTOSENSITIVE DRUG REACTIONS)

Medications may cause phototoxic, photoallergy, and lichenoid reactions, and photodistributed telangiectasias, as well as pseudoporphyria. The mechanisms of photosensitivity are discussed in Chapter 3. In many cases the mechanism for drug-induced photosensitivity is unknown. Most medication- related photosensitivity is triggered by radiation in the UVA range, partly for two reasons. First, most photosensitizing drugs have absorption spectra in the UVA and short-

visible range (315-430 nm), and second, UVA penetrates into the dermis where the photosensitizing drug is present. The most common causes of photosensitivity are NSAIDs, trimethoprim- sulfamethoxazole, thiazide diuretics and related sulfonyl-ureas, quinine and quinidine, phenothiazines, and certain tetracyclines; numerous other medications in many classes induce photosensitivity less commonly. Phototoxic reactions are related to the dose of both the medication and the UV irradiation. They potentially could occur in anyone if sufficient thresholds are reached, and do not require prior exposure or participation by the immune system. Persons of higher skin types are at lower risk of developing phototoxic eruptions in some studies. There is individual variation in the amount of photosensitivity created by a standard dose of medication, independent of serum concentration. This remains unexplained, but reflects the clinical setting, where interindi- vidual variability in development of phototoxic eruptions is seen. Reactions can appear from hours to days after exposure. Tetracyclines (especially demeclocycline), amiodarone, and the NSAIDs are common culprits. The reaction may present as immediate burning with sun exposure (amiodarone, chlorpromazine) or exaggerated sunburn (fluoroquinolone antibiotics, chlorpromazine, amiodarone, thiazide diuretics, quinine, tetracyclines). Hyperpigmentation may complicate phototoxic reactions and may last for many months. Treatment may include dose reduction and photoprotection, with a sunblock with strong coverage through the whole UVA spectrum. Photoallergic reactions are typically eczematous and pru-ritic, and may first appear weeks to months after drug exposure. They involve the immune system. Unfortunately, in the case of photoallergy to systemic medications, photopatch testing is infrequently positive and is of limited clinical value. In general, photoallergic reactions are not as drug dosedependent as phototoxic reactions. Photosensitivity of both the phototoxic and photoallergic types may persist for months to years after the medication has been stopped. Photosensitivity reactions to various drugs are discussed individually below, emphasizing the characteristic patterns seen with each medication group. Amiodarone photosensitivity develops in up to 75% of treated patients, and occurs

after a cumulative dose of 40 g. A reduced minimal erythema dose (MED) to UVA, but not UVB, occurs, and gradually returns to normal between 12 and 24 months after stopping the medication. Stinging and burning may occur as soon as 30 min after sun exposure. Less commonly, a dusky, bluered erythema of the face and dorsa of the hands occurs. At times papular reactions are also seen. Desquamation, as seen following sunburn, is not observed following amiodarone photosensitivity reactions. This reaction may be dosedependent and acute burning may be relieved by dose reduction. Narrow-band UVB may desensitize patients with persistent phototoxicity after stopping amiodarone. NSAIDs, especially piroxicam, are frequently associated with photosensitivity. The characteristic reaction is a vesicular eruption of the dorsa of the hands, sometimes associated with a dyshidrosiform pattern on the lateral aspects of the hands and fingers. In severe cases even the palms may be involved. Histologically, this reaction pattern shows intraepidermal spongiosis, exocytosis, and perivascular inflammatory cells a pattern typical of photoallergy. However, this reaction may occur on the initial exposure to the medication, but phototoxicity tests in animals and humans have been negative. Patients with photosensitivity to piroxicam may also react to thiosalicylic acid, a common sensitizer in thimerosal. Half of patients having a positive patch test to thimerosal with no prior exposure to piroxicam are photopatch test-positive to piroxicam. This suggests that piroxicam reactions seen on initial exposure to the medication may be related to sensitization during prior thimerosal exposure. Topical exposure to ketoprofen (Orudis gel) can lead to a photoallergic contact dermatitis, and contamination of personal objects may lead to persistence despite stopping the use of the product. Sulfonamide antibiotics, related hypoglycemic agents, and the sulfonylurea diuretics may all be associated with photosensitivity reactions. In addition, patients may tolerate one of the medications from this group, but when additional members of the group are added, clinical photosensitivity occurs. The typical pattern is erythema, scale, and in chronic cases, licheni- fication and hyperpigmentation. Fluoroquinolone antibiotics are frequently associated with photosensitivity reactions. Sparfloxacin is highly

photosensitizing; enoxacin, ciprofloxacin, and sitafloxacin are mildly photosensitizing; and levofloxacin rarely, if ever, causes photosensitivity. Photodistributed lichenoid reactions have been reported most commonly from thiazide diuretics, quinidine, and NSAIDs, but also occur from diltiazem and clopidogrel bisul- fate. They present as erythematous patches and plaques. Sometimes, typical Wickham's striae are observed in the lesions. Histologically, photodistributed lichenoid reactions are often indistinguishable from idiopathic lichen planus. Marked hyperpigmentation may occur, especially in persons of higher skin types (IV-VI), and especially in diltiazeminduced cases. The lichenoid nature of the eruption may not be clinically obvious, and histology is required to confirm the diagnosis. This hyperpigmentation may persist for months. Voriconazole, a second-generation triazole, has been associated with an unusual combination of photosensitive phenomena. Photosensitivity occurs in 1-2% or more of patients taking voriconazole for more than 12 weeks. It appears to be UVA- induced, and is not dosedependent. Usually, the photosensitivity is mild and with the use of sun protection and topical treatment the voriconazole can be continued. Cheilitis and facial erythema are typical initial manifestations. In a few patients, however, significant complications occur. Pseudoporphyria (with foot erosions as well), eruptive lentigines and atypical nevi, premature aging, and even the development of highly aggressive and potentially fatal squamous cell carcinomas in sun-exposed sites have been reported. Affected patients can closely resemble patients with xeroderma pigmentosa. Photodistributed granuloma annulare has also been seen by one of the authors (TB). This severe form of photosensitivity rapidly resolves with stopping of the voriconazole. Posaconazole can be an effective alternative. Photodistributed telangiectasias are a rare complication of calcium channel blockers (nifedipine, felodipine, and amlodipine). UVA appears to be the action spectrum. Cefotaxime has also been reported to produce this reaction. Corticosteroids, oral contraceptives, isotretinoin, interferons (IFNs), lithium, thiothixene, lithium, methotrexate, and other medications may induce telangiectasias, but not via photosensitivity. Pseudoporphyria is a

photodistributed bullous reaction clinically and histologically resembling porphyria cutanea tarda. Patients present with blistering on sunexposed skin of the face and hands, and skin fragility. Varioliform scarring occurs in 70% of patients. Facial scarring is especially common in children with pseudoporphyria. Hypertrichosis is very rarely found; dyspigmentation and sclerodermoid changes are not reported. Porphyrin studies are normal. The blistering usually resolves gradually once the offending medication is stopped. However, skin fragility may persist for years. Naproxen is the most commonly reported cause. Up to 12% of children with JIA treated with NSAIDs may develop pseudoporphyria. Pseudoporphyria has also been reported to other NSAIDs (oxaprozin, nabumetone, ketoprofen, mefenamic acid [but not piroxicam]), tetracycline, furosemide, nalidixic acid, isotretinoin, acitretin, 5-fluorouracil, bumetanide, dapsone, oral contraceptives, rofecoxib, celecoxib, cyclosporine, voriconazole, and pyridoxine. Sunbed exposure and even excessive sun exposure can produce pseudoporphyria. Cases in women outnumber men by 24:1. Some women with sunbedinduced pseudoporphyria are on oral contracep- tives. Patients on dialysis may develop pseudoporphyria, and N-acetylcysteine in doses up to 600 mg twice a day may lead to improvement in these cases. Histologically, a pauci-inflammatory subepidermal vesicle is seen. Direct immuno- fluorescence may show immunoglobulin and complement deposition at the dermoepidermal junction and perivascularly, as seen in porphyria cutanea tarda.

ANTICOAGULANT-INDUCED SKIN NECROSIS

Both warfarin and heparin induce lesions of cutaneous necrosis, albeit by different mechanisms. Obese, postmenopausal women are predisposed, and lesions tend to occur in areas with abundant subcutaneous fat such as the breast, abdomen, thigh, or buttocks. Warfarin-induced skin necrosis (WISN) usually occurs 3-5 days after therapy is begun, and a high initial dose increases the risk. Cases with a much more delayed onset (up to 15 years) are ascribed to noncompliance, drugdrug interactions, and liver dysfunction. WISN occurs in 1 in 1000 to 1 in 10 000

persons treated with warfarin. Lesions begin as red, painful plaques that develop petechiae, then form a large bulla. Necrosis follows. Priapism can complicate warfarin necrosis. A less common variant seen in patients with a deep venous thrombosis (DVT) of an extremity is necrosis of a distal extremity, usually the one in which the patient has the DVT. Hereditary or acquired deficiency of protein C, and less commonly protein S, antithrombin III, or factor V Leiden and lupus anticoagulant syndrome are associated. Early in warfarin treatment the serum levels of the vitamin K-dependent antithrombotic protein C fall. Since the half-life of antithrom- botic protein C is shorter than those of the vitamin K-dependent prothrombotic factors II, X, and IX, an acquired state of reduced protein C level occurs before the clotting factors are reduced. This creates a temporary prothrombotic state. This is more likely to occur if the levels of protein C are already low, if other antithrombotic proteins are deficient, or if the patient has an associated hypercoagulable state. This explains why the syndrome does not always recur with gradual reinstitution of warfarin, and has been reported to resolve with continued warfarin treatment. Histologically, noninflammatory thrombosis with fibrin in the subcutaneous and dermal vessels is seen. Treatment is to stop the warfarin, administer vitamin K to reverse the warfarin, and begin heparin or low molecular weight heparin. Administration of purified protein C can rapidly reverse the syndrome, as well as associated priapism. Untreated, the reaction can be fatal. Heparin induces necrosis both at the sites of local injections and in a widespread pattern when infused intravenously or given by local injection. Local reactions are the most common. Heparin can also induce local allergic reactions at injection sites, which are distinct from the necrosis syndrome. Independent of its method of delivery, heparin-induced skin necrosis lesions present as tender red plaques that undergo necrosis, usually 6-12 days after the heparin treatments are started. Unfractionated heparin is more likely to cause this complication than fractionated low molecular weight heparin, and postoperative surgical patients are at greater risk than medical patients. Even the heparin used for dialysis may be associated with cutaneous necrosis, simulating calciphylaxis. Some necrotic reactions to local

injections, and most disseminated reactions occurring with intravenous heparin, are associated with heparin-induced thrombocytopenia (HIT). Patients with underlying prothrombotic conditions, such as factor V Leiden and prothrombin mutations or elevated levels of factor VIII, may develop severe skin lesions if they develop HIT and heparin necrosis. A heparin-dependent antiplatelet antibody is the pathogenic basis of HIT and apparently of heparininduced skin necrosis. This antibody causes both the thrombocytopenia and the aggregation of platelets in vessels, leading to thrombosis (white clot syndrome). The antibody may appear up to 3 weeks after the heparin has been discontinued, so the onset of the syndrome may be delayed. Histologically, fibrin thrombi are less reproducibly found in affected tissues, since the vascular thrombosis is the result of platelet aggregation, not protein deposition. The process may not only produce infarcts in the skin, but also may cause arterial thrombosis of the limbs, heart, lung, and brain, resulting in significant morbidity or mortality. Bilateral adrenal necrosis due to hemorrhagic infarction can occur and, if not detected early, may lead to death due to acute Addisonian crisis. The syndrome must be recognized immediately in anyone receiving heparin with latedeveloping thrombocytopenia. The treatment is to stop the heparin and give a direct thrombin inhibitor and vitamin K. After the platelet count has returned to normal, warfarin therapy is commonly given for 3-6 months. Patients with HIT cannot be treated with warfarin immediately, as the warfarin would be ineffective in stopping the thrombosis (it is NOT antithrombotic) and may worsen the thrombosis by enhancing coagulation. The diagnosis of HIT can be delayed because the antiplatelet antibody may not be present while the platelet count is falling. Adding warfarin at this time can lead to disastrous widespread acral thrombosis resembling disseminated intravascular coagulopathy (DIC). Patients with cancer, an acquired prothrombotic state, are at increased risk for DVT. If they are treated with heparin and develop heparin-induced thrombocytopenia, they are at extreme risk for the development of a prothrombotic state if treated with warfarin. In this setting, digital and limb gangrene has occurred in the face of normal peripheral pulses and

super-therapeutic anticoagulation by standard measures (INR). The consumptive coagulopathy induced by the cancer is the underlying trigger.

VITAMIN K REACTIONS

Several days to 2 weeks after injection of vitamin K, an allergic reaction at the site of injection may occur. Most affected persons have liver disease and are being treated for elevated prothrombin times. The lesions are pruritic red patches or plaques that can be deep-seated, involving the dermis and subcutaneous tissue. There may be superficial vesiculation. Lesions occur most commonly on the posterior arm and over the hip or buttocks. Plaques on the hip tend to progress around the waist and down the thigh, forming a "cowboy gunbelt and holster" pattern. Generalized eczematous small papules may occur on other skin sites in severe reactions. These reactions usually persist for 1-3 weeks, but may persist much longer, or resolve only to recur spontaneously. On testing, patients with this pattern of reaction are positive on intradermal testing to the pure vitamin Kj. In Europe, a second pattern of vitamin K reaction has been reported. Subcutaneous sclerosis with or without fasciitis appears at the site of injections many months after vitamin K treatment. There may have been a preceding acute reaction as described above. Peripheral eosinophilia may be found. These pseudosclerodermatous reactions have been termed Texier's disease, and last several years. The addition of vitamin K to cosmetics has led to allergic contact dermatitis due to the vitamin K, confirmed by patch testing.

INJECTION SITE REACTIONS

In addition to allergic reactions, as described with vitamin K, cutaneous necrosis may occur at sites of medication injections. These are of two typical forms: those associated with intravenous infusions and those related to intramuscular injections. Pharmacologic agents that extravasate into tissue during intravenous infusion may cause local tissue necrosis resulting from inherent tissue-toxic properties. These include chemotherapeutic agents, calcium salts,

radiocontrast material, and nafcillin. Intramuscular injections may produce a syndrome called embolia cutis medicamentosa, livedoid dermatitis, or Nicolau syndrome. Immediately after injection there is local intense pain and the overlying skin blanches (ischemic pallor). Within minutes to hours the site develops an erythematous macule that evolves into a livedoid violaceous patch with dendrites. This becomes hemorrhagic, then ulcerates, often forming a deep ulcer of many centimeters in diameter. Eventually (over weeks to months) the ulcer heals with an atrophic scar. Muscle and liver enzymes may be elevated, and neurologic symptoms and sequelae occur in a third of patients. The circulation of the limb may be affected, rarely leading to amputation. This syndrome has been seen with injection of many unrelated agents, including NSAIDs, local anesthetics, corticosteroids, antibiotics, IFN-a, sedatives, vaccines, and Depo-Provera. It appears to be caused by periarterial injection leading to arterial thrombosis. IFN-P injections into subcutaneous tissue of the abdomen, buttocks, or thighs of patients with multiple sclerosis has resulted in similar lesions. Patient education and auto-injectors can prevent this complication. Biopsy of the interferon injection site reactions resembles lupus panniculitis. Treatment of Nicolau syndrome is conservative: dressing changes, debri- dement, bed rest, and pain control. Surgical intervention is rarely required.

DRUG-INDUCED PIGMENTATION

Pigmentation of the skin may occur as a consequence of drug administration. The mechanism may be postinflammatory hyperpigmentation in some cases but frequently is related to actual deposition of the offending drug in the skin. Minocycline induces many types of hyperpigmentation, which may occur in various combinations in the affected patient. Classically, three types of pigmentation are described. Type I is a blueblack discoloration appearing in areas of prior inflammation, often acne or surgical scars. This may be the most common type seen by dermatologists. It does not appear to be related to the total or daily dose of exposure. In all other types of pigmentation resulting from minocycline,

the incidence increases with total dose, with up to 40% of treated patients experiencing hyperpigmentation with more than 1 year of therapy. The second type (type II) is the appearance of a similarcolored pigmentation on the normal skin of the anterior shins, analogous to that seen in antimalarialinduced hyperpigmentation. It is initially mistaken for ecchymoses, but does not fade quickly. In most cases, types I and II minocycline pigmentation occur after 3 months to several years of treatment. Generalized black hyperpigmentation has occurred after several days or a few weeks of treatment in Japanese patients. In type I and II minocycline hyperpigmentation, histologic evaluation reveals pigment granules within macrophages in the dermis (and at times in the fat), very similar to a tattoo. These granules usually stain positively for both iron and melanin, the usual method for confirming the diagnosis. At times the macrophages containing minocycline are found only in the subcutaneous fat. Stains for iron may be negative in some cases. Calcium stains may also be positive, as minocycline binds calcium. In unusual cases electron microscopy or sophisticated chemical analysis can confirm the presence of minocycline in the granules. The least common type (type III) is generalized, muddy brown hyperpigmentation, accentuated in sun-exposed areas. Tigecycline may produce similar hyperpigmentation. Histologic examination reveals only increased epidermal and dermal melanin. This may represent the consequence of a lowgrade photosensitivity reaction. In addition to the skin, minocycline type I and II pigmentation may also involve the sclera, conjunctiva, bone, thyroid, ear cartilage (simulating alkaptonuria), nailbed, oral mucosa, and permanent teeth. Tetracycline staining of the teeth is usually related to childhood or fetal exposure, is brown, and is accentuated on the gingival third of the teeth. Dental hypepigmentation due to minocycline in contrast occurs in adults, is gray or gray-green, and is most marked in the midportion of the tooth. Some patients with affected teeth do not have hyperpigmentation elsewhere. Cutaneous hyperpigmentation from minocycline fades slowly and the teeth may remain pig-mented for years. The blue-gray pigmentation of the skin may be improved with the Q-switched ruby laser or fractional photothermolysis. Chloroquine,

hydroxychloroquine, and quinacrine all may cause a blue-black pigmentation of the face, extremities, ear cartilage, oral mucosa, and nails. Pretibial hyperpigmentation is the most common pattern and is very similar to that induced by minocycline. The gingiva or hard palate may also be discolored. Quinidine may also rarely cause such a pattern of hyperpigmentation. Quinacrine is yellow and is concentrated in the epidermis. Generalized yellow discoloration of the skin and sclera (mimicking jaundice) occurs reproducibly in patients but fades within 4 months of stopping the drug. In dark-skinned patients this color is masked and not so significant cosmetically. Histologically, in both forms of pigmentation, pigment granules are present within macrophages in the dermis. Amiodarone after 3-6 months causes photosensitivity in 30-57% of treated patients. In 1-10% of patients, a slate-gray hyperpigmentation develops in the areas of photosensitivity. The pigmentation gradually fades after the medication is discontinued. Histologically, periodic acid-Schiffpositive, yellowbrown granules are seen within the cytoplasm of macrophages in the dermis. Electron microscopy reveals membranebound structures resembling lipid-containing lysosomes. It responds to treatment with the Q-switched ruby laser. Clofazimine treatment is reproducibly complicated by the appearance of a pink discoloration that gradually becomes reddishblue or brown and is concentrated in the lesions of patients with Hansen's disease. This pigmentation may be very disfiguring and is a major cause of noncompliance with this drug in the treatment of Hansen's disease. Histologically, a periodic acid-Schiff-positive, brown, granular pigment is variably seen within foamy macrophages in the dermis. This has been called "drug-induced lipofuscinosis". Zidovudine causes a blue or brown hyperpigmentation that is most frequently observed in the nails. The lunula may be blue or the whole nail plate may become dark brown. Diffuse hyperpigmentation of the skin, pigmentation of the lateral tongue, and increased tanning are less common. It occurs in darkly pigmented persons, is dose-dependent, and clears after the medication is discontinued. Hydroxyurea causes a very similar pattern of hyperpigmentation. Chlorpromazine, thioridazine, imipramine, and clomi- pramine may cause a slate-gray

hyperpigmentation in sunexposed areas after long periods of ingestion. Frequently, corneal and lens opacities are also present, so all patients with hyperpigmentation from these medications should have an ophthalmologic evaluation. The pigmentation from the pheno- thiazines fades gradually over years, even if the patient is treated with another phenothiazine. The corneal, but not the lenticular, changes also resolve. Imipramine hyperpigmentation has been reported to disappear within a year. Histologically, in sunexposed but not sunprotected skin, numerous refrac- tile goldenbrown granules are present within macrophages in the dermis, along with increased dermal melanin. The slategray color comes from a mixture of the golden-brown pigment of the drug and the black color of the melanin viewed in the dermis. The heavy metals gold, silver, and bismuth produce blue to slate-gray hyperpigmentation. Pigmentation occurs after years of exposure, predominantly in sun-exposed areas, and is permanent. Silver is by far the commonest form of heavy metalinduced pigmentation seen by dermatologists. It occurs in two forms, local or systemic. Local argyria most commonly follows the topical use of silver sulfadiazine or silvercontaining dressings (Acticoat). Blue-gray pigmentation occurs at the site of application. Implantation into the skin by needles or pierced jewelry may lead to focal areas of argyria. Systemic argyria can also arise from topical application to the skin (in burn and epidermolysis bullosa patients), by inhalation, by mucosal application (nose drops or eye drops), or by ingestion. Patients may purchase or build devices which allow them to make col-loidal silver solutions which they then ingest for arthritis, infections, or general health. After several months of such exposures the skin becomes slate-gray or blue-gray, primarily in areas of sun exposure. Histologically, granules of silver are found in basement membranes at the dermoepidermal junction and around adnexal (especially eccrine) and vascular structures. Sun exposure leads to the silver binding to either sulfur or selenium in the skin, increasing deposition. The deposited silver activates tyrosinase, increasing pigmentation. Most patients with argyria have no systemic symptoms or consequences of the increased silver in their body. In one patient, the use of a Q-switched 1064 Nd:YAG laser improved the

condition. Gold deposition was more common when gold was used as a treatment for rheumatoid arthritis. Cutaneous chrysiasis also presents as blue-gray pigmentation, usually after a cumulative dose of 8 g. Chrysiasis is also more prominent in sunexposed sites. Dermatologists should remain aware of this condition, since patients treated with gold, even decades before, may develop disfiguring hyperpigmentation following Q-switched laser therapy for hair removal or lentigi- nes lightening. Chrysiasis has been treated effectively in one patient using repeated 595 nm pulsed dye laser therapy. Bismuth also pigments the gingival margin. Histologically, granules of the metals are seen in the dermis and around blood vessels. Arsenical melanosis is characterized by black, generalized pigmentation or by a pronounced truncal hyperpigmentation that spares the face, with depigmented scattered macules that resemble raindrops. Diltiazem can cause a severe photodistributed hyperpigmentation. This is most common in African American or Hispanic women, and occurs about 1 year after starting therapy. The lesions are slate-gray or gray-blue macules and patches on the face, neck, and forearms. Perifollicular accentuation is noted. Histology shows a sparse lichenoid dermatitis with prominent dermal melanophages. The action spectrum of the drug appears to be in the UVB range, but hyperpigmen- tation is induced by UVA irradiation. The mechanism appears to be postinflammatory hyperpigmentation from a photosensitive lichenoid eruption rather than drug or drug metabolite deposition. Treatment is broad-spectrum sunscreens, stopping the diltiazem, and bleaching creams if needed. Other calcium channel blockers can be substituted without the reappearance of the hyperpigmentation. Periocular hyperpigmentation occurs in patients treated with prostaglandin analogs for glaucoma. These agents also cause pigmentation of the iris. Eyelash length increases. The periocular hyperpigmentation may gradually resolve when the medications are discontinued. Pigmentary changes induced by chemotherapeutic agents are discussed later in this chapter.

VASCULITIS AND SERUM SICKNESS-LIKE REACTIONS

True leukocytoclastic vasculitis can be induced by many medications, but these events are rare, except in the case of propylthiouracil. True serum sickness is caused by foreign proteins such as antithymocyte globulin. They are produced by circulating immune complexes. In the case of true serum sickness there is a tendency for purpuric lesions to be accentuated along the junction between palmoplantar and glabrous skin (Wallace line). Serum sickness-like reactions refer to adverse reactions that have similar symptoms to serum sickness, but in which immune complexes are not found. This reaction was particularly common with cefaclor. Patients present with fever, an urticarial rash and arthralgias 1-3 weeks after starting the medication (Fig. 6-33). Minocycline, bupropion and rituximab have been reported to cause serum sickness-like reactions.

LICHENOID REACTIONS

Lichenoid reactions can be seen with many medications, including gold, hydrochlorothiazide, furosemide, NSAIDs, aspirin, antihypertensives (ACE inhibitors, P-blockers, and calcium channel blockers), terazosin, quinidine, proton pump inhibitors, pravastatin, phenothiazines, anticonvulsants, antituberculous drugs, ketoconazole, sildenafil, imatinib, and the antimalarials. Hepatitis B immunization may trigger a lichenoid eruption. Reactions may be photodistributed (lichenoid photoeruption) or generalized, and those drugs causing lichenoid photoeruptions may also induce more generalized ones. In either case, the lesions may be plaques (very occasionally with Wickham striae), small papules, or exfoliative erythema. Photolichenoid reactions favor the extensor extremities, including the dorsa of the hands. Oral involvement is less common in lichenoid drug reactions than in idiopathic lichen planus but can occur (and with imatinib may be quite severe). It appears as either plaques or erosions. The lower lip is frequently involved in photolichenoid reactions. The nails may also be affected, and can be the only site of involvement. Lichenoid drug eruptions can occur within months to years of starting the offending medication, and may take months to years

to resolve once the medication has been stopped. Histologically, there is inflammation along the dermoepidermal junction, with necrosis of keratinocytes and a dermal infiltrate composed primarily of lymphocytes. Eosinophils are useful, if present, but are not common in photolichenoid reactions. The histology is often very similar to idiopathic lichen planus, and a clinical correlation is required to determine if the lichenoid eruption is druginduced. Lichenoid reactions may be restricted to the oral mucosa, especially if induced by dental amalgam. In these cases the lesions are topographically related to the dental fillings or to metal prostheses. Patients may be patch testpositive to mercury, or less commonly gold, cobalt, or nickel, in up to two-thirds of cases. Amalgam replacement will result in resolution of the oral lesions in these cases. Patients with cutaneous lesions of lichen planus and oral lesions do not improve with amalgam removal. An unusual form of eruption is the "drug-induced ulceration of the lower lip." Patients present with a persistent erosion of the lower lip that is tender but not indurated. It is induced by diuretics and resolves slowly once they are discontinued.

ADVERSE REACTIONS TO CHEMOTHERAPEUTIC AGENTS

Chemotherapeutic agents can cause adverse reactions by multiple potential mechanisms. Adverse reactions may be related to toxicity either directly to the mucocutaneous surfaces (stomatitis, alopecia), or to some other organ system, and reflected in the skin, such as purpura resulting from thrombocytopenia. Being organic molecules or monoclonal antibodies, they can act as antigens inducing classic immunologic reactions. In addition, since they are inherently immunosuppressive, they can cause skin reactions associated with alterations of immune function. Some of these patterns may be overlapping and clinically difficult to distinguish. For example, oral erosions may occur as a toxic effect of chemotherapy and also by immunosuppression-associated activation of herpes simplex virus. Dermatologists are rarely confronted with the relatively common acute hypersensitivity reactions seen during infusion of chemotherapeutic agents. These reactions resemble type I allergic reactions, with urticaria and hypotension.

Although the type I reactions are IgE-mediated in only some cases, they can be prevented with premedication with systemic steroids and antihistamines in most cases. Numerous macular and papular eruptions have been described with chemotherapeutic agents as well. Many of these occur at the time of the earliest recovery of the bone marrow, as lymphocytes return to the peripheral circulation. They are associated with fever. Horn et al have termed this phenomenon cutaneous eruptions of lymphocyte recovery. Histologically, these reactions demonstrate a nonspecific superficial perivascular mononuclear cell infiltrate, composed primarily of T lymphocytes. Treatment is not required and the eruption spontaneously resolves.

RADIATION ENHANCEMENT AND RECALL REACTIONS

Radiation dermatitis, in the form of intense erythema and vesiculation of the skin, may be observed in radiation ports. Administration of many chemotherapeutic agents, during or in close proximity to the time of radiation therapy, may induce an enhanced radiation reaction. However, in some cases, months to years following radiation treatment the administration of a chemotherapeutic agent may induce a reaction within the prior radiation port with features of radiation dermatitis. This phenomenon has been termed "radiation recall." It has been reported with numerous chemotherapeutic agents, highdose IFN-a, and simvastatin. Not only the skin, but also internal structures such as the gut may be affected. A similar reaction of reactivation of a sunburn after methotrexate therapy also occurs. Exanthems restricted to prior areas of sunburn are not true radiation recall. Chemotherapyinduced acral erythema (palmoplantar erythrodysesthesia syndrome, hand-foot syndrome). This is a relatively common syndrome induced most frequently by 5-fluorouracil (5-FU), doxorubicin, and cytosine arabinoside, but also seen with docetaxel, capecitabine, and high-dose liposomal doxorubicin and daunorubicin. A localized plaque of fixed erythrodysesthesia has been described proximal to the infusion site of docetaxel. The reaction may occur in as many as 40% or more of treated patients. The reac-

tion is dose-dependent, and may appear with bolus short-term infusions or low-dose, long-term infusions. It may present days to months after the treatments are started. It is probably a direct toxic effect of the chemotherapeutic agents on the skin. The large number of sweat glands on the palms and soles that may concentrate the chemotherapeutic agents may explain the localization of the toxicity. In the case of pegylated liposomal doxorubicin localization of the chemotherapeutic agent to the sweat glands has been demonstrated, and the sweat glands appear to be the organ by which the chemotherapy is delivered on to the surface of normal skin. A flexural eruption in the groin and axilla may accompany acral erythema, again from sweat gland accumulation of the drug in these regions. Cases of neutrophilic eccrine hidradenitis and syringometa- plasia all induced by the same agents suggest that the eccrine glands are unique targets for adverse reactions to antineoplas- tic agents. The initial manifestation is often dysesthesia or tingling of the palms and soles. This is followed in a few days by painful, symmetric erythema and edema most pronounced over the distal pads of the digits. The reaction may spread to the dorsal hands and feet, and can be accompanied by a morbilliform eruption of the trunk, neck, scalp, and extremities. Over the next several days the erythema becomes dusky, develops areas of pallor, blisters, desquamates, then re-epithelializes. The desquamation is often the most prominent part of the syndrome. Blisters developing over pressure areas of the hands, elbows, and feet are a variant of this syndrome. The patient usually recovers without complication, although rarely full- thickness ischemic necrosis occurs in the areas of blistering. The histopathology is nonspecific, with necrotic keratino- cytes and vacuolar changes along the basal cell layer. Acute GVHD is in the differential diagnosis. Histologic evaluation may not be useful in the acute setting to distinguish these syndromes. Most helpful are gastrointestinal or liver findings of GVHD. Most cases require only local supportive care. Cold compresses and elevation are helpful, and cooling the hands during treatment may reduce the severity of the reaction. Modification of the dose schedule can be beneficial. Pyridoxine, 100-150 mg daily, decreases the pain of 5-FU-induced acral erythema.

IVIG has been reported to be beneficial in a methotrexateinduced case of acral erythema. Sorafenib and sunitinib are multikinase-inhibiting small molecules with blocking activity for numerous tyrosine kinases, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGFRP), and c-KIT. They both induce a condition very similar to acral erythema, called "hand-foot skin reaction" (HFSR). Patients also present with acral pain and dysesthesia, but usually less severe and with less edema than with classic chemotherapeutic agents. As opposed to classic acral erythema, multikinase inhibitor- induced HFSR causes patchy marked hyperkeratotic plaques over areas of friction. The HFSR is dose-dependent, high- grade in 9% of cases (with blisters, ulceration, and function loss), and results in the sorafenib being stopped in about 1% of patients. The addition of another VEGF inhibitor, bevacizu- mab, leads to worse HFSR. Painful distal subungual splinter hemorrhages can also occur 2-4 weeks after the onset of treat-ment. It has been suggested that the blocking of VEGF may be pathogenically important in causing HFSR splinter hemorrhages. Histologically, there are horizontal layers of necrotic keratinocytes within the epidermis (if the biopsy is taken in the first 30 days) or in the stratum corneum (later biopsies). Topical tazarotene, 40% urea, and fluorouracil cream have been used to treat HFSR from multikinase inhibitors.

CHEMOTHERAPY-INDUCED DYSPIGMENTATION

Many chemotherapeutic agents (especially the antibiotics bleomycin, doxorubicin, and daunorubicin) and the alkylating agents (cyclophosphamide and busulfan) cause various patterns of cutaneous hyperpigmentation. Adriamycin (doxoru- bicin) causes marked hyperpigmentation of the nails, skin, and tongue. This is most common in black patients and appears in locations where constitutional hyperpigmentation is sometimes seen. Hydroxyurea can also cause this pattern of hyperpigmentation. It is very similar to zidovudine-associated pigmentation seen in pigmented persons. Cyclophosphamide causes transverse banding of the nails or diffuse nail hyperpigmentation beginning proximally.

Bleomycin and 5-FU cause similar transverse bands. Busulfan and 5-FU induce diffuse hyperpigmentation that may be photoaccentuated. Paradoxical hyperpigmentation of the skin, nails, and hair has been reported due to imatinib. Eruptive melanocytic nevi and lentigines with an acral predisposition have been seen with sorafenib therapy. Bleomycin induces characteristic flagellate erythematous urticarial wheals associated with pruritus within hours or days of infusion. Lesions continue to appear for days to weeks. While investigators have not always been able to induce lesions, the pattern strongly suggests scratching is the cause of the erythematous lesions. A similar characteristic pattern of flagellate hyperpigmentation occurs following bleomycin treatment. It may have been preceded by the erythema- tous reaction or simply pruritus. Bleomycin hyperpigmentation may be accentuated at areas of pressure, strongly supporting trauma as the cause of the peculiar pattern. Patients may present with linear erythematous wheals 1-2 days after eating raw or cooked shiitake mushrooms. This so-called toxicodermia, or shiitake flagellate dermatitis, is thought to be caused by a toxic reaction to lentinan, a polysaccharide component of the mushrooms. It is self-limited and resolves within days to weeks of its appearance, but can be treated with topical steroids to relieve the associated pruritus some patients experience. Other associations with flagellate eruptions include adult-onset Still's disease, dermatomyositis, and docetaxel therapy. 5-FU, and less commonly other chemotherapeutic agents, may produce a serpentine hyperpigmentation overlying the veins proximal to an infusion site. This represents postinflam- matory hyperpigmentation from a direct cytotoxic effect of the chemotherapeutic agent. Imatinib in doses of 400-600 mg daily leads to generalized or localized depigmentation in 40% or more of pigmented persons. It starts an average of 4 weeks after treatment and progresses over time if treatment with imatinib is continued. Patients also complain of an inability to tan and "photosensitivity". One patient with vitiligo had significant progression with imatinib therapy. The proposed mechanism is inhibition of c-KIT and its ligand "stem cell factor," which are implicated in melanogenesis. By a similar mechanism, sunitinib leads to

depigmentation of the hair after 5-6 weeks of treatment. Sunitinib may lead to yellow pigmentation of the skin due to drug or its metabolites being deposited.

EXUDATIVE HYPONYCHIAL DERMATITIS

Nail toxicity is common (26-40%) during chemotherapy for breast cancer, especially if docetaxel is in the chemotherapeutic regimen. Subungual hemorrhage, subungual abscesses, paronychia, subungual hyperkeratosis, and onychomadesis all occur. In its most severe form, severe exudation and onycholysis may result. All these reactions probably represent various degrees of toxicity to the nailbed. Capecitabine has caused a similar reaction.

PALIFERMIN-ASSOCIATED PAPULAR ERUPTION

Palifermin is a recombinant human keratinocyte growth factor that is used to reduce the severity and duration of mucositis in patients undergoing preparative regimens for hematopoietic stem cell transplantation. An intertriginous erythema accompanied by oral confluent white plaques and small lichenoid papules developed in one patient while on palifermin therapy. The papules resembled flat warts clinically and histologically, but were human papillomavirus (HPV) - negative by in situ hybridization studies. A direct hyperproliferative effect of the keratinocyte growth factor is the proposed mechanism.

SCLERODERMA-LIKE REACTIONS TO TAXANES

Patients treated with docetaxel or paclitaxel may develop an acute, diffuse, infiltrated edema of the extremities and head. This occurs after one to several courses of the taxane. The affected areas, specifically the lower extremities, evolve over months to become sclerotic and at times painful. Flexion contractures of the palm, digits, and large joints may occur. Biopsies of the initial lesion show lymphangiectasia and a diffuse infiltration with mononuclear cells in the superficial dermis. Late fibrotic lesions demonstrate marked dermal fibrosis. Discontinuation of the taxane therapy leads to resolution in most cases.

ADVERSE REACTIONS TO IMMUNOSUPPRESSANTS USED IN DERMATOLOGY

Azathioprine is commonly used as a steroidsparing agent for dermatological conditions. It can cause a hypersensitivity syndrome. In addition, neutrophilic dermatoses resembling Sweet syndrome appear with azathioprine therapy and resolve with its discontinuation. Patients with inflammatory bowel disease appear to be at particular risk. Photosensitivity can also occur with azathioprine, despite its frequent use in severe photodermatoses. Methotrexate can cause erosive skin lesions in two patterns. Rarely, patients with psoriasis will develop ulceration or erosion of their plaques. This can be associated with methotrexate marrow toxicity or can be an apparently idiosyncratic but reproducible phenomenon in rare patients. If coexistent renal failure is present or occurs during low-dose methotrexate therapy, a severe bullous eruption resembling TEN can occur. This apparently represents severe cutaneous toxicity from the prolonged blood and skin levels of methotrexate that result from reduced excretion due to coexistent renal disease and drug-drug interactions. If this scenario is recognized, leucovorin rescue should be given immediately.

CUTANEOUS SIDE EFFECTS OF EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) INHIBITORS

EGFR is expressed by basal keratinocytes, sebocytes, and the outer root sheath, explaining why up to 90% of patients treated with these agents may develop cutaneous side effects. Xerosis is often seen. Painful periungual or finger pulp fissures and paronychia (with or without periungual pyogenic granulomas) may develop. The most common and characteristic adverse skin reaction is a papulopustular eruption that is dosedependent. The eruption begins 7-10 days after therapy is begun and the maximum severity is reached in the second week. The seborrheic areas of the scalp, central face, upper back, and retroauricular regions are primarily affected. The primary lesion is a follicular papule or pustule with few

or no comedones. Hemorrhagic crusting and confluence can occur, resembling rosacea fulminans (pyoderma faciale) in the most severely affected patients. Telangiectasia may be prominent. The eruption may itch. The presence and severity of this skin eruption are correlated with survival, so some oncologists will increase the dose to induce the eruption. Radiation therapy during EGFR inhibitor therapy will enhance the EGFR skin toxicity, but previously radiated skin is often spared from EGFR inhibitor toxicity. Effective topical therapies have included metronidazole, clindamycin, hydrocortisone, pimecrolimus, and tretinoin. Oral tetracyclines can treat or prevent the eruption. In the most severe cases isotretinoin or acitretin can be used. Tumor necrosis factor (TNF)-a and IL-1 are involved in the pathogenesis of EGFR inhibitor toxicity. Etanercept and kineret can, therefore, also be therapeutically useful. Long eyelashes and curlier scalp hair may also occur.

CUTANEOUS SIDE EFFECTS OF MULTIKINASE INHIBITORS

In addition to the reactions listed above, multikinase inhibitors may cause other skin reactions. Psoriasis exacerbation, acral psoriasiform hyperkeratosis, and pityriasis rosea-like eruptions have been described with imatinib. Both imatinib and sunitinib cause facial edema, with a periocular predilection. Increased vascular permeability due to PDGFR inhibition has been the proposed mechanism. Dasatinib has caused a lobular panniculitis. Bevacizumab, a VEGF inhibitor, causes bleeding and wound healing complications. Extensive cutaneous surgery should probably be delayed for 60 days after bevacizumab therapy, and 28 days should pass from the time of surgery until bevacizumab therapy is initiated. Sorafenib has been associated with the rapid development of multiple squamoproliferative lesions called keratoacanthomas or squamous cell carcinomas. Bexarotene was therapeutic in one case. Multiple, monomorphous, follicular, keratotic, skincolored papules resembling keratosis pilaris can develop during sorafenib treatment. Histologically, these papules show hyperplasia of the

follicular isthmus or follicular hyperkeratosis with plugging. Facial and scalp erythema and dysesthesia occur in about 60% of sorafenibtreated patients.

ADVERSE REACTIONS TO CYTOKINES

Cytokines, which are normal mediators of inflammation or cell growth, are increasingly used in the management of malignancies and to ameliorate the hematologic complications of disease or its treatment. Skin toxicity is a common complication of the use of these agents. Many of them cause local inflammation and/or ulceration at the injection sites in a large number of the patients treated. More widespread papular eruptions are also frequently reported, but these have been poorly studied in most cases and are of unclear pathogenesis. Granulocyte colony-stimulating factor (G-CSF) has been associated with the induction of several neutrophil-mediated disorders, most commonly Sweet syndrome or bullous pyo- derma gangrenosum. These occur about a week after cytokine therapy is initiated and are present despite persistent neutro- penia in peripheral blood. A rare complication of G-CSF is a thrombotic and necrotizing panniculitis. Both G-CSF and granulocyte-macrophage (GM)-CSF may exacerbate leukocytoclastic vasculitis. IFN-a, IFN-y, and G-CSF have been associated with the exacerbation of psoriasis. G-CSF can also cause cutaneous eruptions containing histiocytes. Anakinra and rarely erythropoietin can cause similar granulomatous skin reactions. IL-2 commonly causes diffuse erythema followed by desq- uamation, pruritus, mucositis (resembling aphthosis), glossitis, and flushing. While the majority of erythema reactions with IL-2 treatment are mild to moderate, some may be quite severe. Erythroderma with blistering or TEN-like reactions can occur, and be dose-limiting. Administration of iodinated contrast material within 2 weeks of IL-2 therapy will be associated with a hypersensitivity reaction in 30% of cases. Fever, chills, angioedema, urticaria, and hypotension may occur. Subcutaneous injections of IL-2 can lead to injection site nodules or necrosis. Histologically, a diffuse panniculitis with noninflammatory necrosis of the involved tissue is present. Rarely, linear IgA disease can be induced by IFN-a.

ADVERSE REACTIONS TO BIOLOGIC AGENTS TNF INHIBITORS

Injection site reactions (ISRs) are common with etanercept therapy for rheumatologic disease, with 20-40% of patients developing ISR. ISRs present as erythematous, mildly swollen plaques, appearing 1-2 days after the injection. Pruritus occurs in 20% of cases. ISR is most common early in the treatment course (median number of injections was four), and stops appearing with continued treatment. Individual lesions resolve over 2-3 days. Recall ISR (reappearance of the eruption at a site of a previous ISR) occurs in 40% of patients. This adverse reaction appears to be mediated by CD8+ T cells. Cytokine therapy with TNF and IFN-a, P, and y also causes ISRs. The paradoxical appearance of psoriasis or a psoriasiform dermatitis is now a well-recognized complication of TNF inhibitor therapy. It occurs with all three of the commonly used TNF inhibitors: infliximab, etanercept, and adalimumab. The risk may be slightly higher for adalimumab. The psoriasis can appear from days to years following anti-TNF therapy. There is no age or gender predisposition. Several clinical patterns have been described. Palmoplantar pustulosis represents about 40% of cases. Generalized pustular disease may accompany the palmoplantar lesions. Plaque-type psoriasis occurs in about one-third of TNF inhibitorinduced psoriasis. Newonset guttate psoriasis occurs in 10% of cases. Stopping the TNF inhibitor led to improvement or resolution in the vast majority of patients. In some cases therapy was continued and the eruption resolved. There is controversy among experts as to whether switching to a different anti-TNF agent may be tolerated in these patients. Many patients have been rechal- lenged with other TNF inhibitors. In severe cases this is probably not prudent, but in milder or localized cases this could be considered. The psoriasis caused by anti-TNF agents can be treated with topical steroids, UV phototherapy, topical vitamin D analogs, methotrexate, acitretin, or cyclosporine. The proposed mechanism for the appearance with psoriasis with anti- TNF therapy is either overactivity of Th1 cells or increased IFN-a production by skin-resident plasmacytoid dendritic cells. Systemic IFN-a and topical imiquimod (an interferon inducer) have been reported to exacerbate psoriasis, supporting this hypothesis.

Sarcoidosis induced by anti-TNF agents could also be related to increased Th1 function. Around 11% of patients treated for rheumatoid arthritis with etanercept develop new antinuclear antibodies (ANAs) and 15% anti-double-stranded DNA (dsDNA) antibodies. Anti-Sm antibodies can also occur. Similarly, patients treated with infliximab may develop new ANAs, anti-dsDNA (14%), and anticardiolipin antibodies. All of the three commonly used TNF inhibitors have caused drug-induced lupus (DIL) with features of SLE. It begins on average after 41 weeks of treatment. As compared to DIL from other medications, the TNF inhibitors cause more skin disease with malar rash, discoid lesions, and photosensitivity. Many of the patients will fulfill the American Rheumatology Association (ARA) criteria for SLE, and significant internal organ involvement can occur, including renal and CNS involvement. Etanercept, specifically, seems to cause skin lesions more commonly. Etanercept patients also developed vasculitis more frequently. The vast majority of patients improve about 10 months after therapy has been discontinued. Switching from one TNF inhibitor to another has been reported to be successful. Dermatomyositis has also been caused by TNF inhibitor treatment. Vasculitis is also a well-recognized complication of treatment with TNF inhibitors. Etanercept is the most common agent to induce vasculitis. The lesions of vasculitis may begin around the injection sites in some etanerceptinduced vasculi- tis cases. More than 85% of patients present with skin lesions, usually a leukocytoclastic vasculitis. Ulcerations, nodules, digital lesions, chilblains, livedo, and other morphologies have also been described. Visceral vasculitis occurs in about one- quarter of the patients. They may be ANA- or antineutrophil cytoplasmic antibody (ANCA)-positive (usually p-ANCA), or have cryoglobulins. Druginduced antiphospholipid syndrome with TNF inhibitors can be associated with DIL or vasculitis, and presents with thrombosis as well as cutaneous lesions. Some patients with TNF inhibitor-induced vasculitis have died. Stopping the TNF inhibitor leads to resolution of the vasculitis in more than 90% of cases. Rechallenge leads to new vasculitic lesions in three-quarters of cases. Lichenoid drug eruptions have been reported from all three commonly used anti-TNF agents. They are typically pruritic

and affect areas commonly involved by lichen planus: the flexor wrists. However, gluteal cleft lesions are also common. In some cases, the lichenoid eruption superimposes itself on psoriatic lesions presenting as an exacerbation of the "psoriasis." Biopsies show features of both lichen planus and psoriasis, and stopping the anti-TNF therapy leads to improvement of the "psoriasis." Despite these agents' immunosuppressive properties, patients can still develop allergic contact dermatitis while taking them, and patch testing while on anti-TNF treatment may identify relevant allergens. It appears that patients on anti-TNF agents are at slightly increased risk for the development of nonmelanoma skin cancers, especially if they also have used methotrexate.

MERCURY

Mercury may induce multiple cutaneous syndromes. The classic syndrome is acrodynia, also known as calomel disease, pink disease, and erythrodermic polyneuropathy. Acrodynia is caused by mercury poisoning, usually in infancy. The skin changes are characteristic and almost pathognomonic. They consist of painful swelling of the hands and feet, sometimes associated with considerable itching of these parts. The hands and feet are also cold, clammy, and pink or dusky red. The erythema is usually blotchy but may be diffuse. Hemorrhagic puncta are frequently evident. Over the trunk a blotchy macular or papular erythema is usually present. Stomatitis and loss of teeth may occur. Constitutional symptoms consist of moderate fever, irritability, marked photophobia, increased perspiration, and a tendency to cry most of the time. There is always moderate upper respiratory inflammation with soreness of the throat. There may be hypertension, hypotonia, muscle weakness, anorexia, and insomnia. Albuminuria and hematuria are usually present. The diagnosis is made by finding mercury in the urine. An exanthem may occur from inhalation of mercury vapors or absorption by direct contact. A diffuse, symmetrical ery- thematous morbilliform eruption in the flexors and proximal extremities begins within a few days of exposure. Accentuation in the groin and medial thighs produces a "baboon syndrome" appearance. The eruption burns or

itches, and small follicular pustules appear. Extensive desquamation occurs with resolution. Old broken thermometers or the application of mercury- containing creams and herbal medications are potential sources. In Haiti elemental mercury is applied to surfaces for religious purposes and may result in contamination of those coming in contact. Mercury is also a possible cause of foreign body granulomas and hyperpigmentation at the sites of application. An eruption of 1-2 mm, minimally pruritic papules and papulovesicles on the palms (all patients) and soles, arms, and trunk has also been ascribed to levels of mercury in the blood at near the upper limits considered to be safe. Treatment with a seafoodfree diet and chelation with succimer led to resolution of the eruption in some patients. Nummular dermatitis improved in two mercury patch testpositive patients when their dental amalgam was removed.

BROMODERMA

Bromides produce distinctive follicular eruptions, acneiform, papular, or pustular. Vegetative, exudative plaques studded with pustules may develop, resembling Sweet syndrome, pyoderma gangrenosum, or an orthopox virus infection. Characteristically, there are coalescent pustules on a raised border at the periphery of the lesion the diagnostic clue. Histologically, the lesions show epidermal hyperplasia with intraepidermal and dermal neutrophilic abscesses. There is rapid involution of the lesions on cessation of bromide ingestion. Excessive cola or soft-drink ingestion, or the ingestion of bromine-containing medications (ipratropium bromide, dextromethorphan hydrobromide, potassium bromide, pipobroman, Medecitral) may be the cause of a bromoderma. Serum bromide is elevated and confirms the diagnosis.

IODODERMA

Iodides may cause a wide variety of skin eruptions. The most common sources of exposure are oral and intravenous contrast materials, and when iodides are used to treat thyroid disease. Application of povidoneiodine to the skin, or as a

soak in the tub has produced iododerma. The most common type is the acneiform eruption with numerous acutely inflamed follicular pustules, each surrounded by a ring of hyperemia. Dermal bullous lesions are also common and may become ulcerated and crusted, resembling pyoderma gangrenosum or Sweet syndrome. The eruption may involve the face, upper extremities, trunk, and even the buccal mucosa. Acne vulgaris and rosacea are unfavorably affected by iodides. Acute iodo- derma may follow intravenous radiocontrast studies in patients with renal failure. The lesions may be associated with severe leukocytoclastic vasculitis, intraepidermal spongiform pustules, and suppurative folliculitis. Iodine is removed quickly by hemodialysis. Forced diuresis with sodium chloride and furosemide can be used to "wash out" the iodide. The lesions respond to prednisone.

DRUG-INDUCED AUTOIMMUNE DISEASES LUPUS ERYTHEMATOSUS

Drug-induced SLE is rarely associated with skin lesions. It occurs in older patients and affects men as commonly as women. The symptoms are generally mild and include fever, myalgias/arthralgias, and serositis. This form of DIL is associated with a positive ANA, homogenous pattern, and antihistone antibodies, but a negative anti-dsDNA antibody and normal complement levels. Procainamide, hydralazine, quini- dine, captopril, isoniazid, minocycline, carbamazepine, propylthiouracil, sulfasalazine, and the statins are among the reported agents triggering this form of DIL. The TNF inhibitors, especially etanercept, may also cause an SLE-like syndrome but with prominent skin lesions. Women are favored, and nephropathy and CNS involvement can occur. Again, the affected patients are ANA-positive, but also anti-dsDNA antibody-positive, and more than half are hypocomplementemic. Numerous medications have been reported to produce cuta- neous lesions characteristic of subacute cutaneous lupus ery- thematosus (SCLE). The eruption begins days to years after starting the medications. Hydrochlorthiazide, diltiazem (and other calcium channel blockers), and terbinafine are the most common causative agents, but ACE inhibitors, proton

pump inhibitors, statins, NSAIDS, and even agents used to treat lupus, such as hydroxychloroquine and leflunomide, can induce SCLE. These patients may also be ANA-positive and have antihistone antibodies, but in addition have positive anti- SSA antibodies. Cutaneous lesions are photosensitive, but not photodistributed, annular or papulosquamous plaques. Chilblain-like lesions are rarely seen. Treatment is as for SCLE, with sun avoidance, and topical and systemic steroids as required. Drug withdrawal results in resolution over weeks to months. The positive serologies may decrease as the eruption improves. The pathogenesis of drug-induced SCLE is unknown, but most agents that cause it are also agents that cause both photosensitive and lichenoid drug eruptions. Etanercept can produce both classic drug-induced SLE and druginduced SCLE (see above).

HYDROXYUREA DERMOPATHY

Chronic use of hydroxyurea for chronic myelogenous leukemia, thrombocythemia, or psoriasis may be associated with the development of cutaneous lesions characteristic of dermatomyositis. Scaly, linear erythema of the dorsal hands, accentuated over the knuckles, is noted. There may be marked acral atrophy and telangiectasia. Elbow and eyelid involvement characteristic of dermatomyositis may also be seen. Biopsy shows vacuolar degeneration of the basal cells and an interface lymphocytic infiltrate. The skin lesions tend to improve over months, although the atrophy may not improve.

LINEAR IgA BULLOUS DERMATOSIS

Linear IgA disease is frequently associated with medication exposure, especially vancomycin. Men and women are equally affected, and the eruption usually begins within 2 weeks of vancomycin therapy. Clinical morphology is variable and can include flaccid or tense bullae, vesicles, erythematous papules or plaques, exanthematous morbilliform eruptions typical of a drug exanthem, and targetoid papules. TEN or severe SJS may be simulated, but mucosal involvement is not universal (30-45%) and conjunctival involvement is uncommon (10%).

Histology will show subepidermal blistering with neutrophils and eosinophils in biopsies taken from bullous lesions. In non- bullous and TEN/SJS-like lesions, there is a vacuolar/lichenoid dermatitis with eosinophils. Unless a direct immunofluores- cence (DIF) test is performed, this would be interpreted as erythema multiforme or a drug eruption, and the diagnosis of linear IgA disease would be missed. Treatment is to stop the offending drug and to give dapsone at 100-200 mg daily, as needed.

LEUKOTRIENE RECEPTOR ANTAGONIST-ASSOCIATED CHURG-STRAUSS SYNDROME

Asthma patients being treated with leukotriene receptor antagonists may develop a syndrome resembling Churg- Strauss vasculitis. It occurs 2 days to 10 months after the leukotriene receptor antagonist has been started. Inhaled fluticasone has also been reported to produce this syndrome. Involvement may be limited to the skin. Features of the syndrome include peripheral eosinophilia, pulmonary infiltrates, and less commonly neuropathy, sinusitis, pericardial effusion, and cardiomyopathy. Skin lesions occur in about half the patients and are usually purpuric and favor the lower legs. Histologically, the skin lesions show leukocytoclastic vasculi- tis with significant tissue eosinophilia. In one case cutaneous perivascular granulomas with eosinophils were found in the skin with surrounding necrobiotic collagen. Antibodies to neutrophilic cytoplasmic antigens (p-ANCA) may be positive. Withdrawal of the leukotriene receptor antagonist therapy may lead to improvement, but systemic therapy with pred- nisone and cyclophosphamide may be required. The neuropathy may be permanent. The pathogenesis of this drug-induced syndrome is unknown. Some cases occur as steroids are tapered, but others have occurred in steroid-naive asthmatics. Unopposed leukotriene B4 activity, a potent chemoattractant for eosinophils and neutrophils, may explain the clinical findings.

ADVERSE REACTIONS TO CORTICOSTEROIDS

Cutaneous reactions may result from topical, intralesional, subcutaneous, or systemic delivery of corticosteroids.

TOPICAL APPLICATION

The prolonged topical use of corticosteroid preparations may produce distinctive changes in the skin. The appearance of these side effects is dependent on four factors: the strength of the steroid, the area to which it is applied, the amount of coexistent sun damage at the site of application, and the individual's predisposition to certain side effects. Atrophy, striae, telangiectasia, skin fragility, and purpura are the most frequent changes seen. The most striking changes of telangiectasia are seen in fairskinned individuals who use fluorinated corticosteroids on the face. The changes in the skin are enhanced by occlusion. When these side effects occur, the strength of the steroid should be reduced or substituted with pimecrolimus or tacrolimus. Weekly pulse dosing of a potent topical steroid can also reduce the incidence of side effects. Adjunctive measures to reduce steroid requirement could include addition of topical doxepin, pramoxine, or menthol and camphor to the regimen. Usually, the telangiectases disappear a few months after corticosteroid applications are stopped. When corticosteroid preparations are applied to the face over a period of weeks or months, persistent erythema with telangiectases, and often small pustules, may occur. Perioral dermatitis and rosacea are in some cases caused by the use of topical corticosteroids. Steroid rosacea has been reported from long-term use of 1% hydrocortisone cream. For this reason, the authors do not recommend chronic topical steroid preparations of any strength in the adjunctive treatment of rosacea. Atopical calcineurin inhibitor may be used instead as an antiinflammatory, although it can also induce a rosacea-like eruption. When a rosacealike eruption appears in the setting of a topical antiinflammatory, a pustule should be opened and the contents examined for overgrowth of Demodex mites. Repeated application of corticosteroids to the face, scrotum, or vulva may lead to marked

atrophy of these tissues. The tissues become "addicted" to the topical steroid, so that withdrawing the topical steroid treatment results in severe itching or burning and intense erythema. Topical application of corticosteroids can produce epidermal atrophy with hypopig- mentation. If used over large areas, sufficient topical steroids may be absorbed to suppress the hypothalamicpituitary axis. This may affect the growth of children with atopic dermatitis and has led to Addisonian steroid dependency and also Cushing syndrome. Atopic children with more than 50% body surface area involvement have short stature. This may be related to their increased use of potent topical steroids. In addition, bone mineral density is reduced in adults with chronic atopic dermatitis severe enough to require corticoster- oid preparations stronger than hydrocortisone.

INJECTED CORTICOSTEROIDS

Intralesional injection of corticosteroids is valuable in the management of many dermatoses. The injection of corticosteroids may produce subcutaneous atrophy at the site of injection. The injected corticosteroid may also migrate along lymphatics, causing not only local side effects but also linear atrophic hypopigmented hairless streaks. These may take years to resolve. These complications are best avoided by injecting directly into the lesion, not into the fat, and using only the minimal concentration and volume required. Triamcinolone acetonide, not hexacetonide, should be used for injecting cutaneous lesions. Intramuscular steroid injections should always be given into the buttocks with a long needle (at least 112 inches in adults). Injection of corticosteroids into the deltoid muscle sometimes causes subcutaneous atrophy. The patient becomes aware of the reaction by noticing depression and depigmentation at the site of injection. There is no pain, but it is bothersome cosmetically. The patient may be assured that this will fill in but it may take several years to do so.

SYSTEMIC CORTICOSTEROIDS

Prolonged use of corticosteroids may produce numerous changes of the skin. In addition, they have a profound effect on the metabolism of many tissues, leading to predictable, and sometimes preventable, complications. Intramuscular injections are not a safer delivery method than oral administration.

PURPURA AND ECCHYMOSIS

The skin may become thin and fragile. Spontaneous tearing may occur from trivial trauma. Purpura and ecchymoses are especially seen over the dorsal forearms in many patients over the age of 50. It is aggravation of actinic purpura.

CUSHINGOID CHANGES

The most common change is probably the alteration in fat distribution. Buffalo hump, facial and neck fullness, increased supraclavicular and suprasternal fat, gynecomastia, protuberant or pendulous abdomen, and flattening of the buttocks may occur. Aggressive dietary management with reduction in carbohydrate and caloric intake may ameliorate these changes.

STEROID ACNE

Small, firm follicular papules on the forehead, cheeks, and chest may occur. Even inhaled corticosteroids for pulmonary disease can cause acne. Steroid acne can persist as long as the corticosteroids are continued. The management is similar to acne vulgaris with topical preparations and oral antibiotics. Acne from androgen use closely resembles steroid acne.

STRIAE

These may be widely distributed, especially over the abdomen, buttocks, and thighs.

OTHER SKIN CHANGES

There may be generalized skin dryness (xerosis); the skin may become thin and fragile; keratosis pilaris may develop; persistent erythema of the skin in sunexposed areas may occur, and erythromelanosis may rarely occur.

HAIR CHANGES

Hair loss occurs in about half of patients on long-term corticosteroids in large doses. There may be thinning and brittle fracturing along the hair shaft. There may be increased hair growth on the bearded area and on the arms and back with fine vellus hairs.

SYSTEMIC COMPLICATIONS

Hypertension, cataracts, aseptic necrosis of the hip, and osteoporosis are potential consequences of therapy with systemic steroids. Bone loss can occur early in the course of corticosteroid therapy, so it should be managed preemptively. Effective management can reduce steroid-induced osteoporosis. All patients with anticipated treatment courses longer than 1 month should be supplemented with calcium and vitamin D (1.0-1.5 g calcium and 400-800 U cholecalciferol a day) and a bisphosphonate, such as alendronate or risedronate. Smoking should be stopped and alcohol consumption minimized. Bone mineral density can be accurately measured at baseline via dual energy xray absorptiometry (DEXA) scan, and followed during corticosteroid therapy. Hypogonadism, which contributes to osteoporosis, can be treated in men and women with testosterone or estrogen, respectively. Implementation of bone loss prevention strategies by dermatologists is unacceptably low.

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CONTENT

SHEET

ANDIJON DAVLAT TIBBIYOT INSTITUTI

GUVOHNOMA

ANDIJON – 2023

O‘QUV ADABIYOTINING NASHR RUXSATNOMASI

O‘zbekiston Respublikasi Oliy ta’lim, fan va innovatsiyalar vazirligi, Andijon davlat tibbiyot instituti rektorining 2024 yil “31” yanvardagi “01/08/198-T”–sonli buyrug‘iga asosan

A.B.Pakirdinov
(muallifning familiyasi, ismi-sharifi)

Medical treatment - 60910200
(ta’lim yo‘nalishi (mutaxassisligi)

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talabalari (o‘quvchilari) uchun tavsiya etilgan.

Atopic dermatitis, eczema and nonenfectious immunodeficiency disorders *nomli o‘quv qo‘llanmasi*
(o‘quv adabiyotining nomi va turi: darslik, o‘quv qo‘llanma)

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O‘zbekiston Respublikasi Vazirlar Mahkamasi tomonidan litsenziya berilgan nashriyotlarda nashr etishga ruxsat berildi.

Rektor _____ M.M.Madazimov
(imzo)

Ro‘yxatga olish raqami:
25

O‘QUV QO‘LLANMA

ADKHAMJON PAKIRDINOV

“ATOPIC DERMATITIS, ECZEMA AND NONINFECTIOUS IMMUNODEFICIENCY DISORDERS"

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