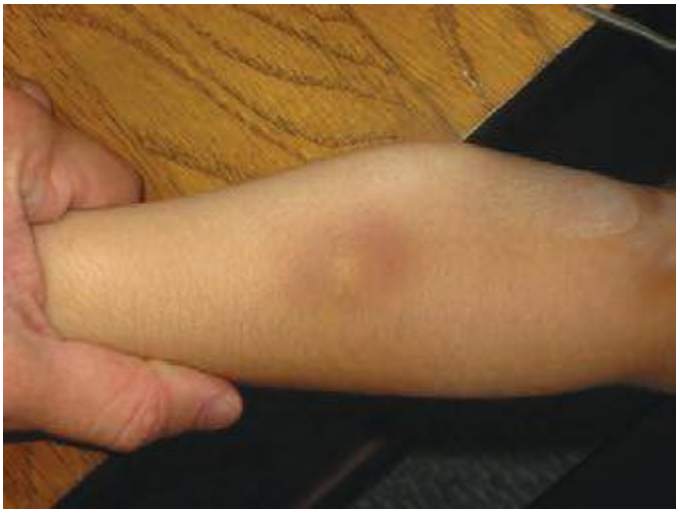

FIGURE 74-7 Fixed drug eruption.

IMMUNE CUTANEOUS REACTIONS: RARE AND SEVERE

Vasculitis Cutaneous small-vessel vasculitis often presents as palpable purpuric lesions that may be generalized or limited to the lower extremities or other dependent areas (Chap. 385). Pustular lesions and hemorrhagic blisters also occur. Vasculitis may involve other organs, including the liver, kidney, brain, and joints. Drugs are implicated as a cause of 10–15% of all cases of small-vessel vasculitides. Infection, malignancy, and collagen vascular disease are responsible for the majority of non-drug-related cases.

Propylthiouracil induces a cutaneous vasculitis that is accompanied by leukopenia and splenomegaly. Direct immunofluorescent changes in these lesions suggest immune-complex deposition. Common drugs implicated in vasculitis include allopurinol, thiazides, sulfonamides, antimicrobials, and NSAIDs. The presence of eosinophils in the perivascular infiltrate of skin biopsy suggests a drug etiology.

Pustular Eruptions AGEP is a rare reaction pattern (3–5 cases per million per year) that is often associated with exposure to drugs (Fig. 74-8). Usually beginning on the face or intertriginous areas, small nonfollicular pustules overlying erythematous and edematous skin may coalesce and lead to superficial erosion. Differentiating this eruption from TEN in its initial stages may be difficult. A skin biopsy is important and shows neutrophil collections and sparse necrotic keratinocytes in the upper part of the epidermis instead of the full-thickness epidermal necrosis that characterizes TEN. Fever and leukocytosis are common, and eosinophilia occurs in one-third of cases. Acute pustular psoriasis is the principal differential diagnostic consideration. DIHS with pustular features must also be clinically considered, although the timing for the onset of DIHS is distinct (much later onset). AGEP often begins within a few days of initiating drug treatment, most notably antibiotics, but may occur as late as 7–14 days after initiation of treatment. A broad range of drug classes (anticonvulsants, mercury, radiocontrast dye) and infections (viral, *Mycoplasma*) are also associated with AGEP. Patch testing with the responsible drug results in a localized pustular eruption.

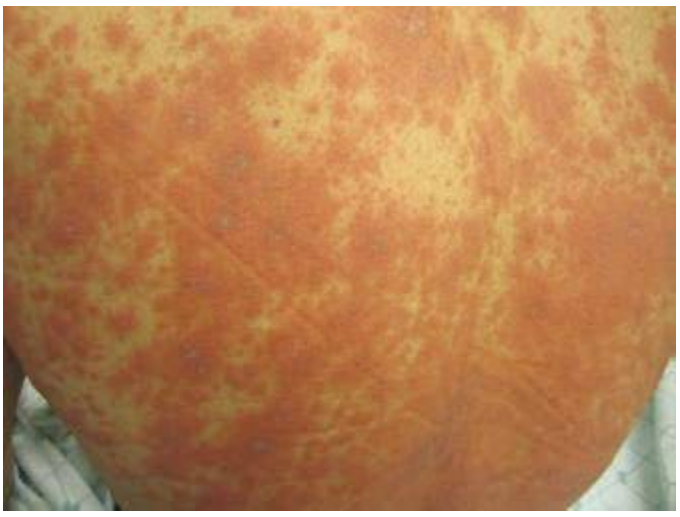

FIGURE 74-8 Acute generalized exanthematous pustulosis.

Drug-induced Hypersensitivity Syndrome Drug-induced hypersensitivity syndrome (DIHS) is a multiorgan drug reaction previously known as DRESS (drug reaction with eosinophilia and systemic symptoms); since eosinophilia is not always present, the term *DIHS* is now preferred. Allopurinol is the most common cause. Although less frequently prescribed, abacavir has been reported to cause DIHS with an incidence as high as 4–8%. It presents as a widespread erythematous eruption that may become purpuric, pustular, or lichenoid and is accompanied by many of the following features: fever, facial edema, lymphadenopathy, leukocytosis (often with atypical lymphocytes and eosinophilia), hepatitis, myositis (including myocarditis), and sometimes nephritis (with proteinuria) or pneumonitis. Distinct patterns of timing of onset and organ involvement may exist; e.g., allopurinol classically induces DIHS with renal involvement. Cardiac and lung involvement is more common with minocycline; gastrointestinal involvement is almost exclusively seen with abacavir, and some medications typically lack eosinophilia (abacavir, dapsone, lamotrigine). The cutaneous reaction usually begins 2–8 weeks after the drug is started and lasts longer than mild eruptions after drug cessation. Signs and symptoms may persist for several weeks, especially those associated with hepatitis. The eruption recurs with rechallenge, and cross-reactions among aromatic anticonvulsants, including phenytoin, carbamazepine, and barbiturates, are frequent. Other drugs causing this syndrome include sulfonamides and other antibiotics. Hypersensitivity to reactive drug metabolites, hydroxylamine for sulfamethoxazole, and arene oxide for aromatic anticonvulsants may be involved in the pathogenesis of DIHS. Reactivation of herpes viruses, especially herpesvirus 6 and Epstein-Barr virus (EBV), has been frequently reported in this syndrome, although the causal role of viral infection has been debated. Recent research suggests that inciting drugs may reactivate quiescent herpes viruses, resulting in expansion of viral-specific CD8+ T lymphocytes with subsequent end-organ damage. Viral reactivation may be associated with a worse clinical prognosis. Mortality rates as high as 10% have been reported; mortality is highest in association with hepatitis. Systemic glucocorticoids (prednisone, 1–2 mg/kg daily) should be started with slow taper over 8–12 weeks. A steroid-sparing agent, such as mycophenolate mofetil, may be indicated in cases of rapid recurrence upon steroid taper. In all cases, rapid withdrawal of the suspected drug is required. Given the severe long-term complications of myocarditis, patients should undergo cardiac evaluation if heart involvement is suspected by hypotension or arrhythmia. Patients should be closely monitored for resolution of organ dysfunction and for development of late-onset autoimmune thyroiditis (up to 6 months).

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis *SJS* and *TEN* are characterized by blisters and mucosal/epidermal detachment resulting from full-thickness epidermal necrosis in the absence of substantial dermal inflammation (Fig. 74-9). The term *Stevens-Johnson syndrome* describes cases with blisters developing on target lesions, dusky or purpuric macules in which mucosal involvement is significant, and total body surface area blistering and eventual detachment in <10% of cases. The term *Stevens-Johnson syndrome/toxic epidermal necrolysis overlap* is used to describe cases with 10–30% detachment, and *TEN* is used to describe cases with >30% detachment.

Other blistering eruptions with mucositis associated with infections may be confused with SJS/TEN. Erythema multiforme (EM) associated with herpes simplex virus is characterized by mucosal involvement and target lesions often more acrally distributed and with limited skin detachment. *Mycoplasma* infection in children causes a clinically distinct presentation with prominent mucositis and limited blistering