the POEMS (*p*olyneuropathy; *o*rganomegaly [liver, spleen, lymph nodes]; *e*ndocrinopathies [impotence, gynecomastia]; *M*-protein; and *s*kin changes) syndrome. The skin changes include hyperpigmentation, induration, hypertrichosis, angiomas, clubbing, and facial lipoatrophy.

Diffuse hyperpigmentation that is due to drugs or metals can result from one of several mechanisms—induction of melanin pigment formation, complexing of the drug or its metabolites to melanin, and deposits of the drug in the dermis. Busulfan, cyclophosphamide, 5-fluorouracil, and inorganic arsenic induce pigment production. Complexes containing melanin or iron plus the drug or its metabolites are seen in patients receiving minocycline, and a diffuse, blue-gray, muddy appearance within sun-exposed areas may develop, in addition to pigmentation of the mucous membranes, teeth, nails, bones, and thyroid. Administration of amiodarone can result in both a phototoxic eruption (exaggerated sunburn) and/or a slate-gray to violaceous discoloration of sun-exposed skin. Biopsy specimens of the latter show yellow-brown granules in dermal macrophages, which represent intralysosomal accumulations of lipids, amiodarone, and its metabolites. Actual deposits of a particular drug or metal in the skin are seen with silver (argyria), where the skin appears blue-gray in color; gold (chrysiasis), where the skin has a brown to blue-gray color; and clofazimine, where the skin appears reddish brown. The associated pigmentation is accentuated in sun-exposed areas, and discoloration of the eye is seen with gold (sclerae) and clofazimine (conjunctivae).

VESICLES/BULLAE

(Table 72-12) Depending on their size, cutaneous blisters are referred to as *vesicles* (<1 cm) or *bullae* (>1 cm). The primary autoimmune blistering disorders include *pemphigus vulgaris*, *pemphigus foliaceus*, *paraneoplastic pemphigus*, *bullous pemphigoid*, *gestational pemphigoid*, *cicatricial pemphigoid*, *epidermolysis bullosa acquisita*, *linear IgA bullous dermatosis* (*LABD*), and *dermatitis herpetiformis* (Chap. 73).

Vesicles and bullae are also seen in *contact dermatitis*, both allergic and irritant forms (Chap. 71). When there is a linear arrangement of vesicular lesions, an exogenous cause or herpes zoster should be suspected. Bullous disease secondary to the ingestion of drugs can take one of several forms, including phototoxic eruptions, isolated bullae, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) (Chap. 74). Clinically, phototoxic eruptions resemble an exaggerated sunburn with diffuse erythema and bullae in sun-exposed areas. The most commonly associated drugs are doxycycline, quinolones, thiazides, NSAIDs, voriconazole, and psoralens. The development of a phototoxic eruption is dependent on the doses of both the drug and ultraviolet (UV)-A irradiation.

Toxic epidermal necrolysis is characterized by bullae that arise on widespread areas of tender erythema and then slough. This results in large areas of denuded skin. The associated morbidity, such as sepsis, and mortality rates are relatively high and are a function of the extent of epidermal necrosis. In addition, these patients may also have involvement of the mucous membranes and respiratory and intestinal tracts. Drugs are the primary cause of TEN, and the most common offenders are aromatic anticonvulsants (phenytoin, barbiturates, carbamazepine), sulfonamides, aminopenicillins, allopurinol, and NSAIDs. Severe acute graft-versus-host disease (grade 4), vancomycin-induced LABD, and the acute syndrome of apoptotic pan-epidermolysis (ASAP) in patients with lupus can also resemble TEN.

In *erythema multiforme* (EM), the primary lesions are pink-red macules and edematous papules, the centers of which may become vesicular. In contrast to a morbilliform exanthem, the clue to the diagnosis of EM, and especially SJS, is the development of a "dusky" violet color in the center of the lesions. Target lesions are also characteristic of EM and arise as a result of active centers and borders in combination with centrifugal spread. However, target lesions need not be present to make the diagnosis of EM.

EM has been subdivided into two major groups: (1) EM minor due to herpes simplex virus (HSV) and (2) EM major due to HSV; *Mycoplasma pneumoniae*; or, occasionally, drugs. Involvement of the mucous membranes (ocular, nasal, oral, and genital) is seen more commonly in the latter form. Hemorrhagic crusts of the lips are characteristic of EM major and SJS as well as herpes simplex, pemphigus vulgaris, and paraneoplastic pemphigus. Fever, malaise, myalgias, sore throat, and cough may precede or accompany the eruption. The lesions of EM usually resolve over 2–4 weeks but may be recurrent, especially when due to HSV. In addition to HSV (in which lesions usually appear 7–12 days after the viral eruption), EM can also follow vaccinations, radiation therapy, and exposure to environmental toxins, including the oleoresin in poison ivy.

Induction of SJS is most often due to drugs, especially sulfonamides, phenytoin, barbiturates, lamotrigine, aminopenicillins, nonnucleoside reverse transcriptase inhibitors (e.g., nevirapine), and carbamazepine. Widespread dusky macules and significant mucosal involvement are characteristic of SJS, and the cutaneous lesions may or may not develop epidermal detachment. If the latter occurs, by definition, it is limited to <10% of the body surface area (BSA). Greater involvement leads to the diagnosis of SJS/TEN overlap (10–30% BSA) or TEN (>30% BSA).

In addition to primary blistering disorders and hypersensitivity reactions, bacterial and viral infections can lead to vesicles and bullae. The most common infectious agents are HSV (Chap. 216), varicella-zoster virus (Chap. 217), and *S. aureus* (Chap. 172).

TABLE 72-12 CAUSES OF VESICLES/BULLAE

- I. Primary mucocutaneous diseases
  - A. Primary blistering diseases (autoimmune)
    1. Pemphigus, foliaceus and vulgaris[a]
    2. Bullous pemphigoid[b]
    3. Gestational pemphigoid[b]
    4. Cicatricial pemphigoid[b]
    5. Dermatitis herpetiformis[b,c]
    6. Linear IgA bullous dermatosis[b]
    7. Epidermolysis bullosa acquisita[b,d]
  - B. Secondary blistering diseases
    1. Contact dermatitis[a,b]
    2. Erythema multiforme[e]
    3. Stevens-Johnson syndrome[e]
    4. Toxic epidermal necrolysis[e]
  - C. Infections
    1. Varicella-zoster virus[a,f]
    2. Herpes simplex virus[a,f]
    3. Enteroviruses, e.g., hand-foot-and-mouth disease[f]
    4. Staphylococcal scalded-skin syndrome[a,g]
    5. Bullous impetigo[a]
- II. Systemic diseases
  - A. Autoimmune
    1. Paraneoplastic pemphigus[a]
  - B. Infections
    1. Cutaneous emboli[b]
  - C. Metabolic
    1. Diabetic bullae[a,b]
    2. Porphyria cutanea tarda[b]
    3. Porphyria variegata[b]
    4. Pseudoporphyria[b]
    5. Bullous dermatosis of hemodialysis[b]
  - D. Ischemia
    1. Coma bullae

[a]Intraepidermal. [b]Subepidermal. [c]Associated with gluten enteropathy. [d]Associated with inflammatory bowel disease. [e]Degeneration of cells within the basal layer of the epidermis can give impression split is subepidermal. [f]Also systemic. [g]In adults, associated with renal failure and immunocompromised state.