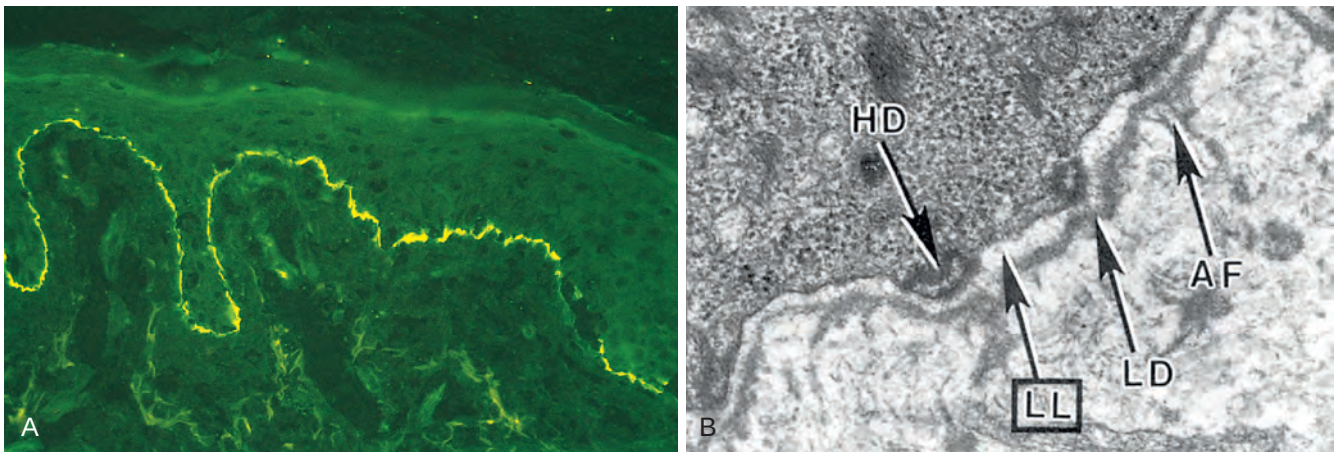

Figure 25-33 **A,** Linear deposition of complement along the dermoepidermal junction in bullous pemphigoid. **B,** Electron micrograph showing the ultrastructural features of the dermoepidermal junction. The bullous pemphigoid antigen (BPAG) is located in the basal portion of basal keratinocytes in association with hemidesmosomes (HD), which attach the epidermis to the lamina lucida (LL) of the basement membrane. AF, Anchoring fibrils; LD, lamina densa. (See also Fig. 25-31.)

decades of life. In some cases it occurs in association with intestinal celiac disease and responds to a gluten-free diet (Chapter 17). The plaques and vesicles are extremely pruritic.

Pathogenesis. The association of dermatitis herpetiformis with celiac disease provides a clue to its pathogenesis. Genetically predisposed individuals develop IgA antibodies to dietary gluten (derived from the wheat protein *gliadin*). The antibodies cross-react with reticulin, a component of the anchoring fibrils that tether the epidermal basement membrane to the superficial dermis. The resultant injury and inflammation produce a subepidermal blister. In some people with dermatitis herpetiformis and gluten-sensitive enteropathy, both disorders respond to a gluten-free diet.

MORPHOLOGY

The lesions are bilateral, symmetric and grouped, involving preferentially the extensor surfaces, elbows, knees, upper back, and buttocks (Fig. 25-34*C*). Fibrin and neutrophils accumulate selectively at the **tips of dermal papillae**, forming small microabscesses (Fig. 25-34*A*). The basal cells overlying these microabscesses show vacuolization and focal dermoepidermal separation that ultimately coalesce to form a true **subepidermal blister**. By direct immunofluorescence, dermatitis herpetiformis shows discontinuous, **granular deposits of IgA** that selectively localize in the tips of dermal papillae (Fig. 25-34*B*).

Noninflammatory Blistering Disorders

Epidermolysis Bullosa and Porphyria

Some disorders characterized by vesicles and bullae are mediated by inherited or in some cases acquired defects involving structural proteins that maintain the normal organization of the skin. Two such disorders are epidermolysis bullosa and porphyria.

Epidermolysis Bullosa. Epidermolysis bullosa is a blanket term for a group of disorders caused by inherited defects in structural proteins that lend mechanical stability to the skin. The common feature is a proclivity to form blisters at sites of pressure, rubbing, or trauma, at or soon after birth. The histologic changes in all forms are so subtle that electron microscopy may be required to differentiate among the various types.

- In the *simplex type,* defects of the basal cell layer of the epidermis almost always result from mutations in the genes encoding keratin 14 or keratin 5. These two proteins normally pair with one another to make a functional keratin fiber, thus explaining the similar phenotype resulting from mutations in either gene. The mutated proteins have a dominant negative activity, and as a result the disorder shows an autosomal dominant mode of inheritance. This is the most common type of epidermolysis bullosa, encompassing 75% to 85% of cases.
- In the *junctional type*, blisters occur in otherwise histologically normal skin at precisely the level of the lamina lucida (Figs. 25-35 and 25-28). Most cases are caused by autosomal recessive defects in one of the subunits of laminin, a multicomponent protein located in the lamina lucida that binds to both hemidesmosomes and anchoring filaments. Some of the remaining cases are caused by mutations in BPAG2, the same protein that is targeted by autoantibodies in bullous pemphigoid.
- In the scarring *dystrophic types*, blisters develop beneath the lamina densa in association with rudimentary or defective anchoring fibrils. Dystrophic epidermolysis bullosa usually results from mutations in the *COL7A1* gene, which encodes type VII collagen (Chapter 3), a major component of the basement membrane anchoring fibrils. Depending on the mutation, the disorder may follow an autosomal dominant or autosomal recessive mode of inheritance.
- *Mixed types*, marked by defects at several levels, are also recognized.

Porphyria. *Porphyria* refers to a group of uncommon inborn or acquired disturbances of porphyrin metabolism.