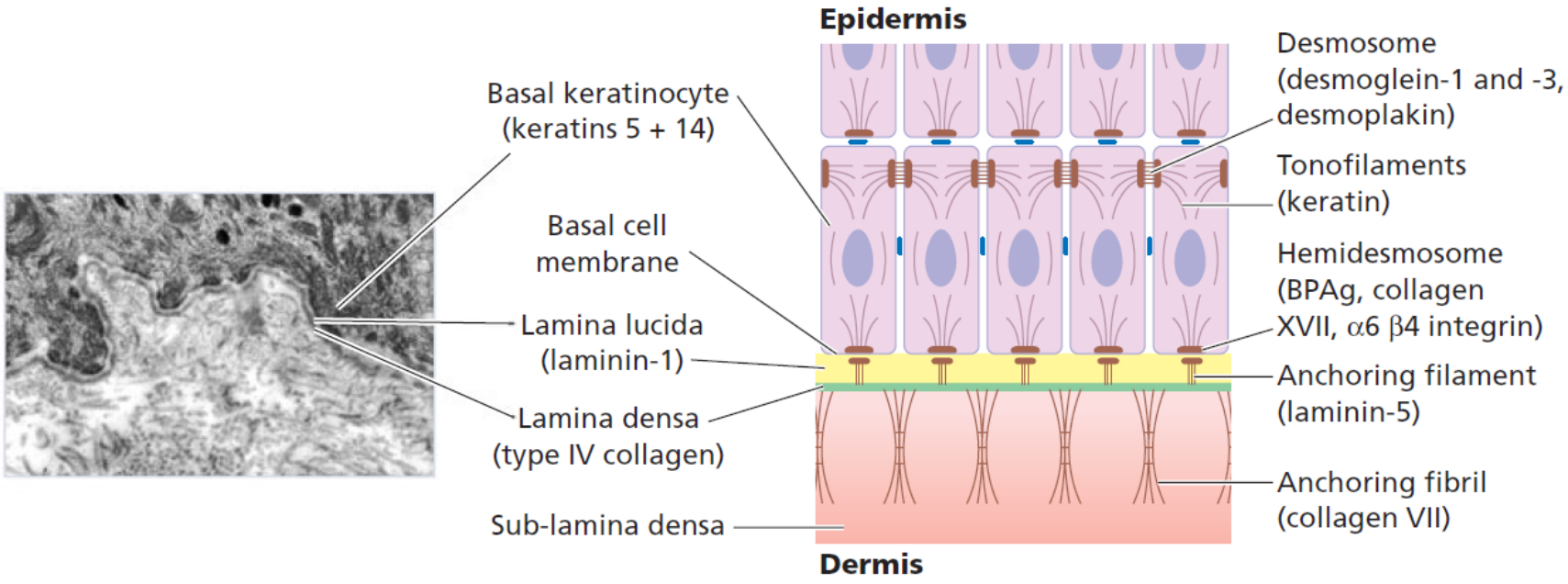
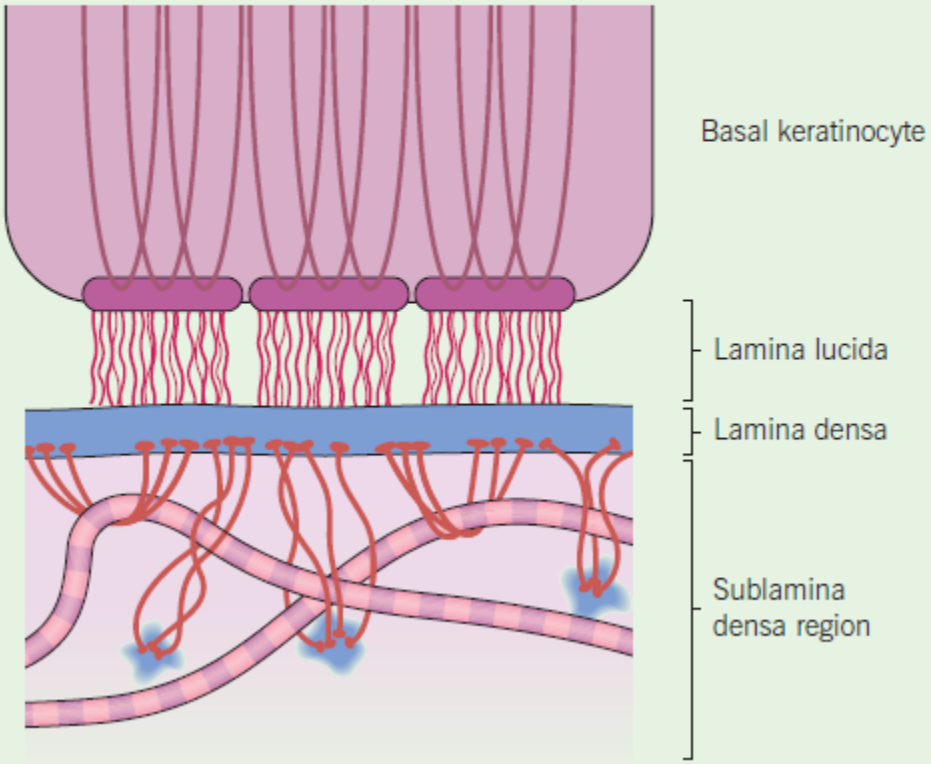
BULLOUS DISEASES

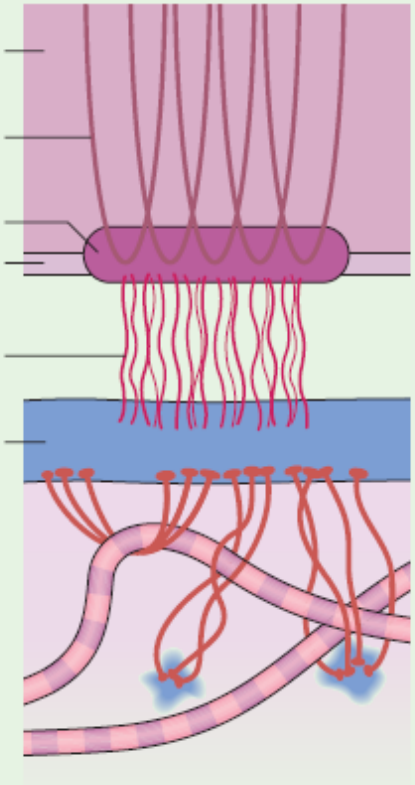
- Basement membrane is located between different cell types, lies between epidermis and dermis, contain and electron-dense that is referred as lamina densa. Major components of the lamina densa is type IV collagen. Lamina lucida is near the basal cells. The lamina lucida contains laminin 1, laminin 5, adhesive molecules and entactin.


Epidermis
Basal keratinocyte
(keratins 5 + 14)
Basal cell
membrane
Lamina lucida
(laminin-1)
Lamina densa
(type IV collagen)
Sub-lamina densa
Dermis
Desmosome
(desmoglein-1 and -3,
desmoplakin)
Tonofilaments
(keratin)
Hemidesmosome
(BPAg, collagen
XVII, α6 β4 integrin)
Anchoring filament
(laminin-5)
Anchoring fibril
(collagen VII)

FOUR MAJOR ULTRASTRUCTURAL SUBREGIONS OF THE EPIDERMAL BASEMENT MEMBRANE



'LAMINATED' MODEL OF THE EPIDERMAL BASEMENT MEMBRANE



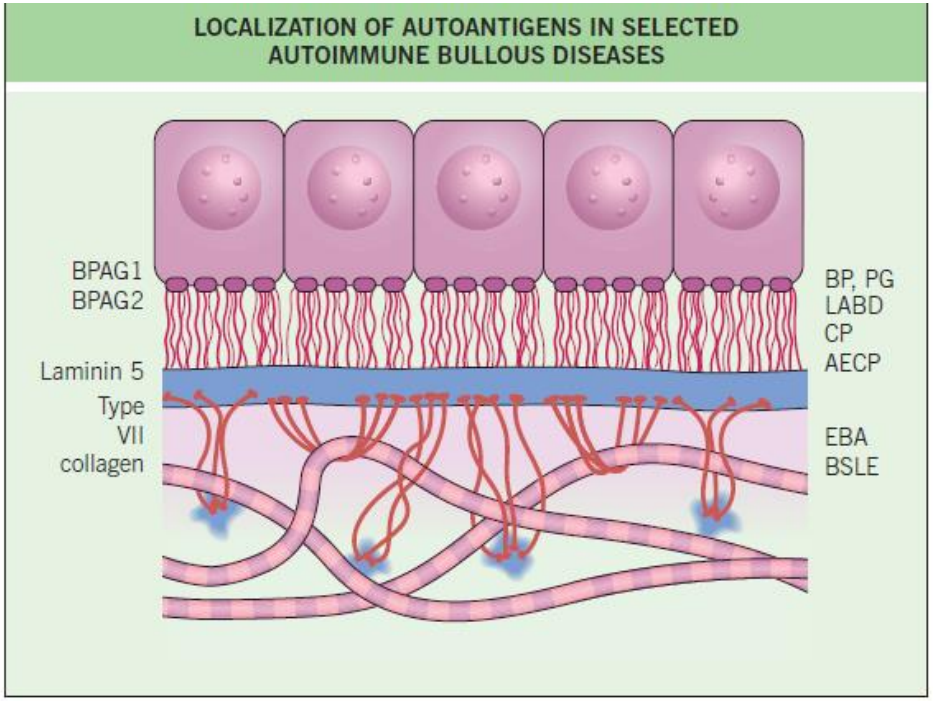
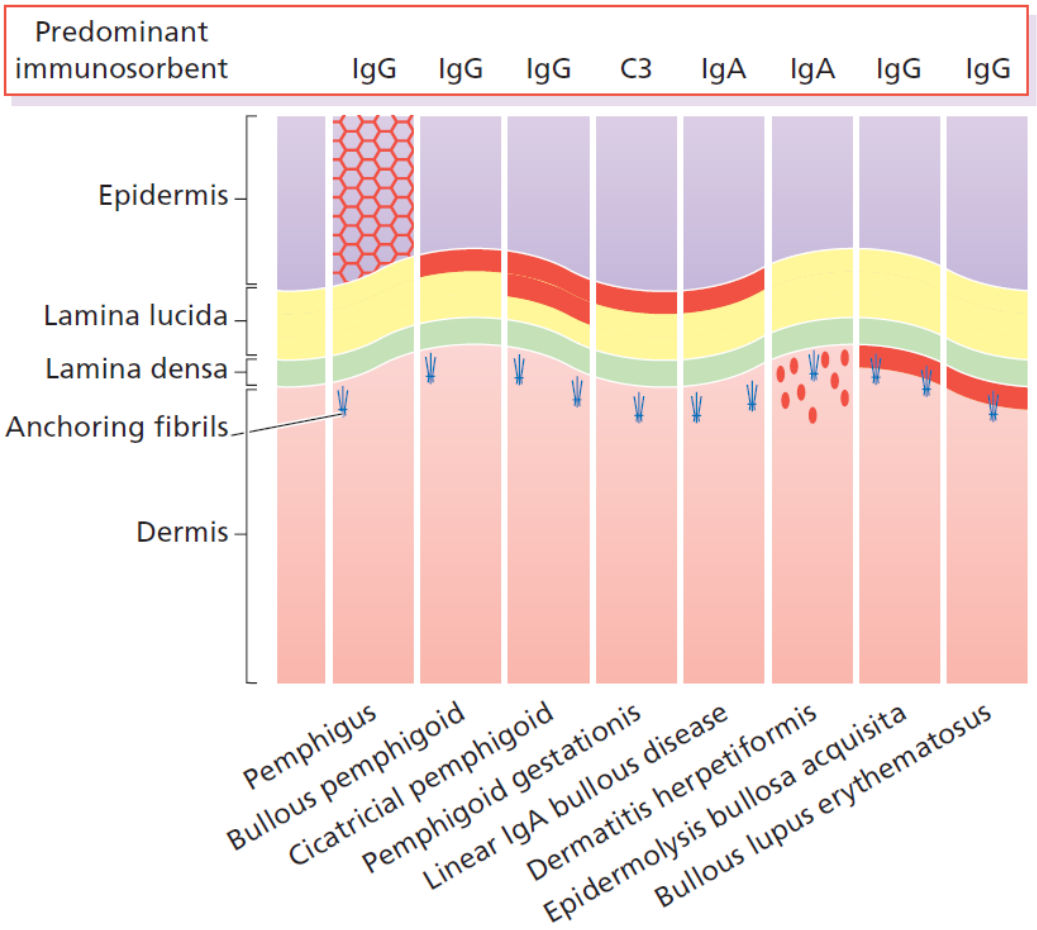


Fig. 29.6 Autoantigens in selected autoimmune bullous diseases. The approximate localization of major autoantigens in selected subepidermal immunobullous diseases. AECP, antiepiligrin cicatricial pemphigoid; BP, bullous pemphigoid; BSLE, the bullous eruption of systemic lupus erythematosus; CP, cicatricial pemphigoid; EBA, epidermolysis bullosa acquisita; LABD, linear IgA bullous dermatosis; PG, pemphigoid gestationis.

- Anchoring filaments (laminin 5) cross LL and connect LD to the plasma membrane of the basal cells.
- Anchoring fibrils (type VII collagen) extend from the papillary dermis to the deep part of the lamina densa.
- The plasma membrane of the basal cells have *hemidesmosomes* (containing bullous pemphigoid antigens, collagen XVII and integrin).

- Laminins are large non collagen glycoproteins produced by keratinocytes and promote adhesion between the basal cells and type IV collagen.

- Bullous diseases are caused with antibodies binding to normal tissue antigens. In the pemphigus family cadherins holding keratinocytes of the epidermis together. In the pemphigoid antigens are synthesized by basic cells and are in close asociation with the hemidesmosomes and laminin. In dermatitis herpetiformis antigen is transglutaminase.


Predominant immunosorbent
IgG
IgG
IgG
C3
IgA
IgA
IgG
IgG
Epidermis
Lamina lucida
Lamina densa
Anchoring fibrils
Dermis
Pemphigus
Bullous pemphigoid
Cicatricial pemphigoid
Pemphigoid gestationis
Linear IgA bullous disease
Dermatitis herpetiformis
Epidermolysis bullosa acquisita
Bullous lupus erythematosus

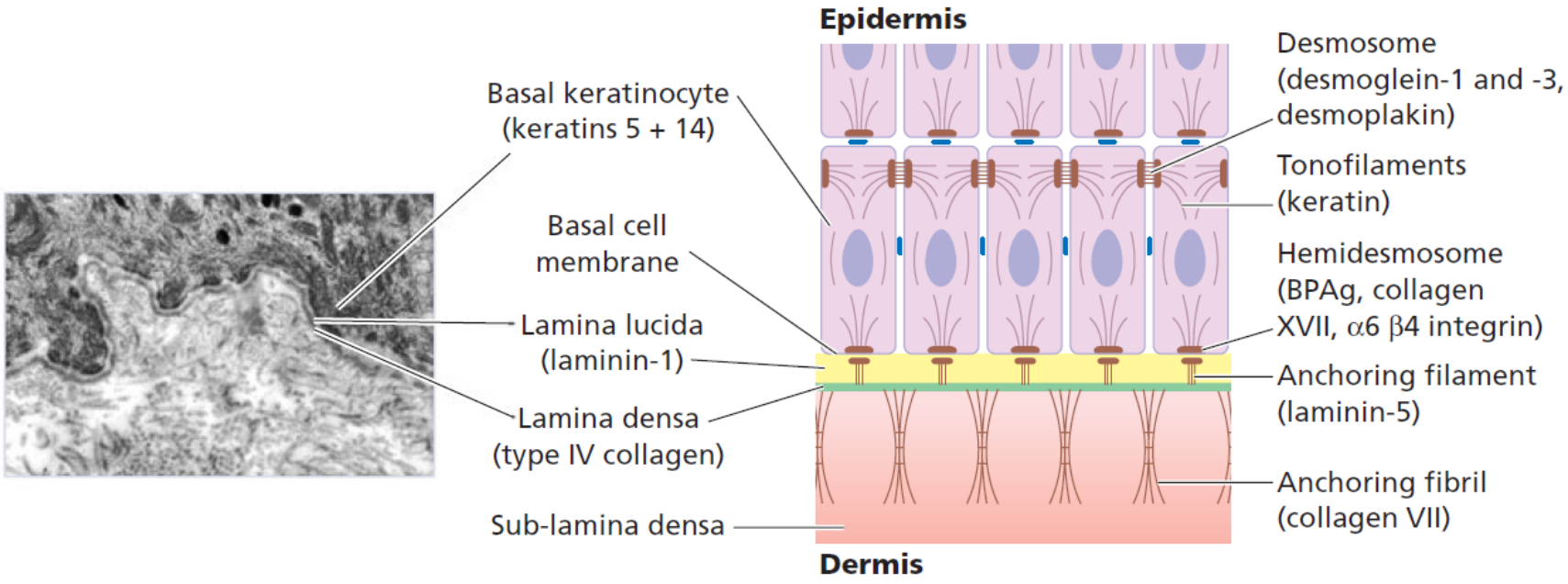
The pemphigus family

Pemphigus is severe and potentially life treatening.

Subtypes:

- pemphigus vulgaris
- pemphigus vegetans
- p. foliaceus
- p. erythematosus
- p. paraneoplasticus

- The pemphigus is autoimmune disease in which pathogenic immunoglobulin G antibodies bind to antigens within the epidermis.
- The main antigens are *desmoglein 3 (*PV) *and desmoglein 1* (PF)
- These are cell-adhesion molecules of the cadherin family found in desmosomes. The antigen-antibody reaction leads to *acantholysis.*

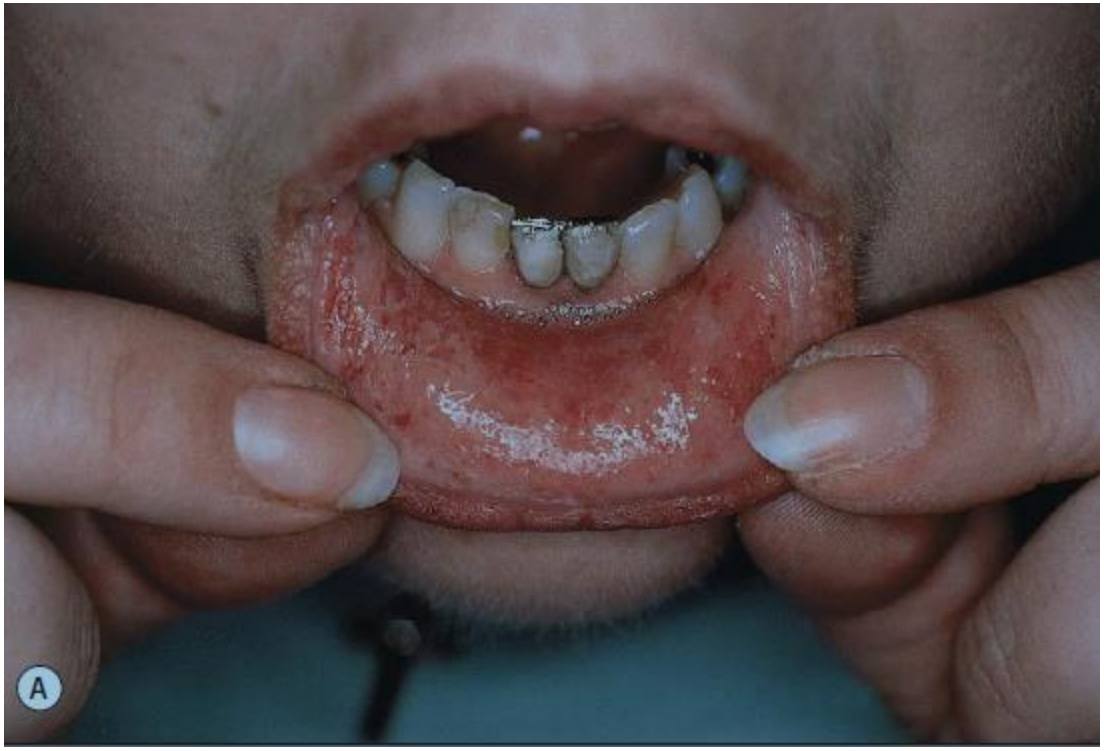

Epidermis
Basal keratinocyte
(keratins 5 + 14)
Basal cell
membrane
Lamina lucida
(laminin-1)
Lamina densa
(type IV collagen)
Sub-lamina densa
Dermis
Desmosome
(desmoglein-1 and -3,
desmoplakin)
Tonofilaments
(keratin)
Hemidesmosome
(BPAg, collagen
XVII, α6 β4 integrin)
Anchoring filament
(laminin-5)
Anchoring fibril
(collagen VII)

Clinical features

- Flaccid blisters of the skin and mouth. The blisters rupture easily to leave painful erosions.
- Positive Nikolsky sign-shearing stresses on normal skin can cause new erosions.
- The blisters in PF are superficial than in clinical picture are only erosions. In PE the facial lesions are pink and scaly.

TARGET ANTIGENS IN PEMPHIGUS			
Disease	**Autoantibodies**	**Antigens**	**MW (kDa)**
Pemphigus vulgaris			
Mucosal-dominant type	IgG	Desmoglein 3	130
Mucocutaneous type	IgG	Desmoglein 3	130
		Desmoglein 1	160
Pemphigus foliaceus	IgG	Desmoglein 1	160
Paraneoplastic pemphigus	IgG	Desmoglein 3	130
		Desmoglein 1	160
		Plectin*	500
		Desmoplakin I*	250
		Desmoplakin II*	210
		BPAG1*	230
		Envoplakin*	210
		Periplakin*	190
		?	170
Drug-induced pemphigus	IgG	Desmoglein 3	130
		Desmoglein 1	160
IgA pemphigus			
SPD type	IgA	Desmocollin 1	110/100
IEN type	IgA	?	?
**Members of plakin family.*			

Table 30.2 Target antigens in pemphigus. BPAG1, bullous pemphigoid antigen 1; IEN, intraepidermal neutrophilic; SPD, subcorneal pustular dermatosis.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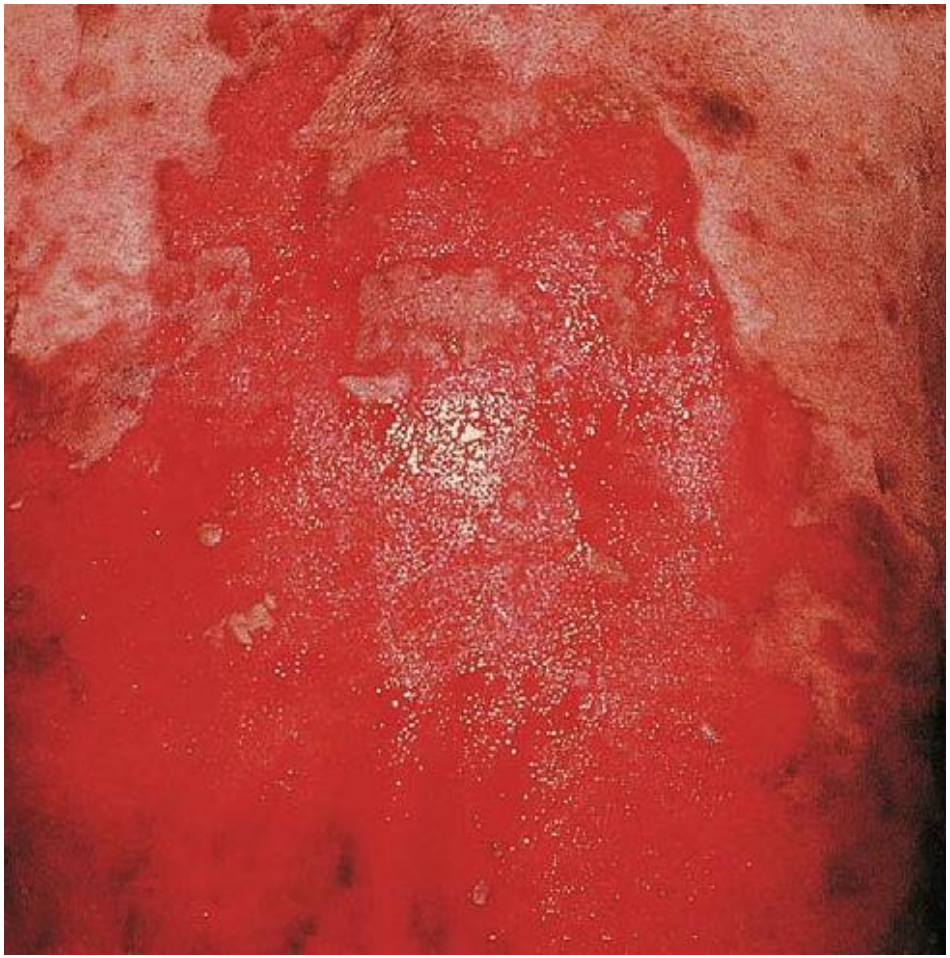


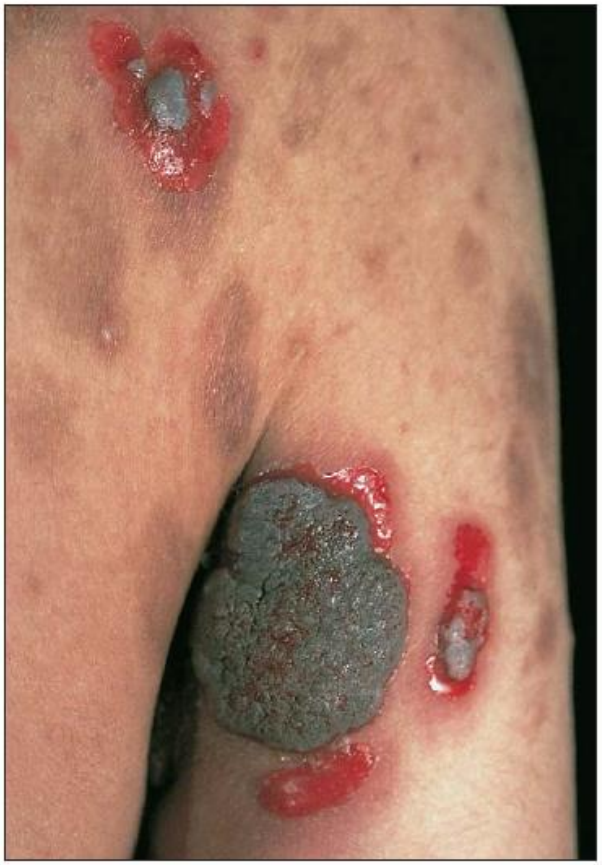


Fig. 30.6 Pemphigus vegetans. Extensive vegetating papillomatous lesions are noted.

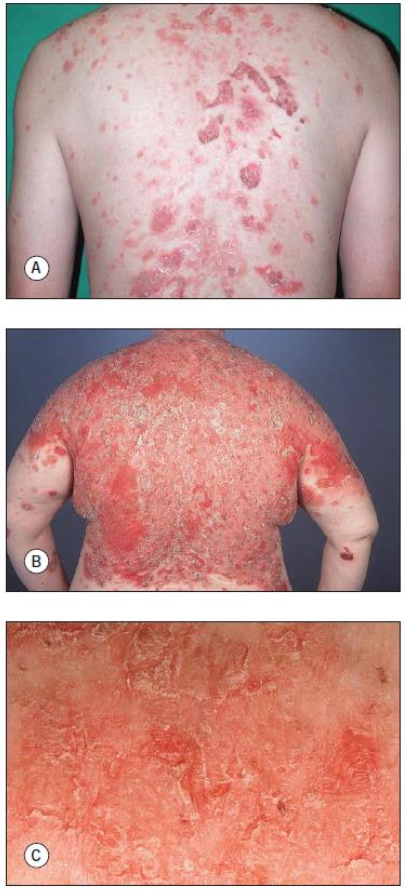


Fig. 30.7 Pemphigus foliaceus. A Scaly, crusted erosions widely distributed on the back. **B** As the disease progresses, the lesions become confluent. **C** Because the vesicles are fragile and rupture easily, the typical lesions of pemphigus foliaceus are erosions with scale-crust; the scales have been likened to corn flakes.

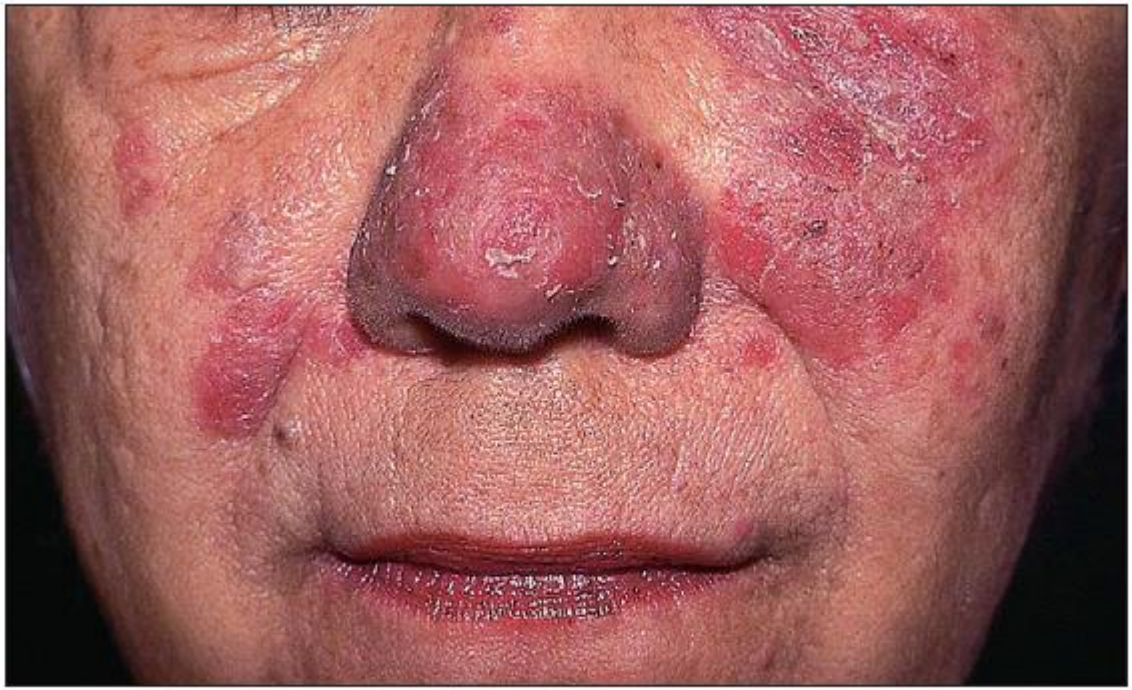


Fig. 30.8 Pemphigus erythematosus. Scaly crusted erosions are seen on the nose and malar area of the face. Courtesy of Ronald P Rapini MD.

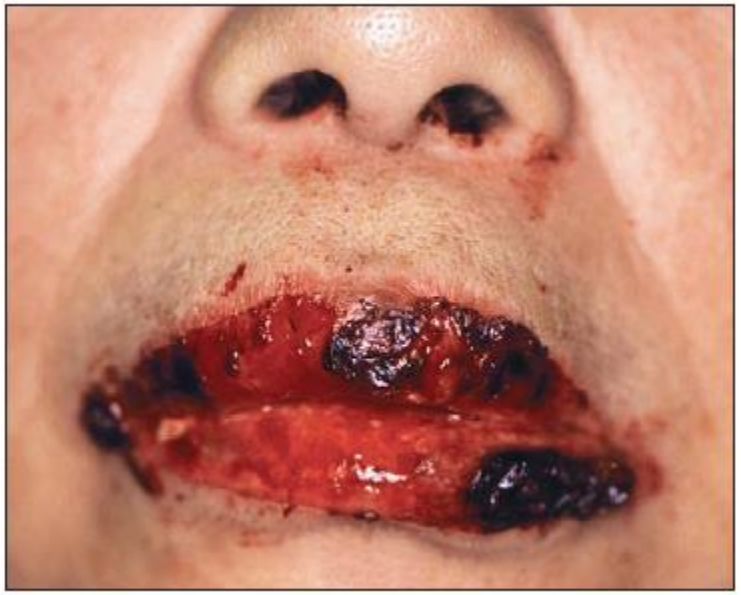


Fig. 30.9 Paraneoplastic pemphigus. The characteristic clinical feature is severe intractable stomatitis that extends onto the vermilion lip.

Differential diagnosis

- Pyoderma
- Impetigo
- Epidermolysis bullosa
- Aphthae
- Behcet’s disease
- Herpes simplex infection

Investigations

1. Biopsy: the vesicles are intra-epidermal with keratinocytes floating within the blister cavity (acantholysis)
2. Direct immunofluorescence: intercellular epidermal deposits of IgG and C3
3. Indirect immunofluorescence: serum from a patient contains antibodies that bind to the desmogleins in the desmosomes.
4. ELISA

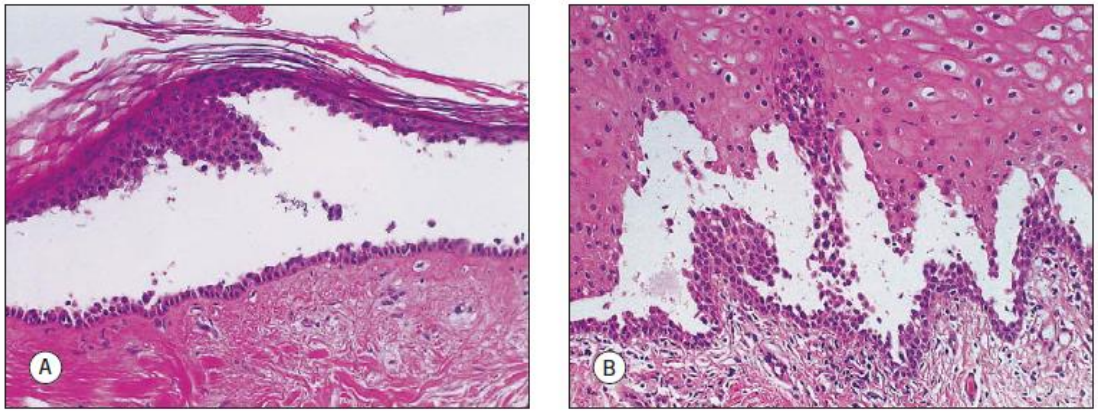
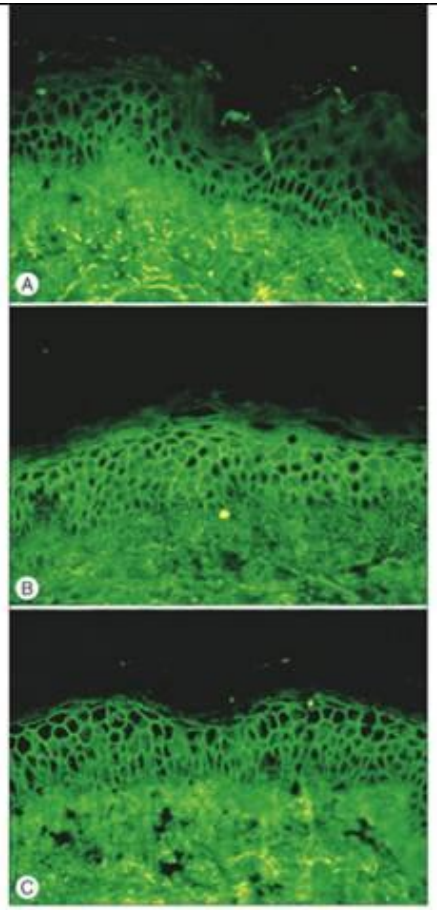
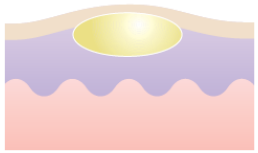
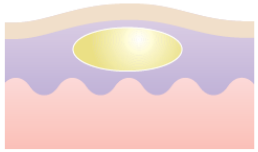
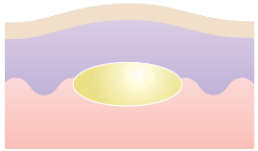


Fig. 30.11 Histology of pemphigus vulgaris.
A Blisters in the skin show suprabasilar acantholysis with a few acantholytic cells in the blister cavity.
B The border of a blister on the buccal mucosa shows intraepithelial separation in the lower part of the mucosal epithelia.



Location of bullae	Diseases
 Subcorneal bulla	Bullous impetigo Miliaria crystallina Staphylococcal scalded skin syndrome
 Intra-epidermal bulla	Acute eczema Viral vesicles Pemphigus Miliaria rubra Incontinentia pigmenti
 Subepidermal bulla	Bullous pemphigoid Cicatricial pemphigoid Pemphigoid gestationis Dermatitis herpetiformis Linear IgA disease Bullous erythema multiforme Bullous lichen planus Bullous lupus erythematosus Porphyria cutanea tarda Toxic epidermal necrolysis Cold or thermal injury Epidermolysis bullosa

Treatment

- Very high doses of systemic steroides (prednisolone)
- Immunosuppressive agents (azathioprine, cyclophosphamide, mycophenylate mofetil)
- IVIG
- Plasmapheresis
- Rituximab
- Dapsone

THERAPEUTIC LADDER FOR PEMPHIGUS VULGARIS	
Standard treatment	
Oral prednisone:	1.0 mg/kg/day as an initial dose (usually 60 mg/day) (1)
Aggressive treatment	
Immunosuppressive agents in combination with oral prednisone:	
Azathioprine	2–4 mg/kg/day (usually 100 to 300 mg/day) (1)
Cyclophosphamide	1–3 mg/kg/day (usually 50 to 200 mg/day) (2)
Mycophenolate mofetil	2–3 g/day (2)
Cyclosporine	5 mg/kg/day (2)
Pulse methylprednisolone	1 g/day over a period of 2–3 hours for 3–5 consecutive days (2)
Methotrexate	7.5–20 mg/week (3)
Pulse cyclophosphamide	50 mg/kg/day × 4 days (3)
Plasmapheresis	1–2 times per week, at the onset (2)
High-dose IVIg	400 mg/kg/day for 5 consecutive days (2); may need to be repeated
Rituximab	375 mg/m^2 once weekly for 4 weeks (2)
Extracorporeal photopheresis	2 days per month (3)
Topical treatment	
Topical corticosteroids (1), especially Class I to localized persistent sites	
Topical antibiotics (2)	
Topical immunomodulators (e.g. cyclosporine, tacrolimus) (3)	

Table 30.4 Therapeutic ladder for pemphigus vulgaris. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

- The course of pemphigus is prolonged, the mortality rate is at least 15 %
- Many have side effects from systemic steroids therapy

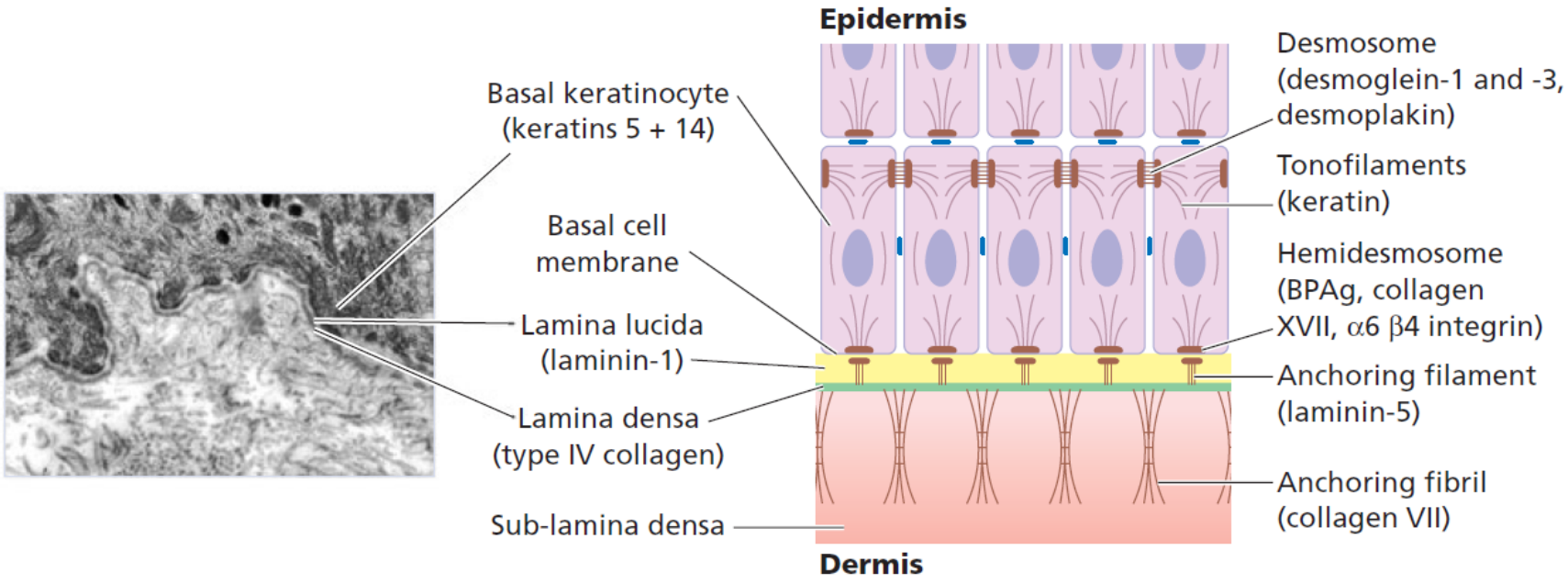
Other causes of subcorneal and intraepidermal blistering

1. bullous impetigo
2. scalded skin sindrome (S.aureus)
3. miliaria
4. subcorneal pustular dermatosis
5. acute contact dermatitis
6. pompholyx
7. viral infections
8. Grover’s disease

Subepidermal immunobullous disorders

PEMPHIGOID BULLOSUS

- Is an autoimmune disease
- The IgG antibodies bind to two main antigens: BP230 and BP180, components of junctional adhesion complexes called hemidesmosomes that promote dermo-epidermal cohesion
- Complement is activated and started an inflammatory cascade.


Epidermis
Basal keratinocyte
(keratins 5 + 14)
Basal cell
membrane
Lamina lucida
(laminin-1)
Lamina densa
(type IV collagen)
Sub-lamina densa
Dermis
Desmosome
(desmoglein-1 and -3,
desmoplakin)
Tonofilaments
(keratin)
Hemidesmosome
(BPAg, collagen
XVII, α6 β4 integrin)
Anchoring filament
(laminin-5)
Anchoring fibril
(collagen VII)

Clinical features

- Pemphigoid is a chronic, itchy, blistering disease in elderly patients.
- Tense vesicles and bullae are on itchy red plaques.
- The mucous membranes are usually not effected. The Nikolsky test is negative.
- The disease is usually self-limiting

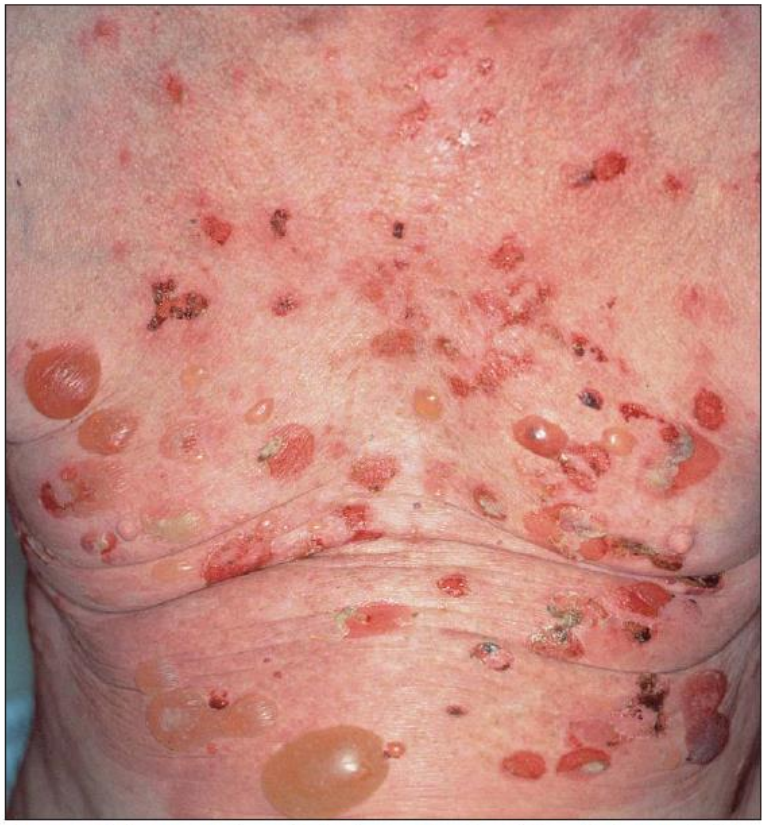


Fig. 31.2 Bullous pemphigoid. Classic presentation with multiple tense bullae arising on normal and erythematous skin. Several of the bullae have ruptured, leaving circular erosions.

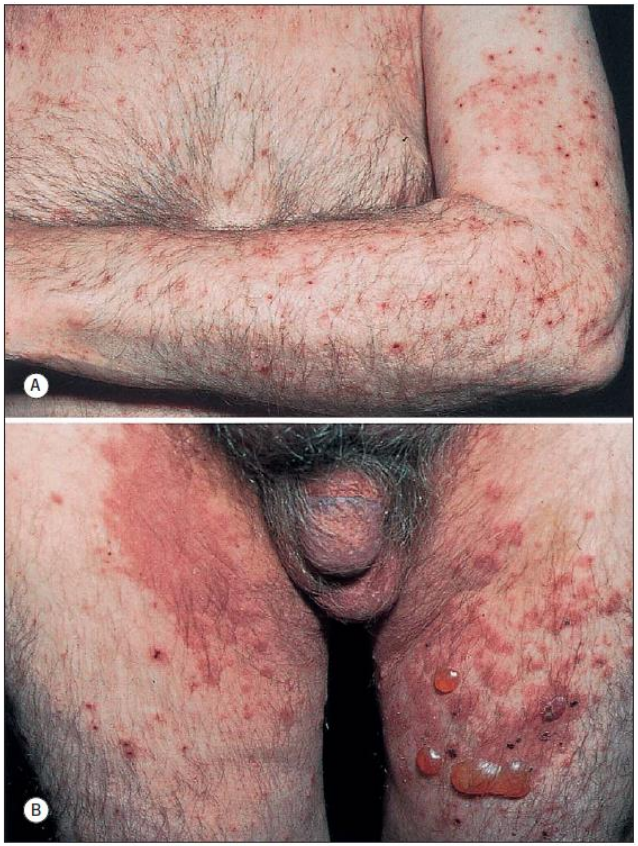


Fig. 31.4 Bullous pemphigoid. A Excoriated eczematous lesions on the upper extremity. **B** Confluent plaques with tense blisters in the inguinal area and inner aspect of the thighs in the same patient.

Investigations

- Biopsy: subepidermal blister is often filled with eosinophils
- Direct immunofluorescence: linear bend of IgG and C3 are long the basal membrane
- Indirect immunofluorescence identifies IgG antibodies that react with the basal membrane
- The association of malignant diseases (digestive tract, urinary, lung carcinoma, lymphoproliferative disorders)

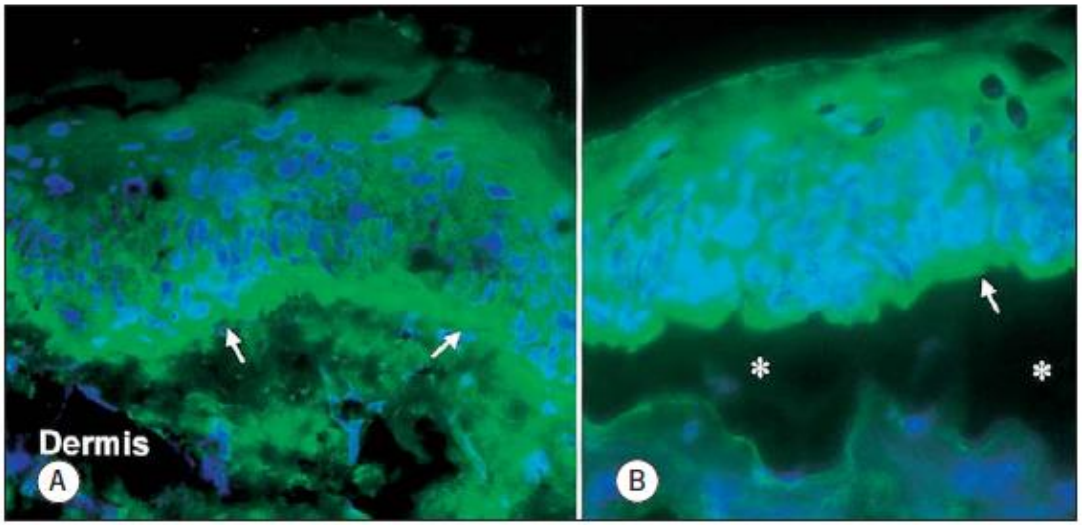


Fig. 31.9 Bullous pemphigoid – direct and indirect immunofluorescence microscopy. A Direct immunofluorescence microscopy studies of perilesional skin demonstrating linear continuous deposits of IgG along the epidermal basement membrane zone (arrows). The same pattern of labeling is observed in cicatricial pemphigoid and epidermolysis bullosa acquisita. **B** Indirect immunofluorescence microscopy study utilizing salt-split normal human skin as a substrate. IgG autoantibodies from the patient's serum are bound to the epidermal side (roof) of the split (arrow). The level of the artificial separation is indicated by asterisks. The same pattern of labeling is observed in a subset of patients with cicatricial pemphigoid. Cell nuclei are stained blue.

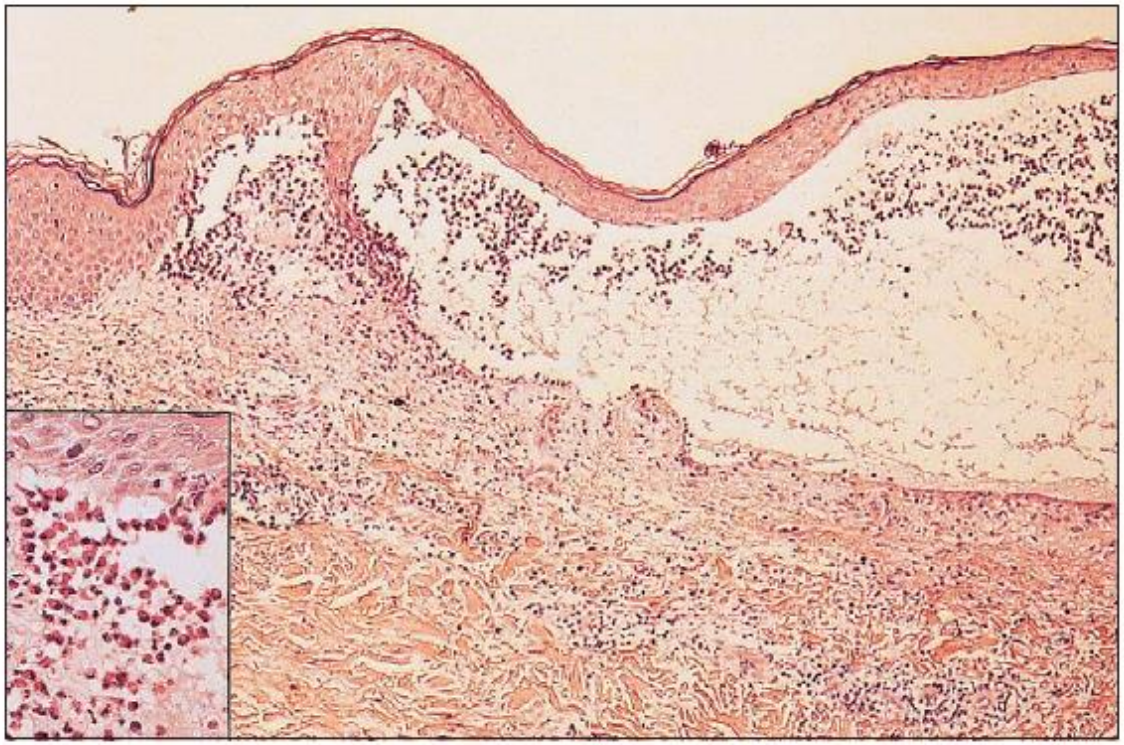


Fig. 31.8 Histology of bullous pemphigoid. Subepidermal blister formation and an inflammatory infiltrate composed of neutrophils and eosinophils in the dermis and bulla cavity. Inset (higher magnification) shows that the infiltrate is rich in eosinophils.

Treatment

- Potent topical steroids alone
- Systemic steroids at a dosage of 40 – 60 mg/day
- Immunosuppressive

THERAPEUTIC LADDER FOR BULLOUS PEMPHIGOID
Mild and/or localized disease
Superpotent topical corticosteroids (1*) Nicotinamide in association with minocycline or tetracycline (3) Erythromycin, penicillins (3) Dapsone, sulfonamides (3) Topical immunomodulators (e.g. tacrolimus) (3)
Extensive/persistent cutaneous disease
Superpotent topical corticosteroids (1*) Oral corticosteroids† (1‡) Azathioprine (2) Mycophenolate mofetil (3) Methotrexate (3) Chlorambucil (3) Cyclophosphamide (3) IVIg (3) Plasma exchange (2) Rituximab (3)
Note: Superpotent topical corticosteroids should be considered in any patient and may be combined with a systemic therapy.
*Validated. †Prednisone doses of at least 0.5–0.75 mg/kg/day seem to be necessary to control extensive disease. ‡Validated for prednisone.

Table 31.3 Therapeutic ladder for bullous pemphigoid. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

Pemphigoid gestationis (herpes gestationis)

- In pregnancy or in the presence of a choriocarcinoma
- Most patients have linear deposits of C3 along the basal membrane, less often IgG
- Remic after the birth
- Treatment with systemic steroids

Cicatricial pemphigoid

- The blisters and ulcers occure mainly on mucous membranes (conjuctivae, mouth, genital tract)
- Lesions heal with scarring and may cause blindness

Key features

- Cicatricial pemphigoid is a chronic, autoimmune, subepithelial blistering disorder characterized by a predominant involvement of the external mucosal surfaces and a tendency for scarring
- It is associated with tissue-bound and, less often, circulating autoantibodies directed against distinct structural components of basement membranes in stratified and some complex epithelia, e.g. the bullous pemphigoid antigen 180 (BP180, BPAG2 or type XVII collagen) or laminin 5
- The condition should not be regarded as a clinical entity, but as a 'disease phenotype' shared by a heterogeneous group of diseases with lesions that favor the mucosal surfaces and, less frequently, the skin
- When scarring and fibrosis affect the conjunctivae, the disorder can be devastating and ultimately lead to blindness
- Diagnosis relies on immunopathologic examinations, especially immunofluorescence and immunoelectron microscopy studies

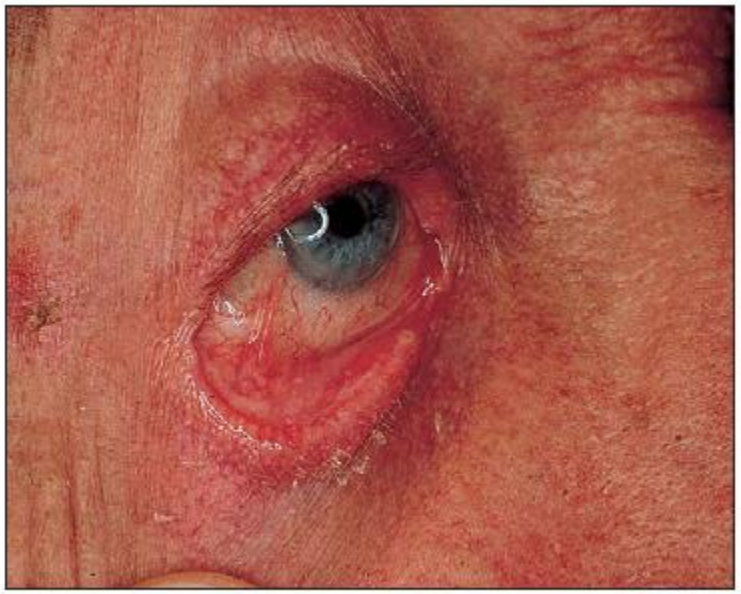


Fig. 31.15 Cicatricial pemphigoid. Typical ocular involvement as manifested by fibrous tracts and eventual symblepharon.

Linear IgA bullous disease

- Clinicaly similar to pemphigoid but affects children and adults.
- Blisters arise on urticarial plaques and are grouped
- Linear deposits of IgA and C3 at the basal membrane
- Treatment with oral dapsone

Acquired epidermolysis bullosa

- Many blisters arise in response to trauma on normal skin
- The target of the autoantibodies is type VII collagen in anchoring fibrils

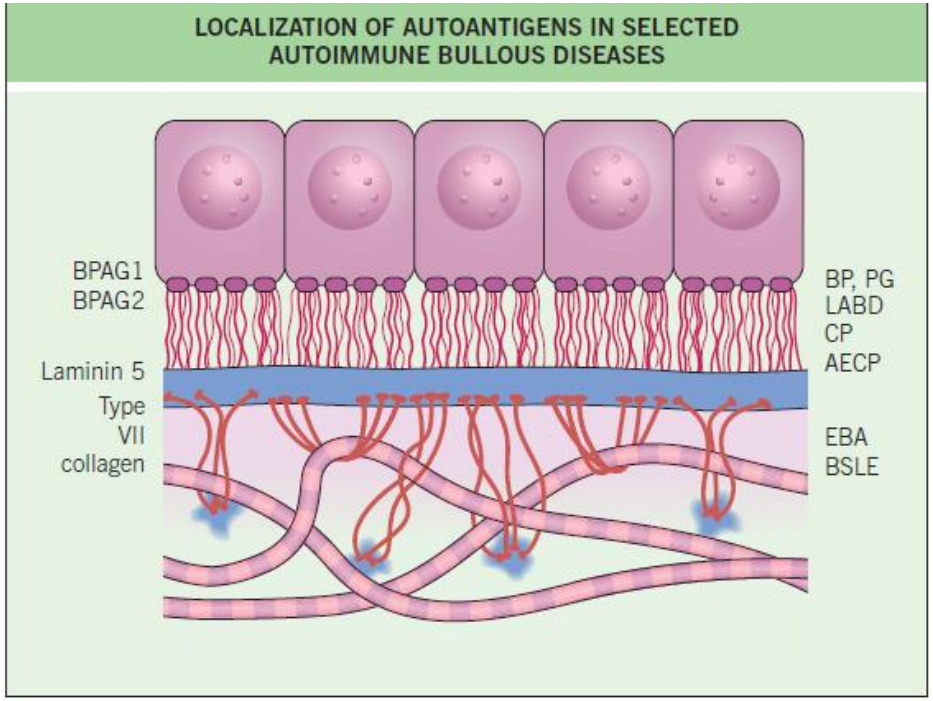
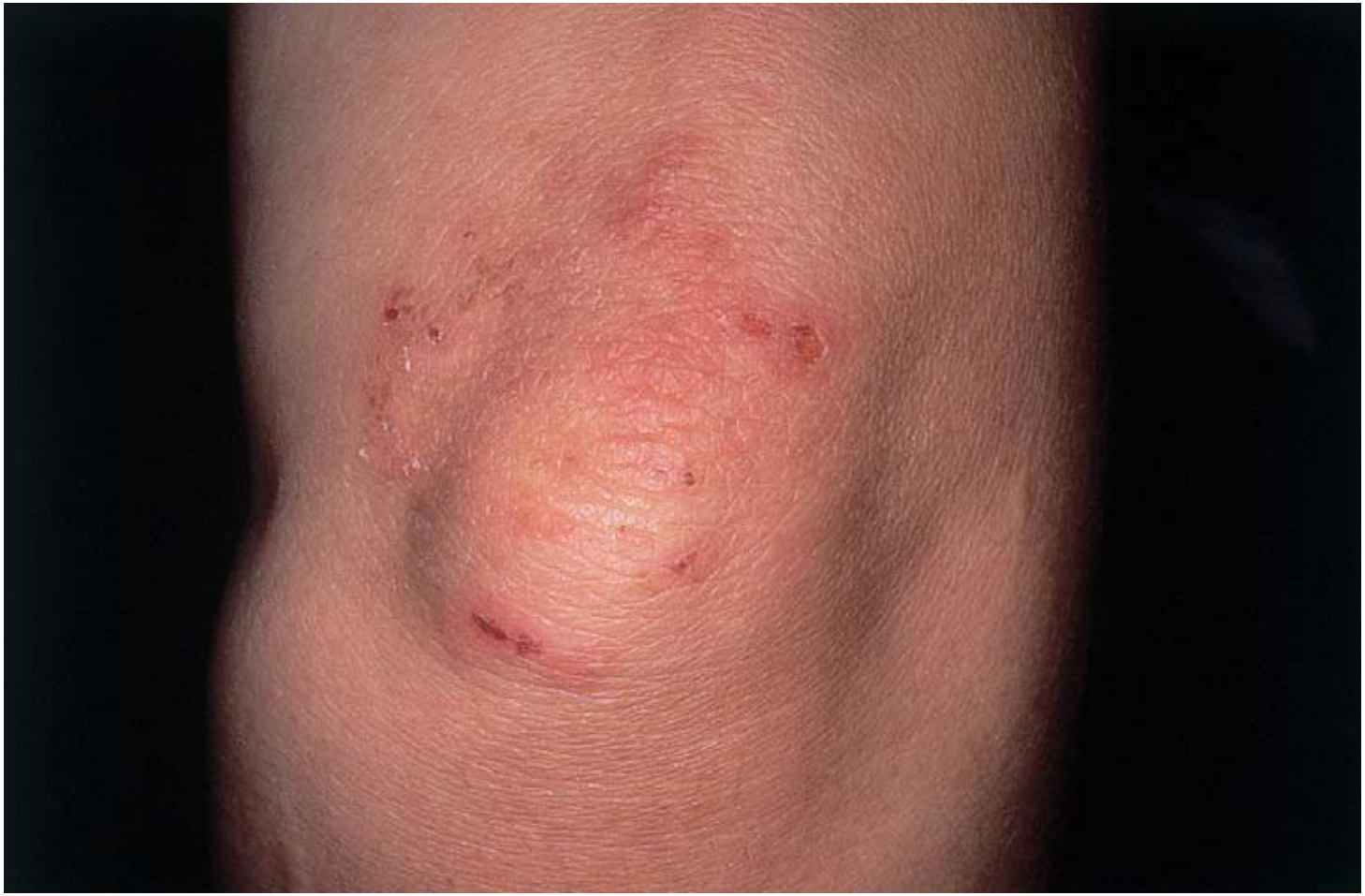


Fig. 29.6 Autoantigens in selected autoimmune bullous diseases. The approximate localization of major autoantigens in selected subepidermal immunobullous diseases. AECP, antiepiligrin cicatricial pemphigoid; BP, bullous pemphigoid; BSLE, the bullous eruption of systemic lupus erythematosus; CP, cicatricial pemphigoid; EBA, epidermolysis bullosa acquisita; LABD, linear IgA bullous dermatosis; PG, pemphigoid gestationis.

Dermatitis herpetiformis

- DH is a cutaneous manifestation of gluten sensitivity. Over 90 % of patients have a gluten-sensitive enteropathy
- There is a strong genetic association with HLA class DQw2, DR3
- The autoantigen in DH is epidermal transglutaminase leading to granular deposits of IgA and C3 in the superficial dermis and under the basal membrane.

- These induce a neutrophil inflammation which separate the epidermis from the dermis.
- Clinical features: the itchy grouped vesicles and urticarted papules over the elbows, knees, buttocks
- Autoimmune disorders associated with DH: Hashimoto thyroiditis, lymphoma, alopecia areata, SLE, scleroderma, vitiligo.



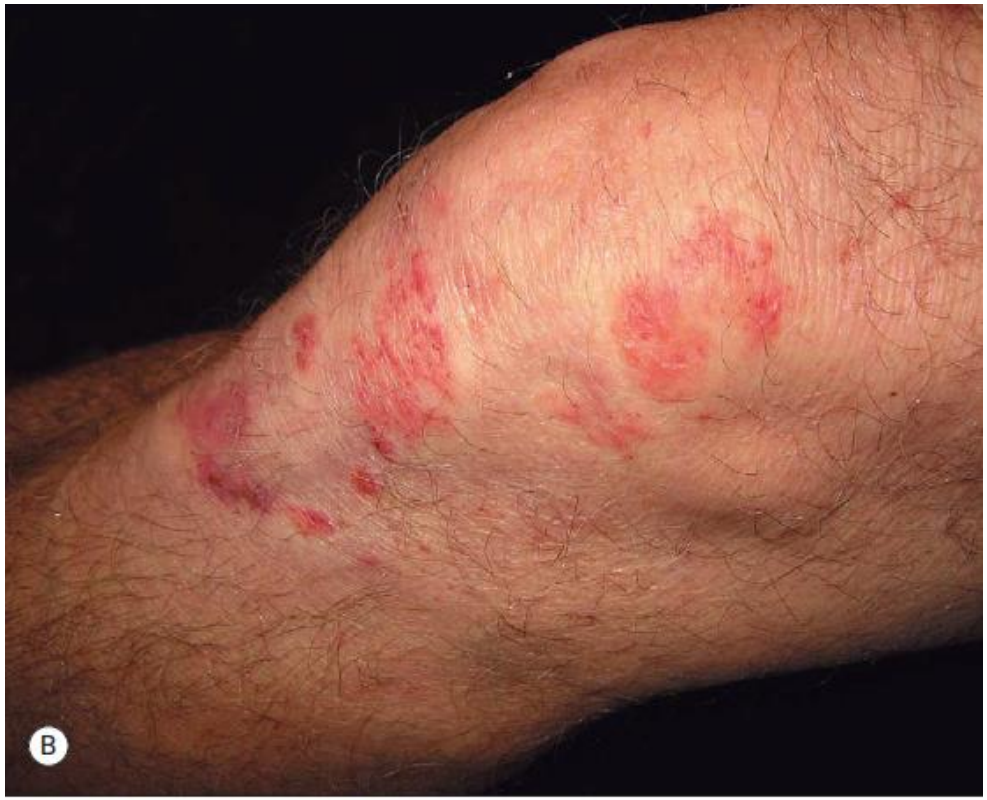


Fig. 32.2 Dermatitis herpetiformis. A Erythematous papulovesicles and erosions on the elbow. **B** Grouped vesicles and papules on the knee with hemorrhagic crusts. B, Courtesy of Thomas Horn MD.

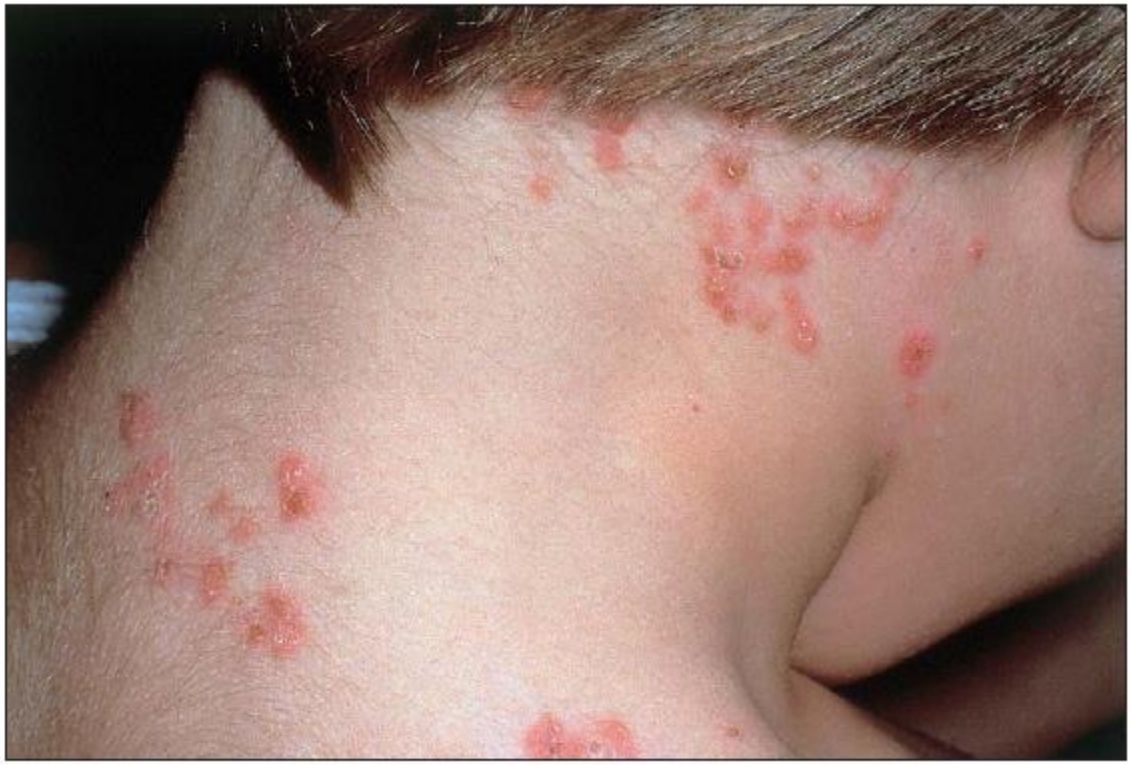


Fig. 32.3 Dermatitis herpetiformis. Grouped papulovesicles on the neck and scalp.

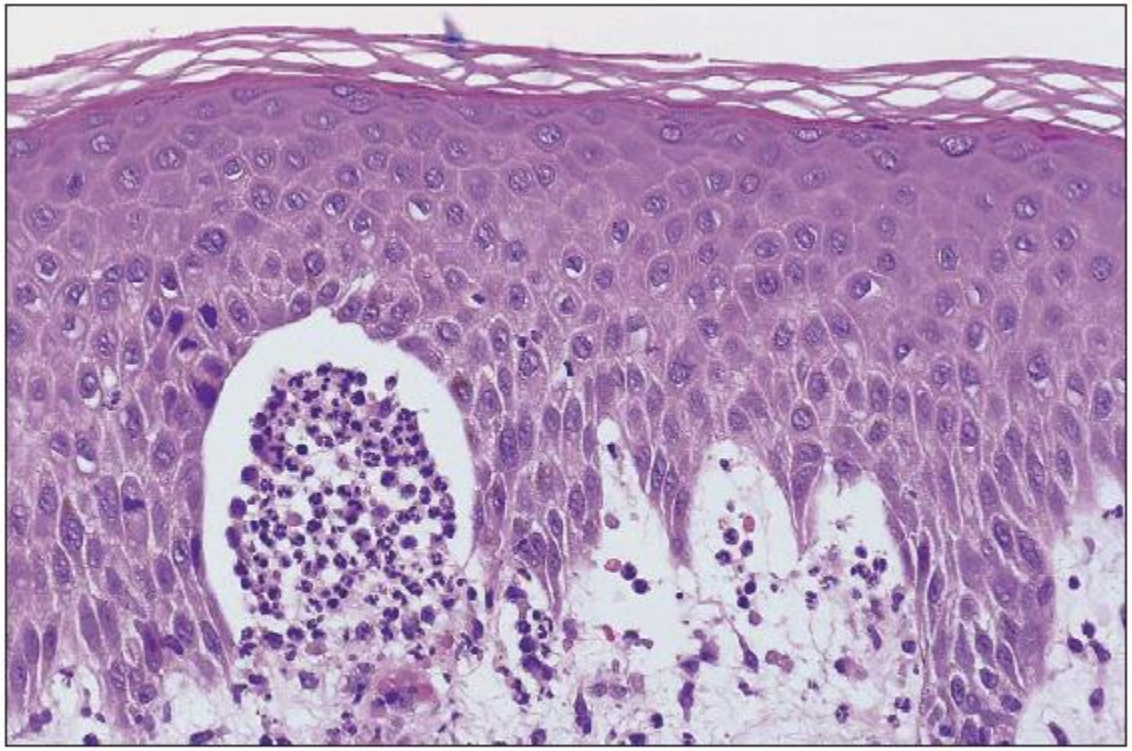


Fig. 32.4 Histology of dermatitis herpetiformis. Neutrophilic microabscess within a dermal papilla. Courtesy of Ronald P Rapini MD.

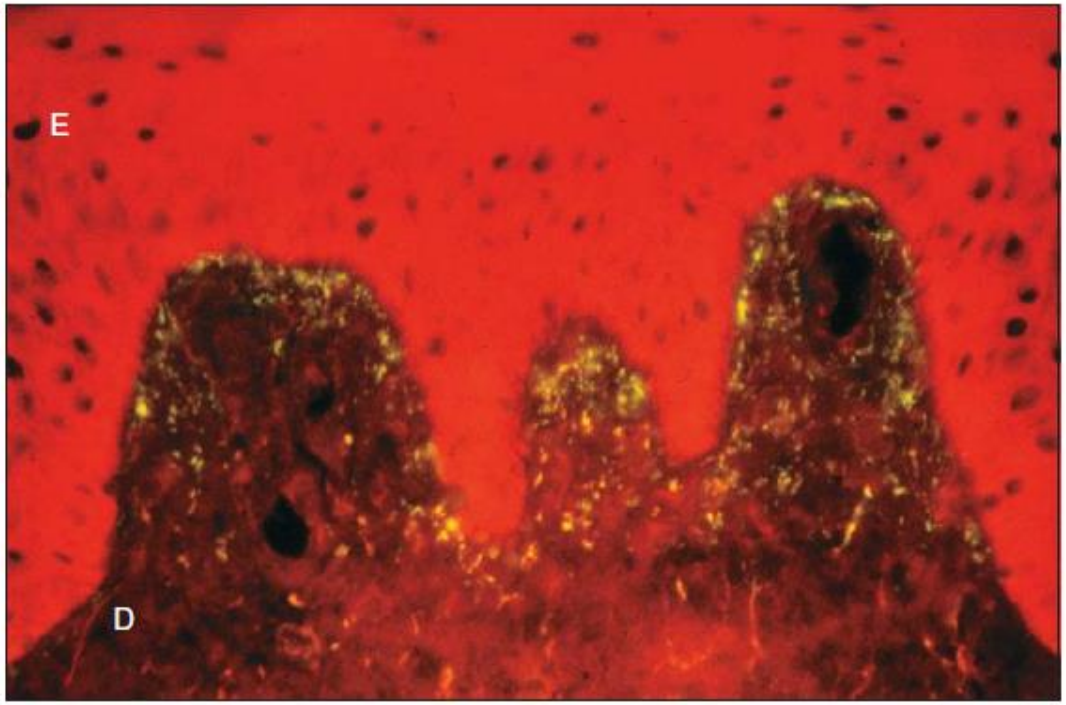


Fig. 32.5 Direct immunofluorescence of dermatitis herpetiformis. Granular IgA deposition (yellow) along the dermal–epidermal junction of normal-appearing skin adjacent to a lesion. D, dermis; E, epidermis.

Investigations:

- biopsy: subepidermal blisters with neutrophils
- direct immunofluorescence: granular deposits of IgA and C3 in the dermal papillae
- serum antibody tests: antiendomisial antibodies (gluten sensitive enteropaty)
- small bowel biopsy is not routine

Treatment:

- gluten-free diet
- dapsone or sulfapyridine (regular blood checks)

SIDE EFFECTS OF DAPSONE	
Red blood cell toxicity	• Hemolytic anemia • Methemoglobinemia
White blood cell toxicity	• Leukopenia • Agranulocytosis
Dapsone hypersensitivity syndrome	• Hepatitis, lymphadenopathy, fatigue, anorexia
Cutaneous reactions	• Morbilliform eruption • Urticaria • Fixed drug eruption • Erythema nodosum • Exfoliative dermatitis • Stevens-Johnson syndrome • Toxic epidermal necrolysis • Phototoxicity • Drug-induced lupus erythematosus
Gastrointestinal manifestations*	• Anorexia, nausea • Hepatitis • Cholestatic jaundice • Severe hypoalbuminemia
Neurologic associations*	• Headache, dizziness • Peripheral neuropathy • Blurred vision, tinnitus • Insomnia • Psychosis
Miscellaneous	• Fever • Nephrotic syndrome

**In decreasing order of frequency.*

Other causes of subepidermal blisters

- Diabetes and renal disease
- LE
- Bullous erythema multiforme
- Toxic epidermal necrolysis (Lyell's disease)

Toxic epidermal necrolysis (Lyell's disease)

- Is usually a drug reaction (sulfonamides, barbiturates, allopurinol)
- The skin becomes red, intensenly painful then come off in sheets
- Nikolsky sign is positive.
- The mucous membranes may be affected.
- The disease can be fatal (loss of fluids, electrolytes, infection)

Treatment

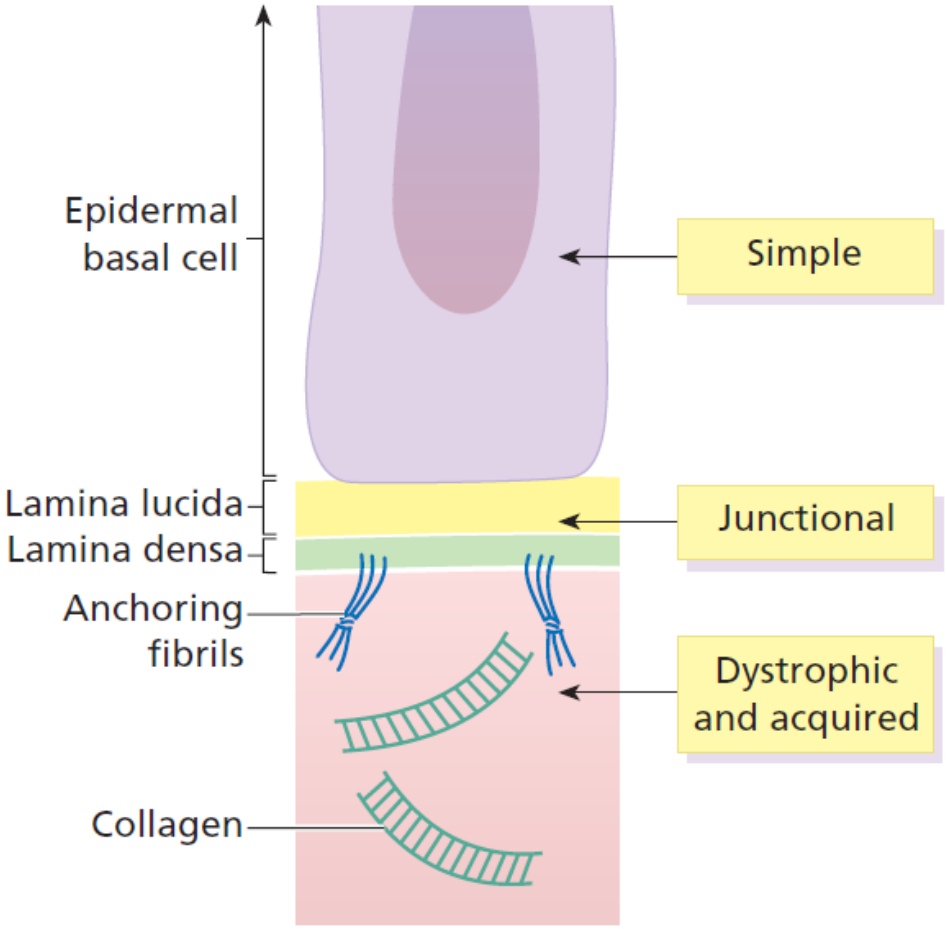
- the drug must be stopped
- intensive nursing care
- intravenous IgG
- ciclosporin
- plasmapheresis

Epidermolysis bullosa

Inherited tendency to develop blisters after minimal trauma

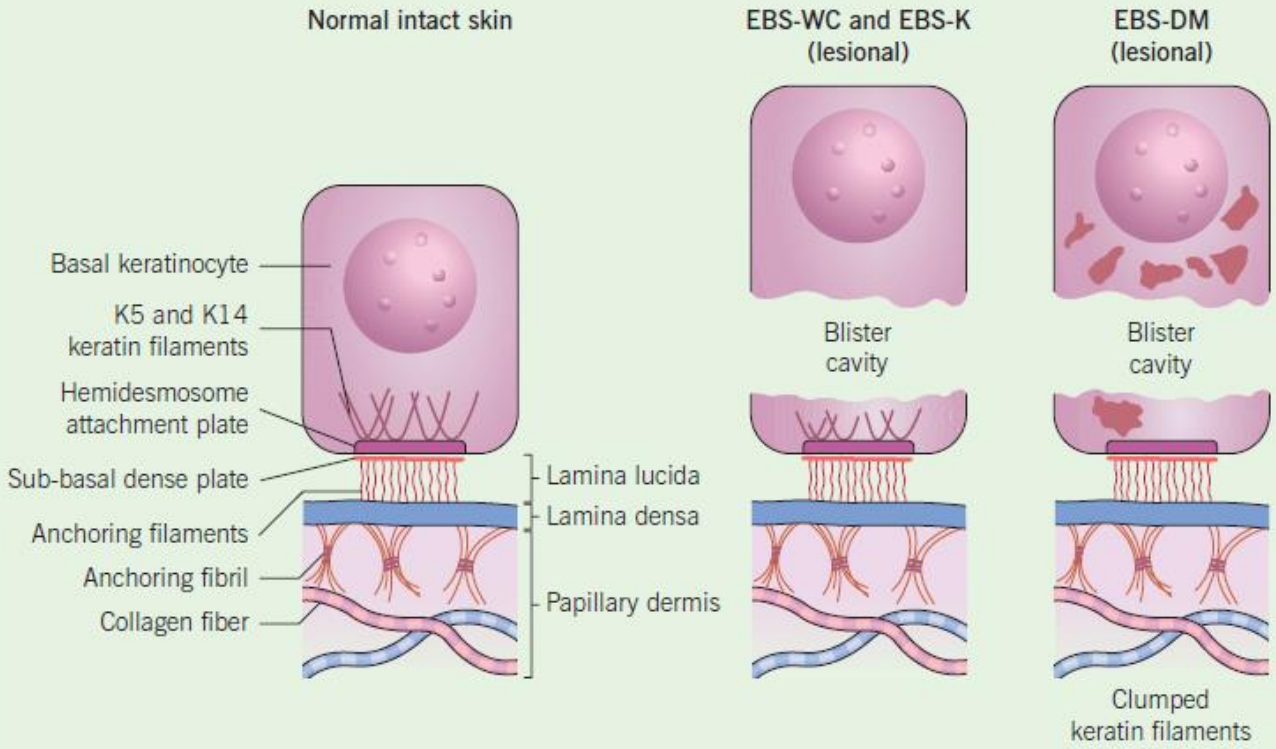
1. simple epidermolysis bullosa: usually autosomal dominant, the level of split is intraepidermal. Mutations is in keratin 5 and 14 which are in basal keratinocytes. The genetic defects lies on chromosomes 17 and 12.

The subtypes are: Weber-Cockayne,Dowling-Meara


Epidermal basal cell
Lamina lucida
Lamina densa
Anchoring fibrils
Collagen
Simple
Junctional
Dystrophic and acquired

BLISTER FORMATION IN EPIDERMOLYSIS BULLOSA

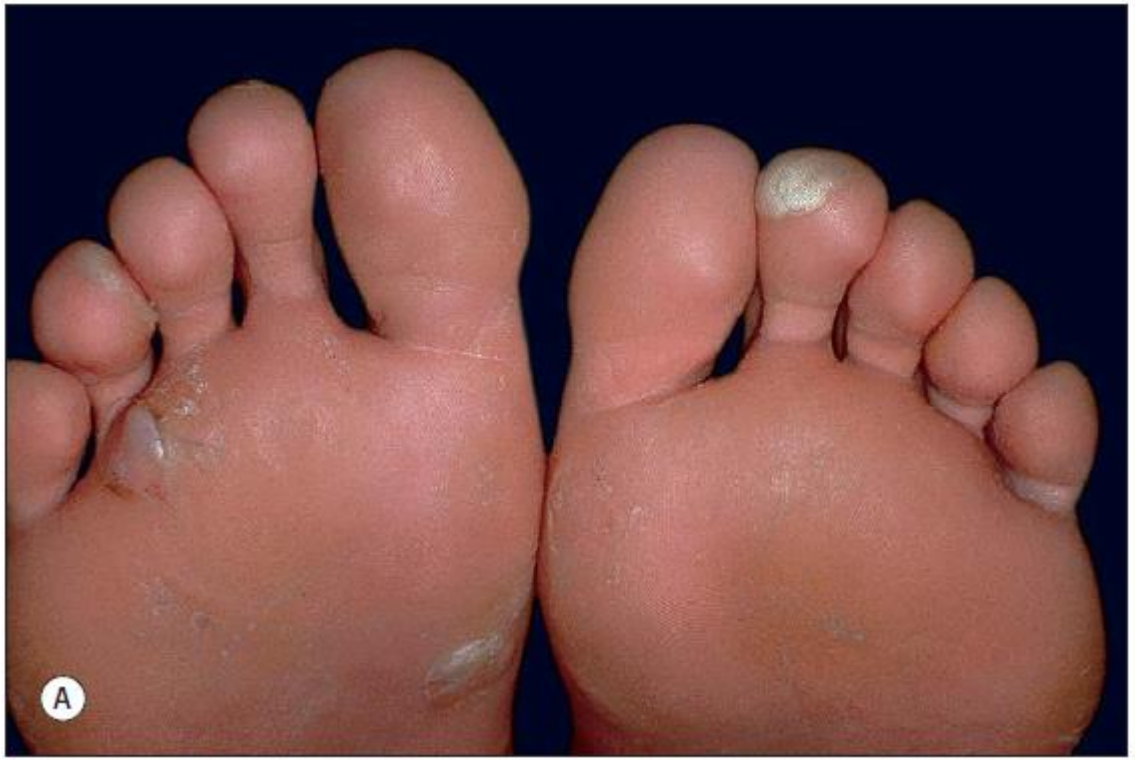
(A) Ultrastructural site of blister formation in three major subtypes of EB simplex

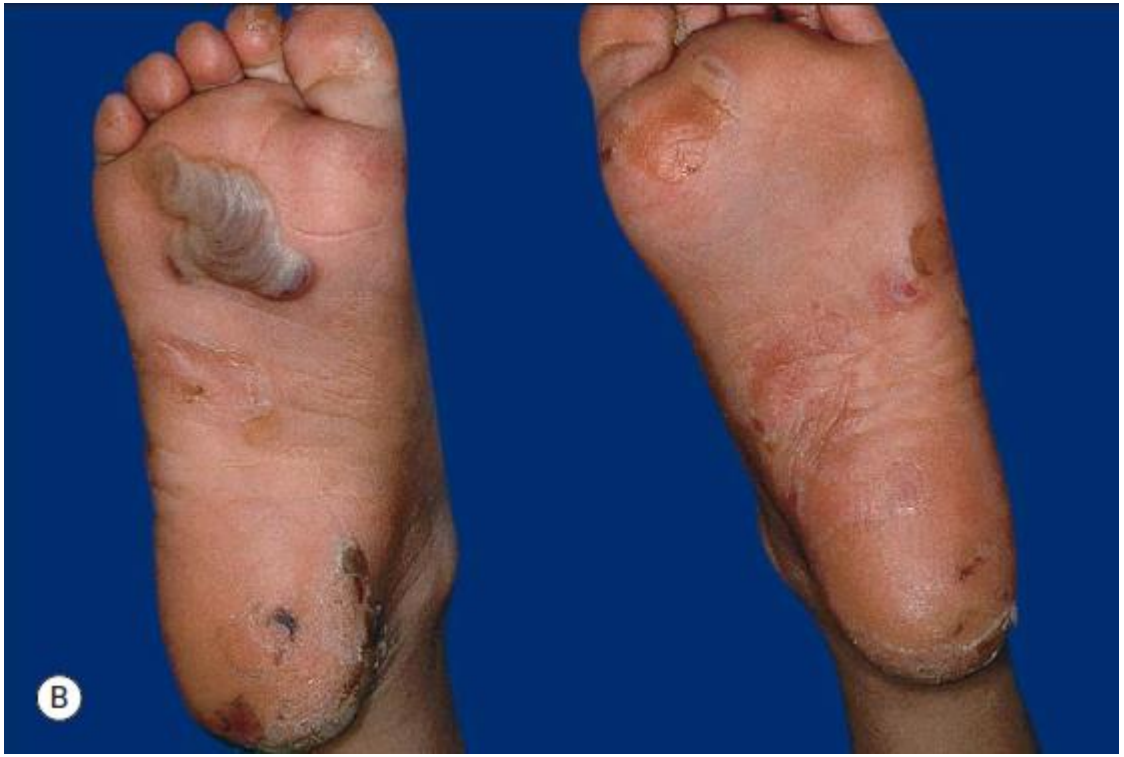


Blisters form within or just above the basal cell layers on the epidermis and tend to heal without scarring

EPIDERMOLYSIS BULLOSA TYPES AND THEIR ASSOCIATED TARGET PROTEINS, STRUCTURES AND LEVEL OF CLEAVAGE			
EB type or subtype	**Targeted protein(s)**	**Targeted structure(s)**	**Ultrastructural level of skin cleavage or blister formation**
EB simplex (excluding EBSS and EBS due to plectin defects)	Keratins 5 and 14	Keratin tonofilaments	Within the lower half of the basilar keratinocyte
EBSS	?Type VII collagen (one family only); ?other protein	Unknown	Intraepidermal, just beneath the granular layer
EBS-MD EBS, Ogna* EBS-PA	Plectin	Hemidesmosome	Intraepidermal, just above the level of the intracytoplasmic portion of the hemidesmosome (within the inferior pole of the basilar keratinocyte)
JEB (excluding JEB-PA)	Laminin 332 (5) Bullous pemphigoid antigen 2 (type XVII collagen)	Anchoring filament Hemidesmosome	Intralamina lucida
JEB-PA	$\alpha_6\beta_4$ integrin	Hemidesmosome	Intralamina lucida
DDEB	Type VII collagen	Anchoring fibril	Sublamina densa
RDEB	Type VII collagen	Anchoring fibril	Sublamina densa

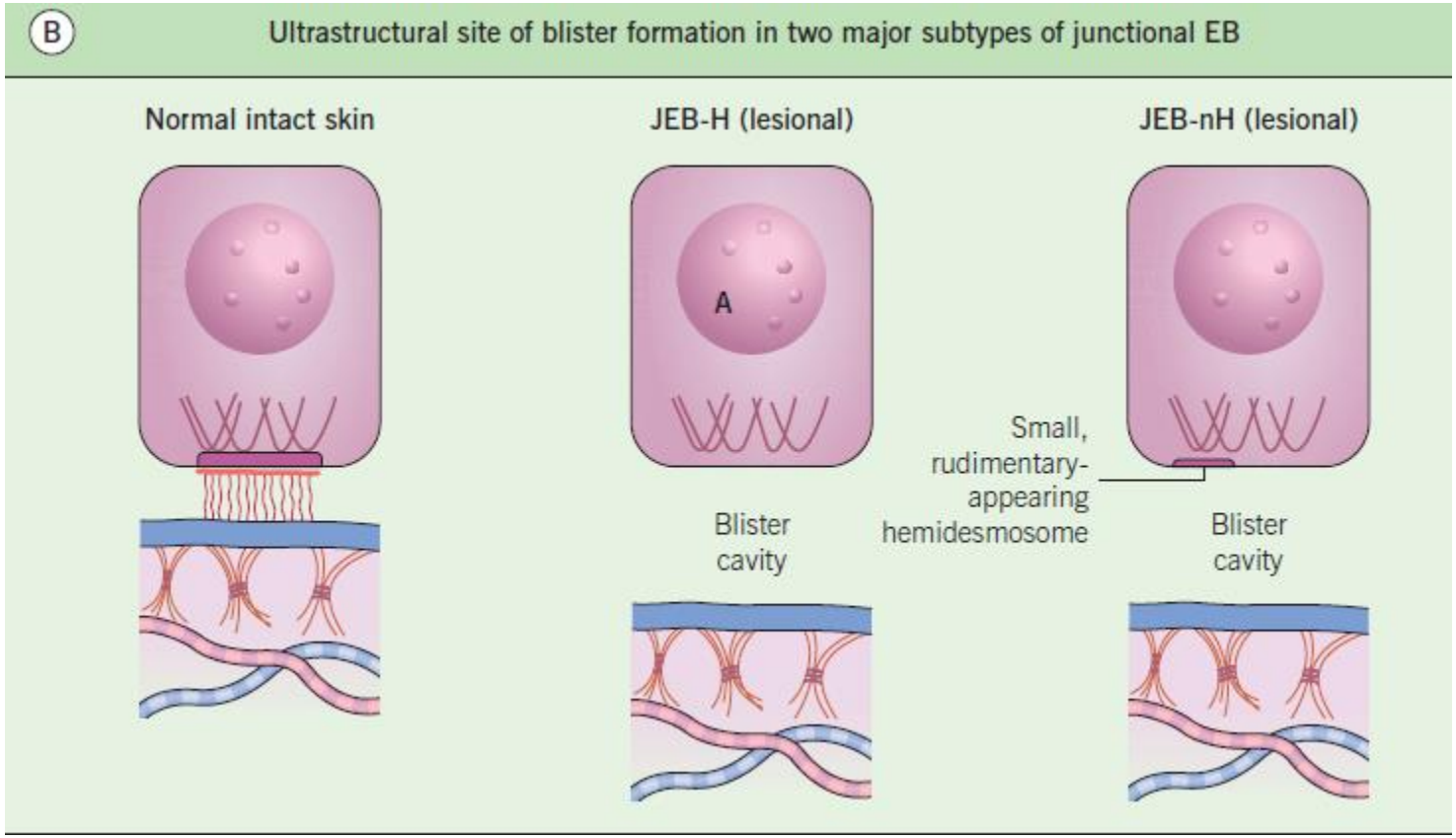
**Autosomal dominant.*


A


B

2. Junctional EB

The separation occurs in the lamina lucida of the basal membrane. Mutations are in the genes responsible for laminin formation. The rare lethal condition is evident at birth.


B
Ultrastructural site of blister formation in two major subtypes of junctional EB
Normal intact skin
JEB-H (lesional)
JEB-nH (lesional)
A
Small, rudimentary-appearing hemidesmosome
Blister cavity
Blister cavity

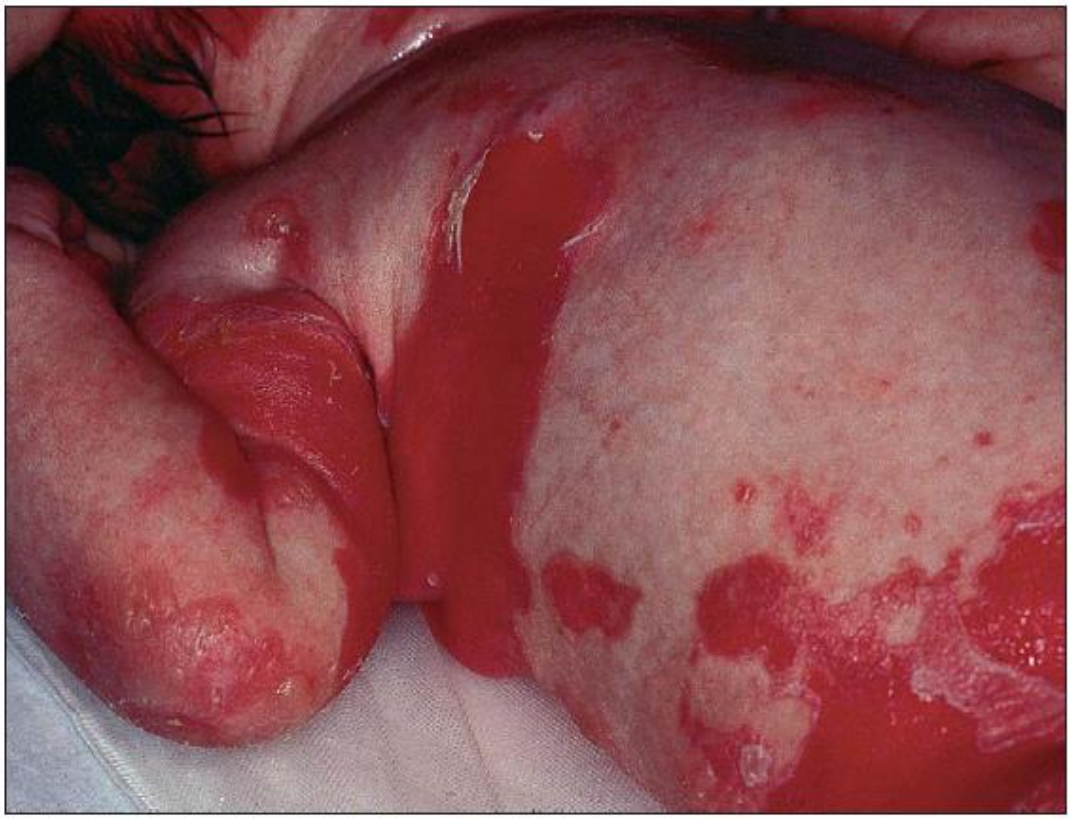


Fig. 33.8 Junctional epidermolysis bullosa, Herlitz. Blisters on the elbow and large areas of denuded skin; note the bright red color in the axilla and groin.

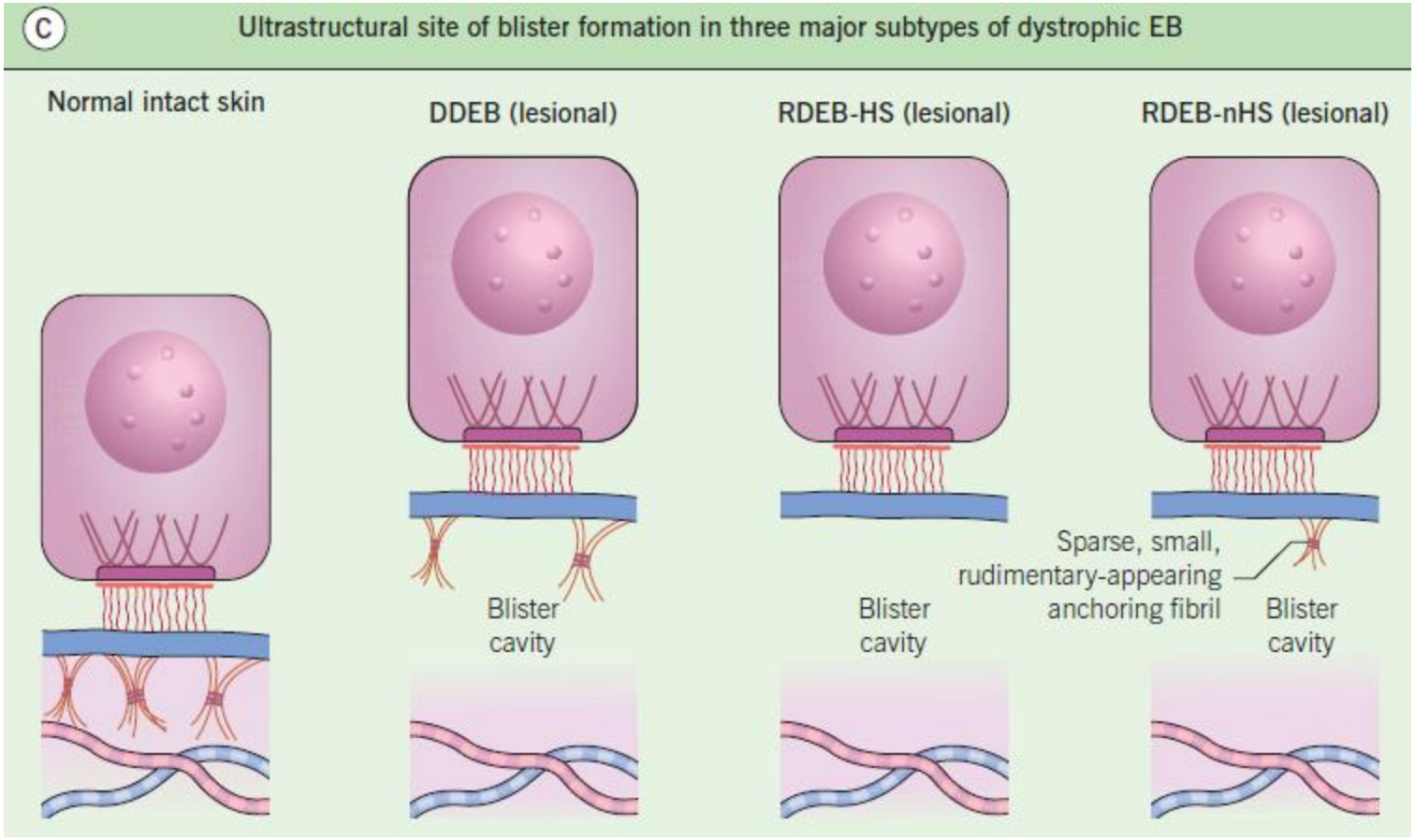
3. Dystrophic EB

Result from abnormalities of collagen VII- major structural component of anchoring fibrils

- autosomal dominant DEB
- autosomal recessive DEB

Healing with scarring and milia. The nails are deformed or lost. The hands and feet become like balls. The teeth, mouth and oesohageal strictures.

- Autosomal dominant dystrophic EB : Blisters appear in late infancy, on friction sites healing with scarring and milia. The nails are deformed or lost, the mouth is not affected.
- Autosomal recessive dystrophic EB : Blisters appear in infancy, nhands and feet became balls.


C
Ultrastructural site of blister formation in three major subtypes of dystrophic EB
Normal intact skin
DDEB (lesional)
RDEB-HS (lesional)
RDEB-nHS (lesional)
Blister cavity
Blister cavity
Sparse, small, rudimentary-appearing anchoring fibril
Blister cavity

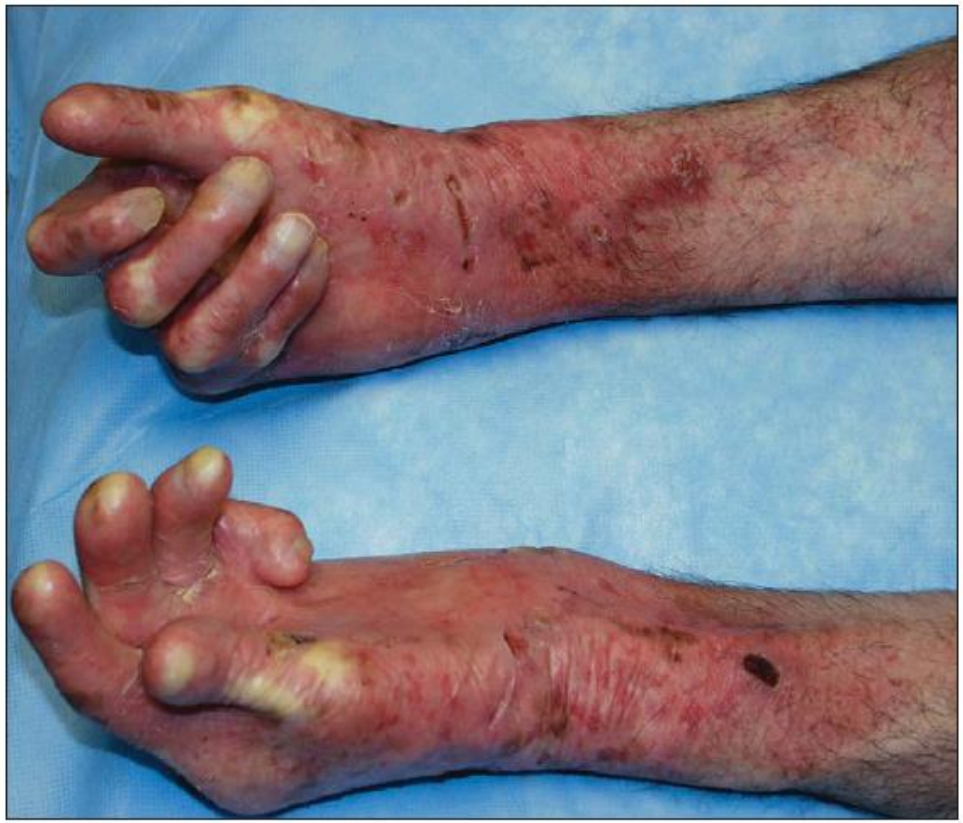


Fig. 33.9 Recessive dystrophic epidermolysis bullosa, Hallopeau–Siemens. Note the partial mitten deformities of the hands in this child.

Treatment is unsatisfactory. Phenytoin prevention of infection and trauma, regulation of anaemia.