Bullous diseases of the Skin

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Aims

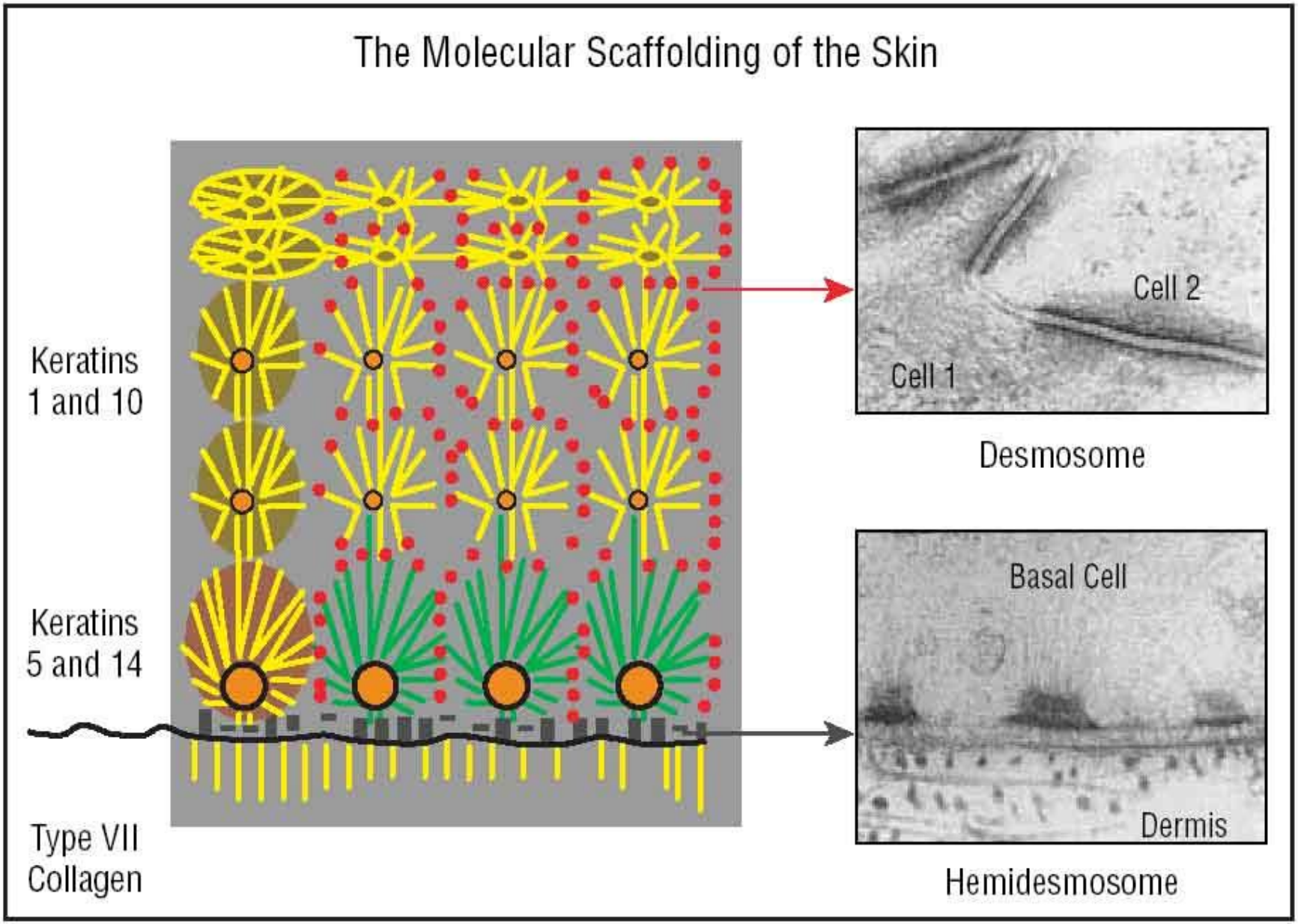
- Basic understanding of the ultrastructure of the epidermis
- Genetic and immunological pathologies
- Histopathology of major types
- Slide seminar

Bullous diseases

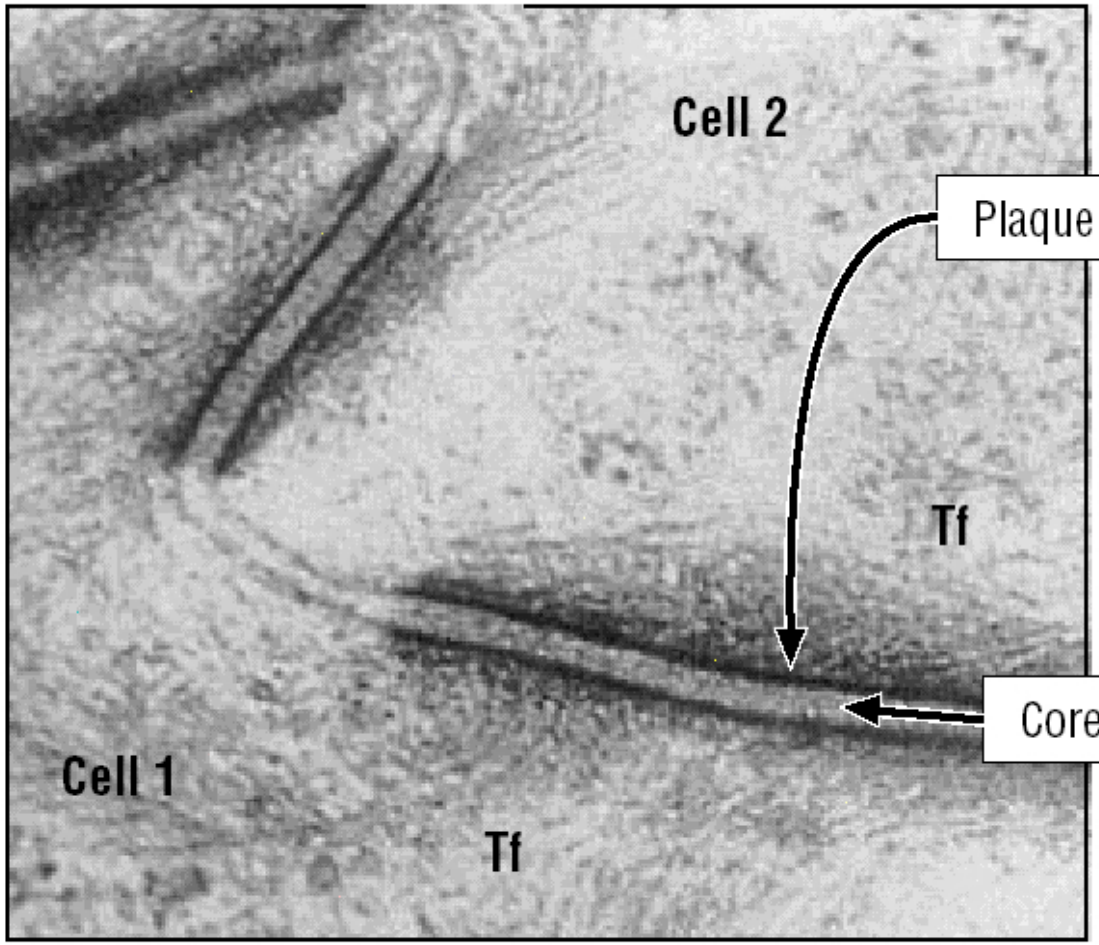
- Primary
  - Genetic
  - Immunological
- Secondary
  - Lichen planus
  - Mastocytosis
  - Infective – herpes simplex, impetigo
  - Chemical/physical burn

Primary bullous dermatoses

Epidermolytic hyperkeratosis
Epidermolysis bullosa simplex
Epidermolysis bullosa simplex (muscular dystrophy)
Junctional epidermolysis bullosa (Herlitz syndrome)
Junctional epidermolysis bullosa (pyloric atresia)
Generalized atrophic benign epidermolysis bullosa
Epidermolysis bullosa dystrophica (dominant and recessive)
Pemphigus foliaceus
Pemphigus vulgaris
IgA pemphigus
Paraneoplastic pemphigus
Bullous pemphigoid
Herpes gestationis
Cicatricial pemphigoid
Lichen planus pemphigoides
Linear IgA dermatoses
Epidermolysis bullosa acquisita
Dermatitis herpetiformis
Erythema multiforme



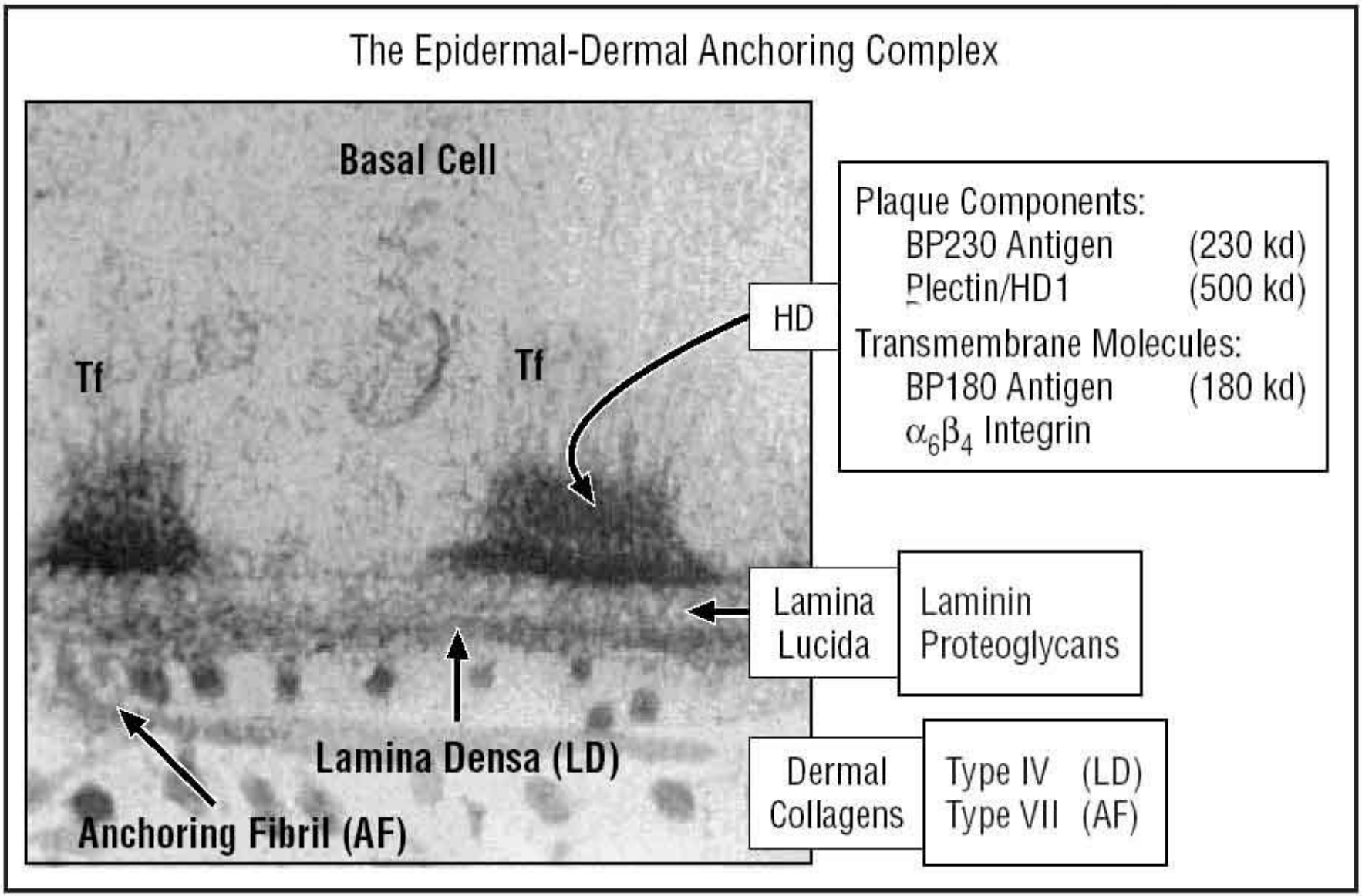
The Molecular Structure of the Desmosome



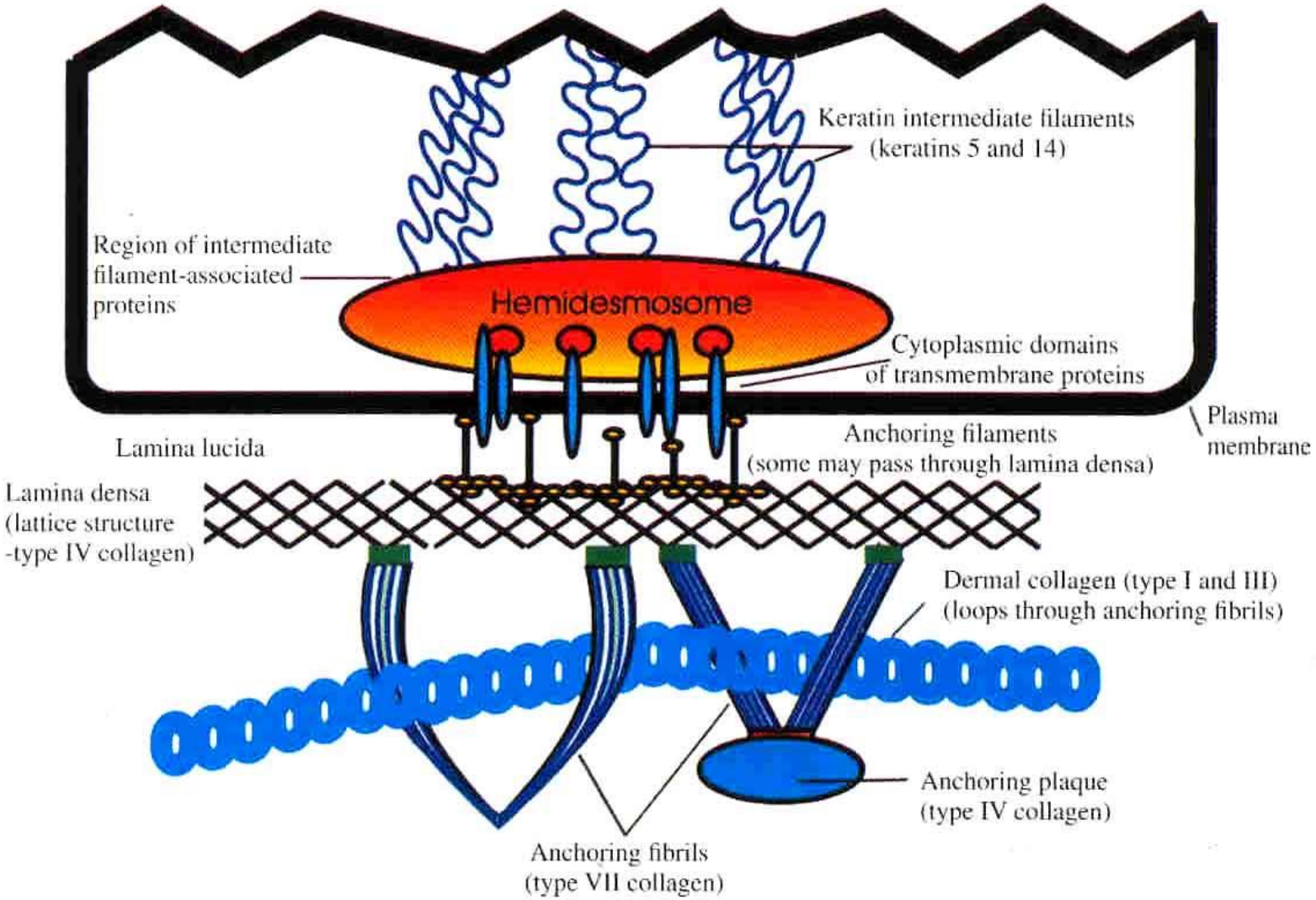
Desmoplakin 1	(245 kd)
Desmoplakin 2	(215 kd)
Plakoglobin	(85 kd)
Plakophilin 1, 2, 3	(75 kd)
Keratocalmin	(250 kd)

Desmoglein 1	(165 kd)
Desmoglein 2	(Colon)
Desmoglein 3	(130 kd)
Desmocollins:	1a, b 2a, b 3a, b

Other Plaque Components: Envoplakin, Periplakin, and Corneodesmosin (Keratinocyte Envelopes)



LOWER PORTION OF BASAL KERATINOCYTE



Classification

Genodermatoses	Genetic Mutation
Epidermolytic hyperkeratosis	Keratin 1 or 10
Epidermolysis bullosa simplex	Keratin 5 or 14
Epidermolysis bullosa simplex (muscular dystrophy)	Plectin
Plakophilin deficiency	Plakophilin
Junctional epidermolysis bullosa (Herlitz syndrome)	Laminin 5
Junctional epidermolysis bullosa (pyloric atresia)	Integrin $\alpha_6\beta_4$
Generalized atrophic benign epidermolysis bullosa	BP180 antigen
Epidermolysis bullosa dystrophica	Type VII collagen
Autoimmune Bullous Dermatoses	**Targeted Antigen**
Pemphigus foliaceus	Dsg1 (desmosome)
Pemphigus vulgaris	Dsg3 and 1 (desmosome)
IgA pemphigus	Desmocollin 1 (desmosome)
Paraneoplastic pemphigus	Dsg3, plakins (desmosome)
BP	BP230 and BP180 (hemidesmosome)
Lichen planus pemphigoides	BP180 (hemidesmosome)
Cicatricial pemphigoid (subset)	BP180 (hemidesmosome)
Cicatricial pemphigoid (subset)	Laminin 5 (lamina lucida)
Junctional epidermolysis bullosa–like (BP-like) disease	Laminin 5 (lamina lucida)
Linear IgA dermatoses	BP180 (hemidesmosome)
BP-like disease	Type IV collagen (lamina densa)
Epidermolysis bullosa acquisita	Type VII collagen (anchoring fibers)
Erythema multiforme	Desmoplakins 1 and 2 (desmosome)
Dermatitis herpetiformis	?

Bullous Genodermatoses

Keratins
1 and 10

Keratins
5 and 14

Type VII
Collagen

Epidermolytic Hyperkeratosis

Other: Plakophilin Deficiency
Syndrome

EB Simplex: AD
AR + MD

Junctional EB: Herlitz
Pyloric Atresia
GABEB

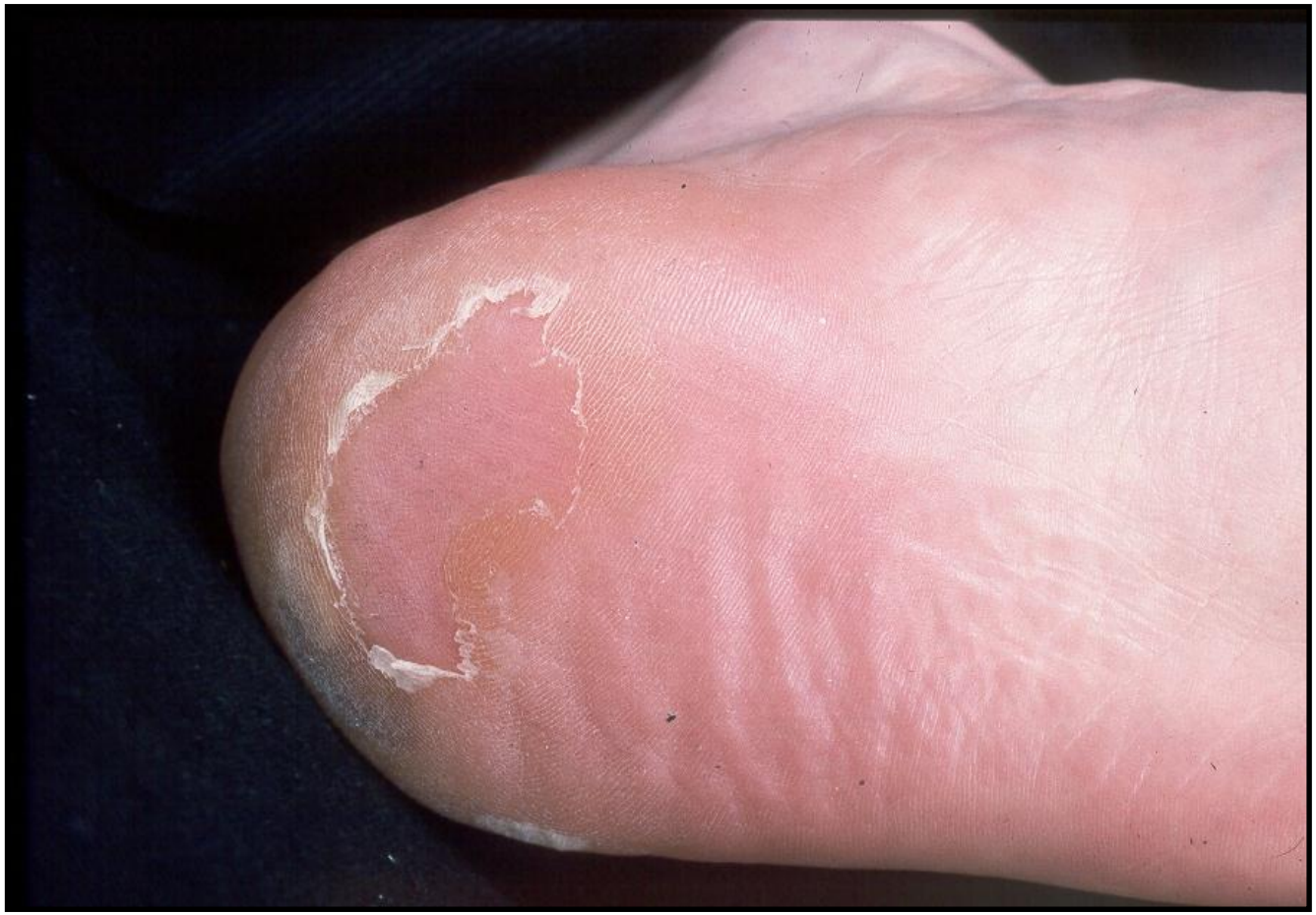
EB Dystrophica

Experimentally induced genodermatoses

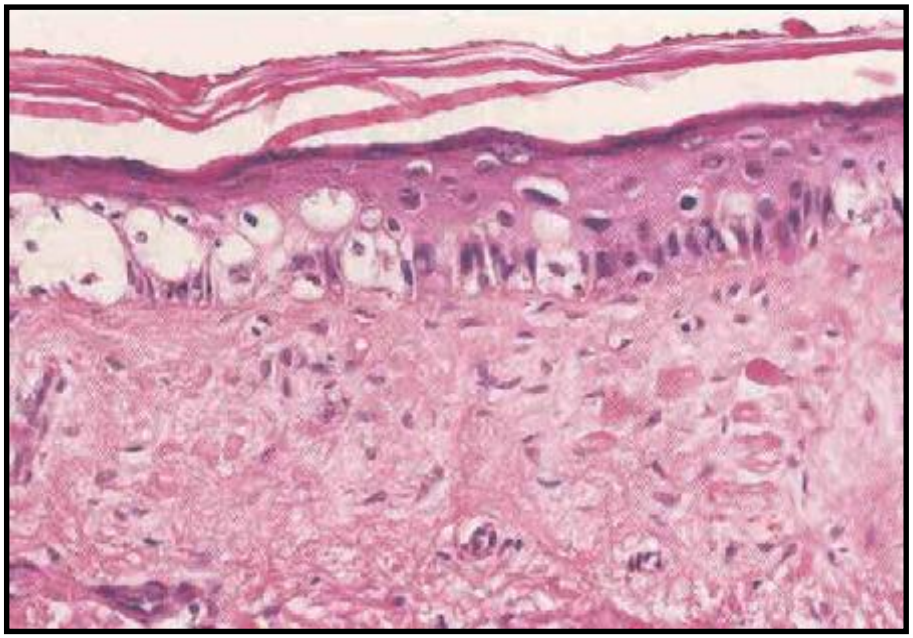
Knockout	Animal Phenotype	Resemblance to Human Disease
Keratin 5 or 14	Blisters (basal cells)	EB simplex
Desmoglein 3	Blisters (suprabasilar)	No human disease reported, as yet
Plakoglobin	Blisters (suprabasilar)	No human disease reported, as yet
Laminin 5	Blisters (junctional)	Junctional EB (Herlitz syndrome)
Integrin α_6 β_4	Blisters (junctional)	Junctional EB (pyloric atresia)
Type VII collagen	Blisters (subepidermal)	EB dystrophica

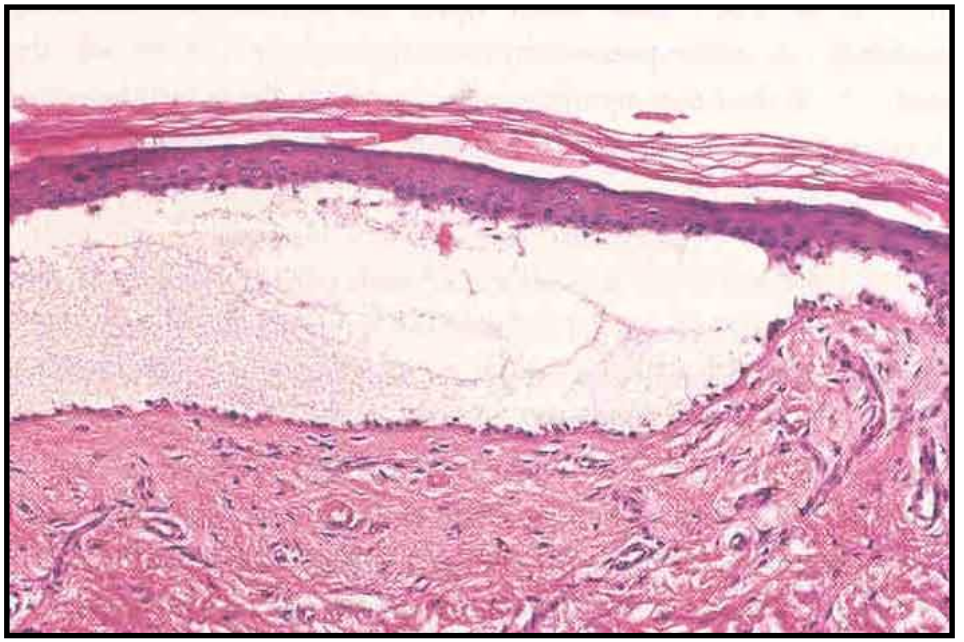
Epidermolysis bullosa simplex

- Localised type (Weber Cockayne)
- Onset first 2 years
- 1/50000 births
- Autosomal dominant
- Mutation K5 or K14 gene
- Localised blisters to hands and feet



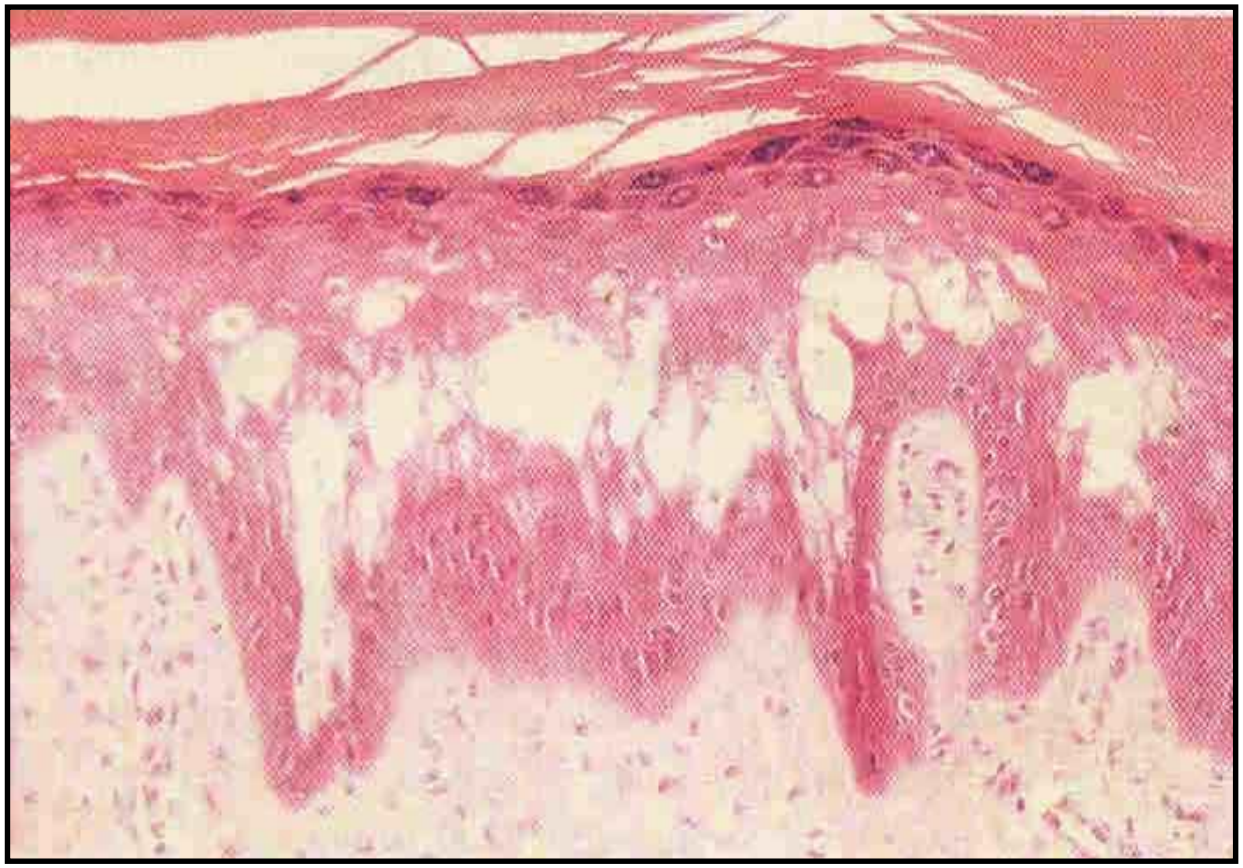
Epidermolysis bullosa simplex





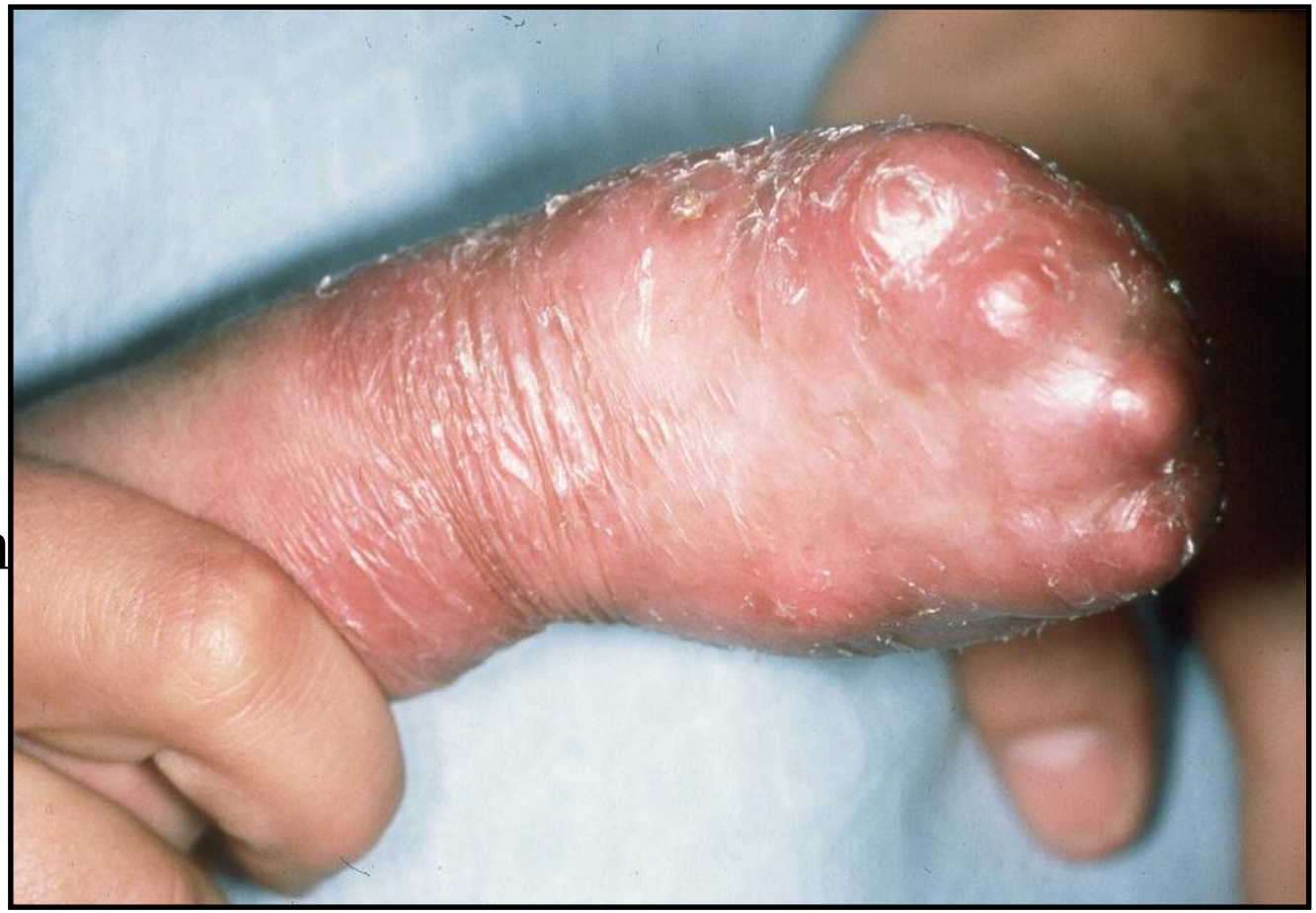
Early → Late

Epidermolysis bullosa (Weber-Cockayne type)



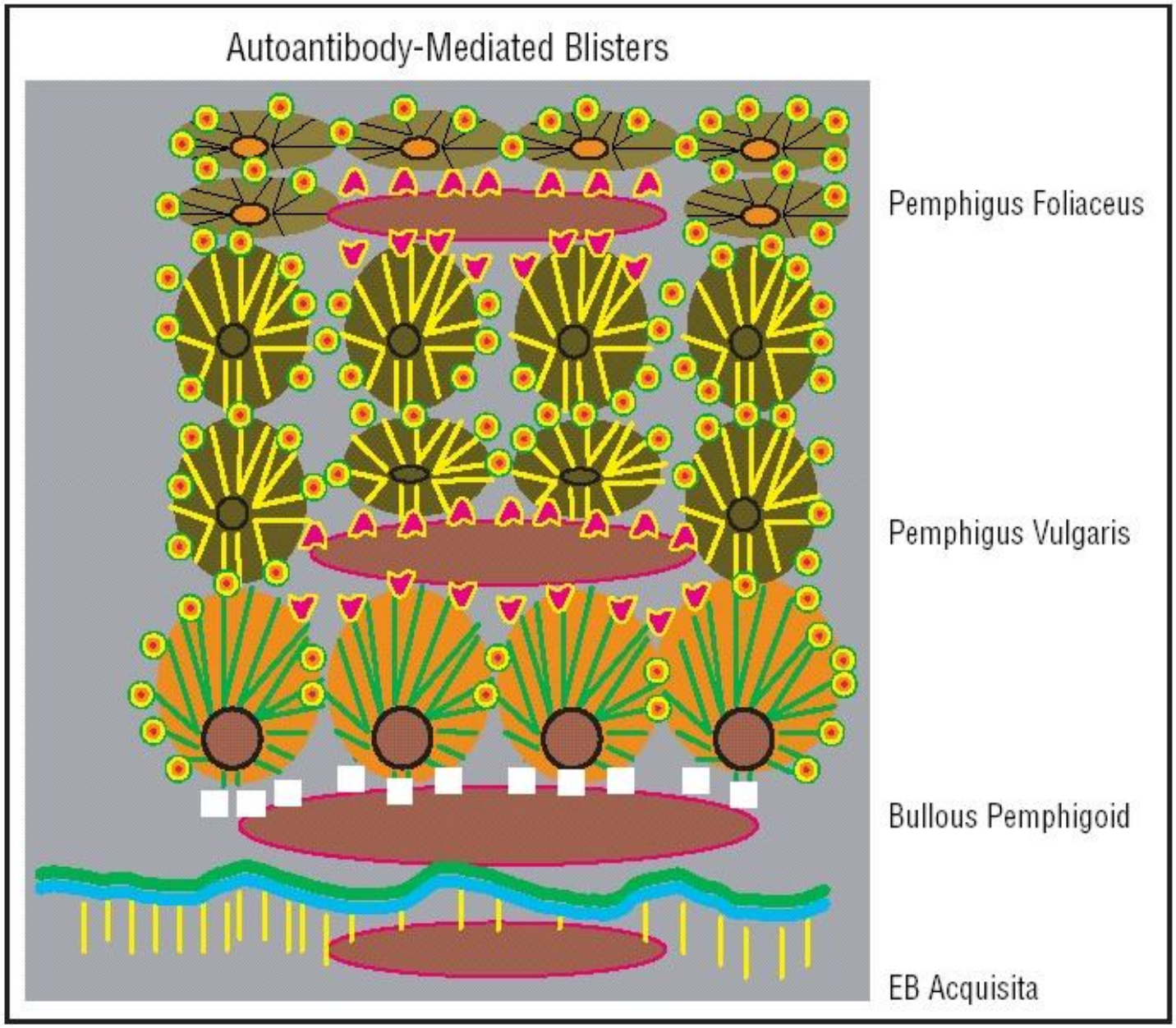
Dermolytic (dystrophic) epidermolysis bullosa

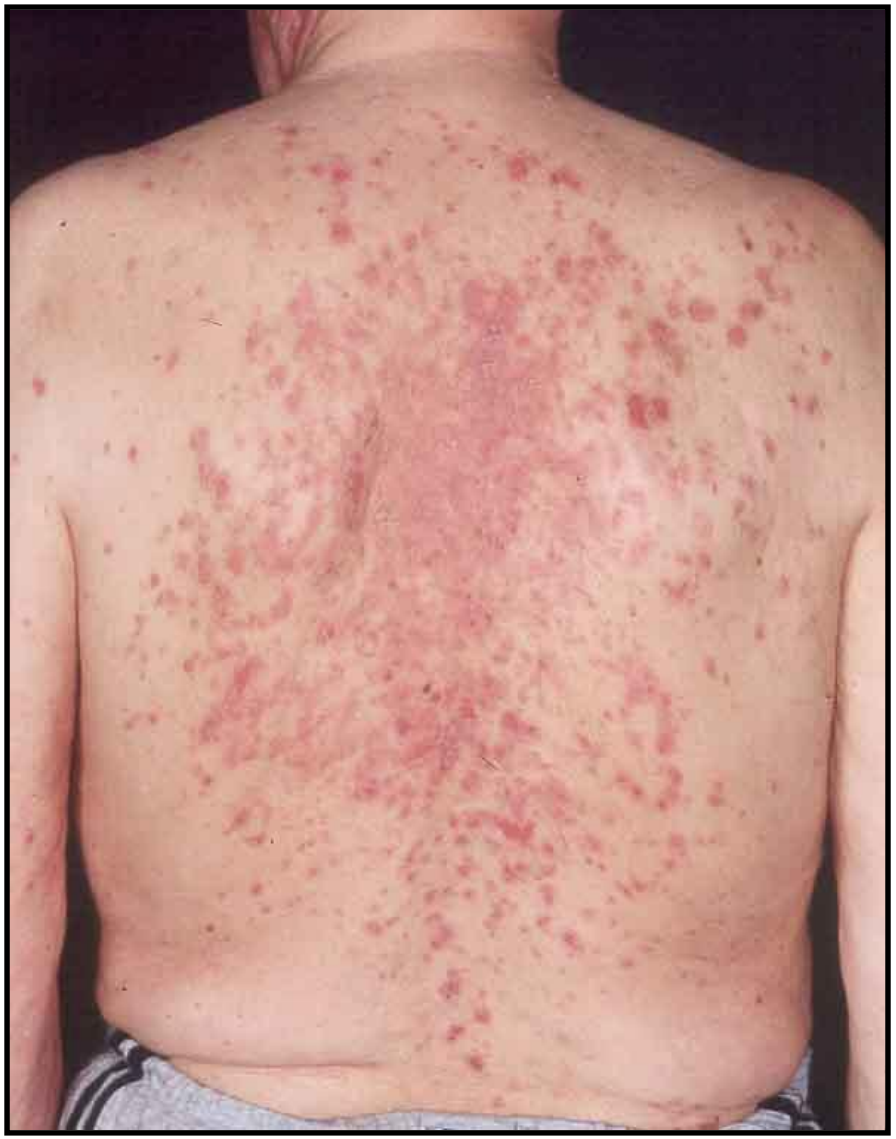
- Split below lamina densa
- Type VII collagen decreased
- Digital fusion "mitten deformity"



Immunobullous

Human Autoimmune Disease	Antibody	Skin Phenotype (Mice)
Pemphigus foliaceus	Anti-dsg1 IgG (human)	Subcorneal vesicles
Pemphigus vulgaris	Anti-dsg3 IgG (human)	Suprabasilar vesicles
	Anti-dsg1 IgG (human)	Subcorneal vesicles
Paraneoplastic pemphigus	Anti-dsg3 (human)	Suprabasilar vesicles
Bullous pemphigoid	Anti-BP180 IgG (human and rabbit)	Subepidermal vesicles
Cicatricial pemphigoid	Anti–laminin 5 (rabbit)	Subepidermal vesicles

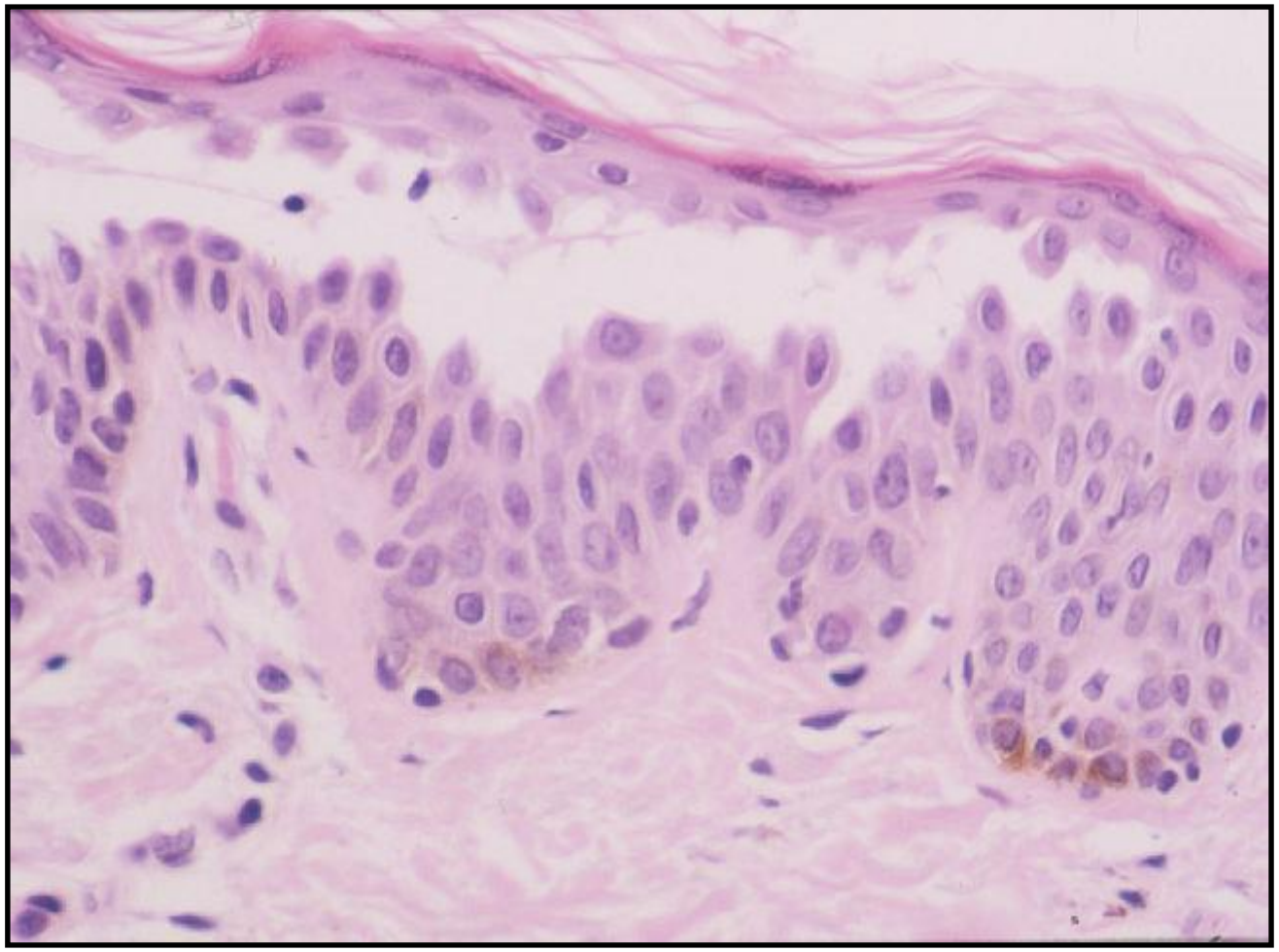




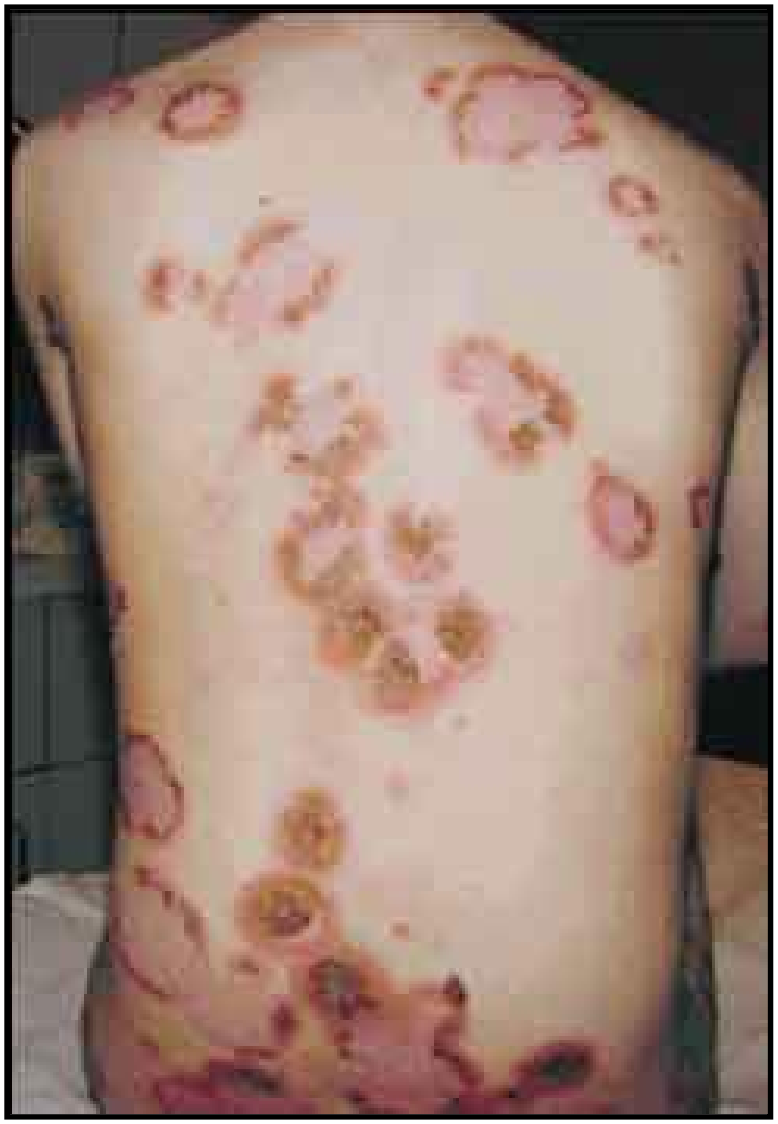
Pemphigus foliaceus

- 10% of pemphigus cases
- Flaccid bullae
- Crusted
- Penicillamine
- Endemic form - Brazil

Pemphigus foliaceus



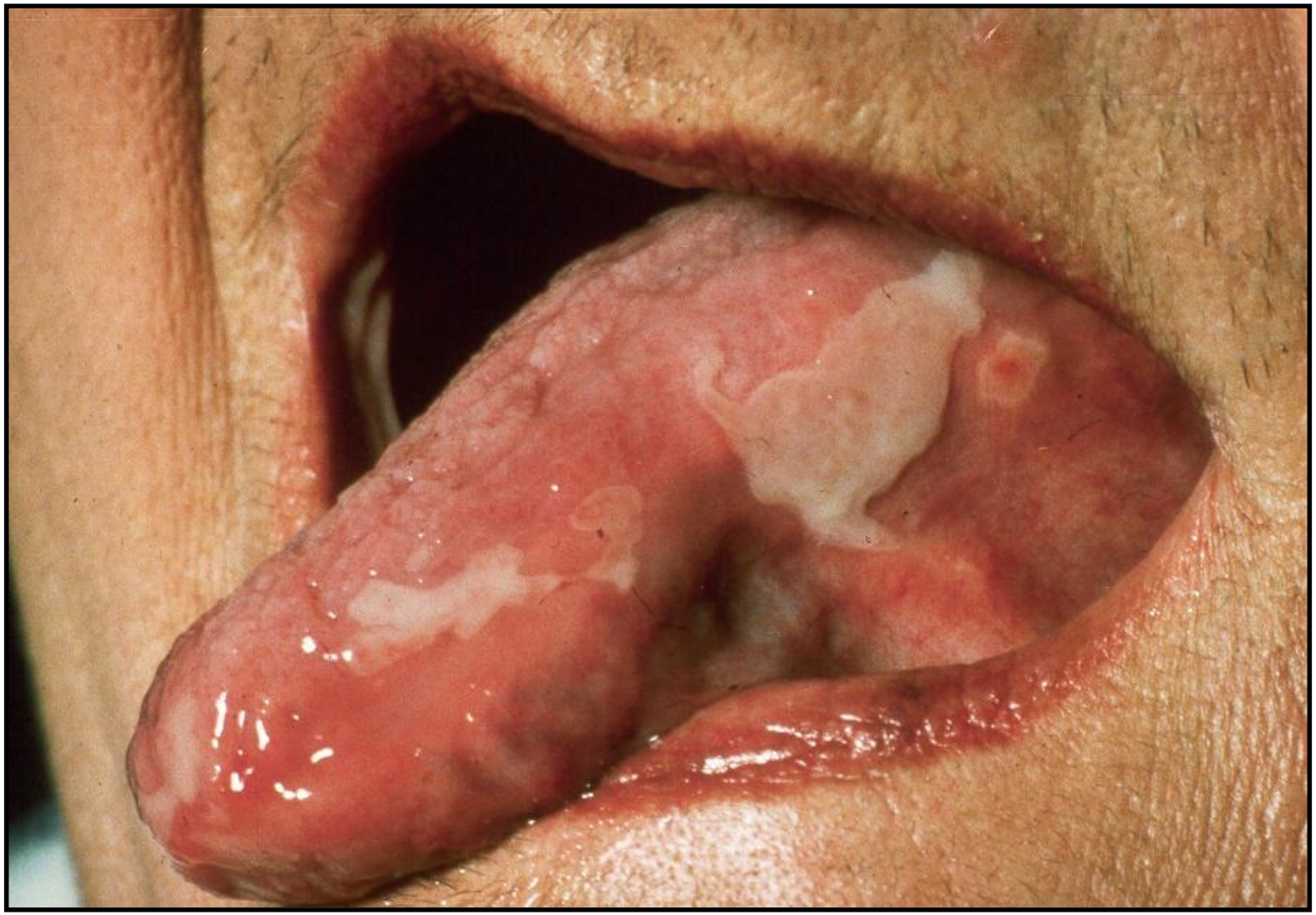
- Split high in granular layer or subcorneal
- Bulla contains fibrin, neutrophils
- IMF –intercellular IgG, C3 in both affected & normal skin (when IgA rather than IgG then called ‘IgA pemphigus’)



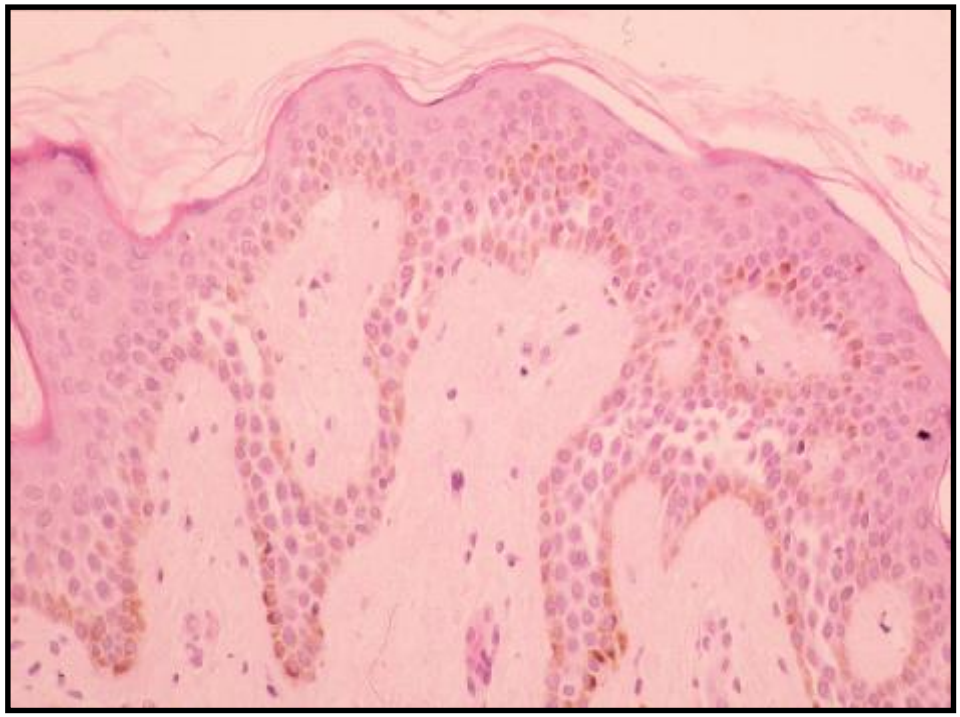
Pemphigus vulgaris

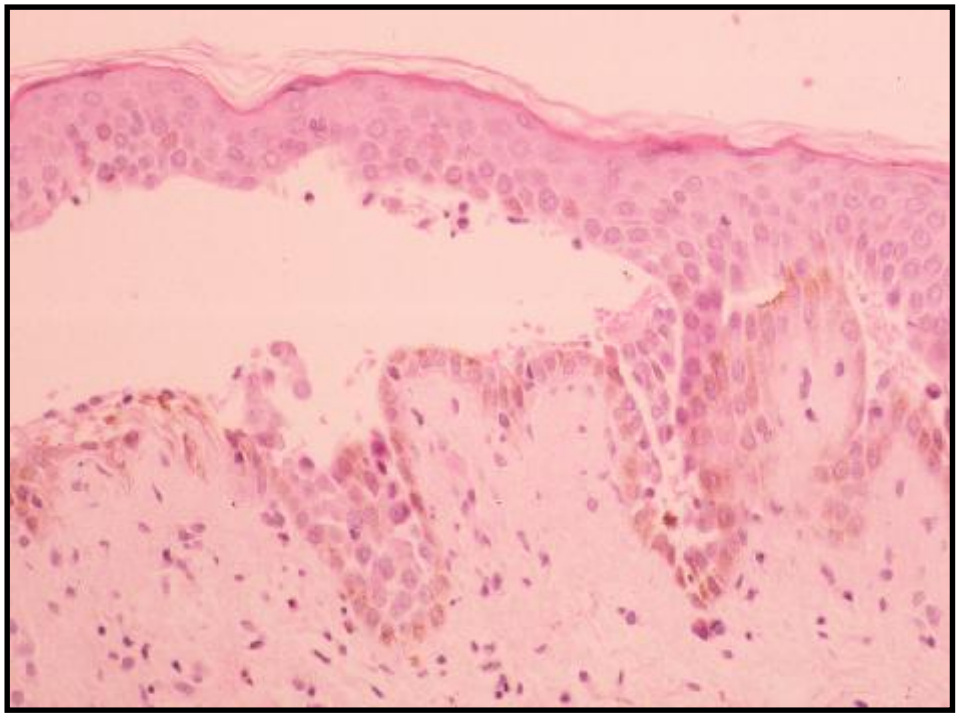
- Rare
- Vulgaris 80% of pemphigus cases
- Oral then cutaneous
- Blisters break to leave ulcers
- Nikolsky's sign
- Mortality 5-15%

Pemphigus vulgaris - Clinical

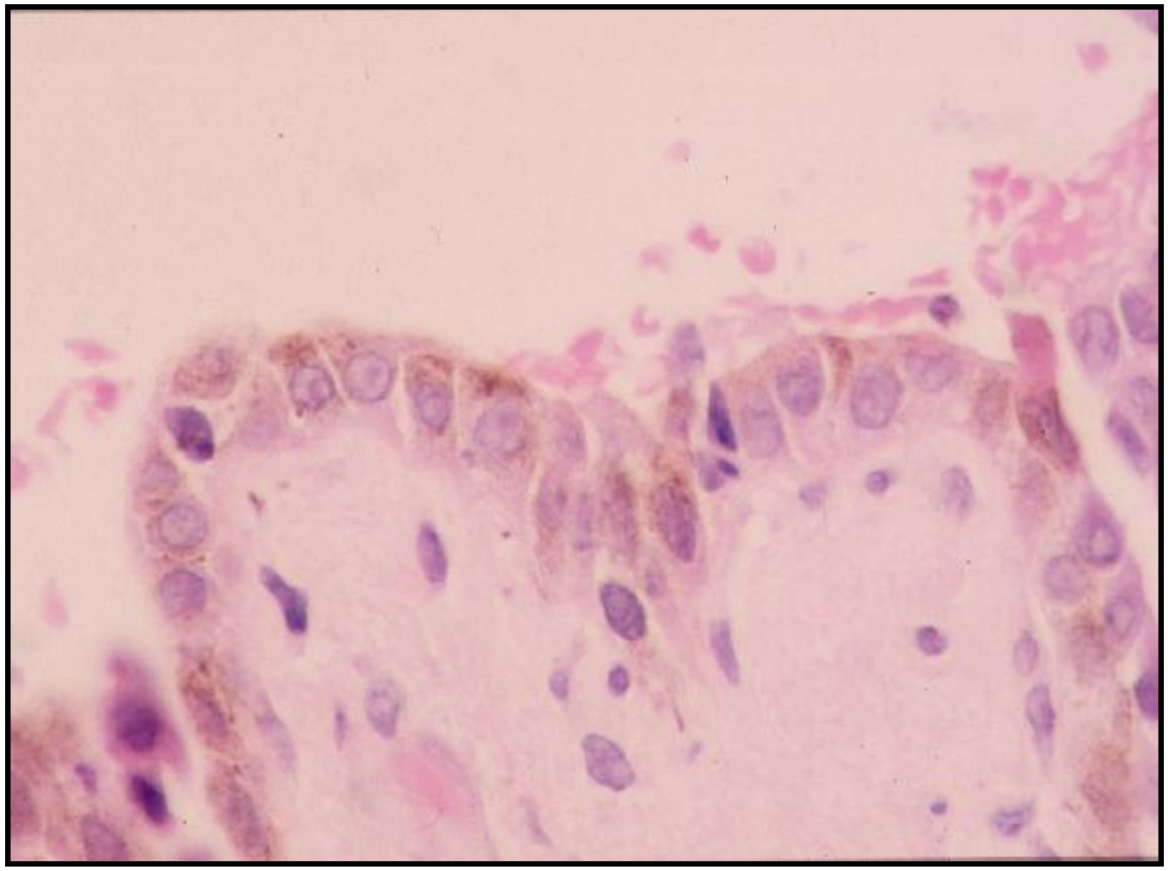


Pemphigus vulgaris - Histology



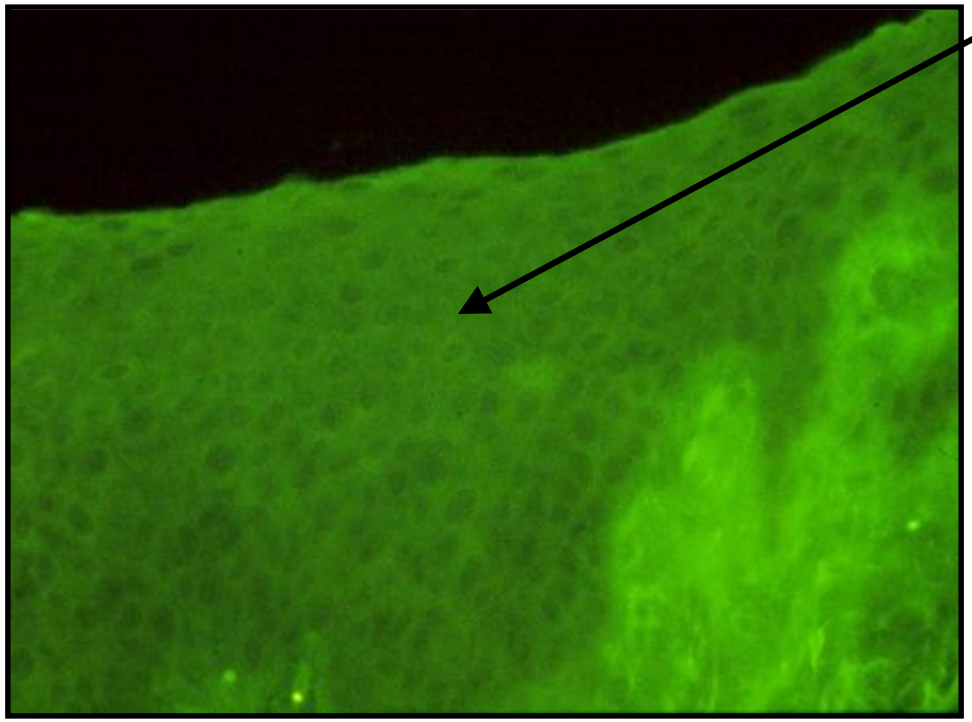


Pemphigus vulgaris - Histology

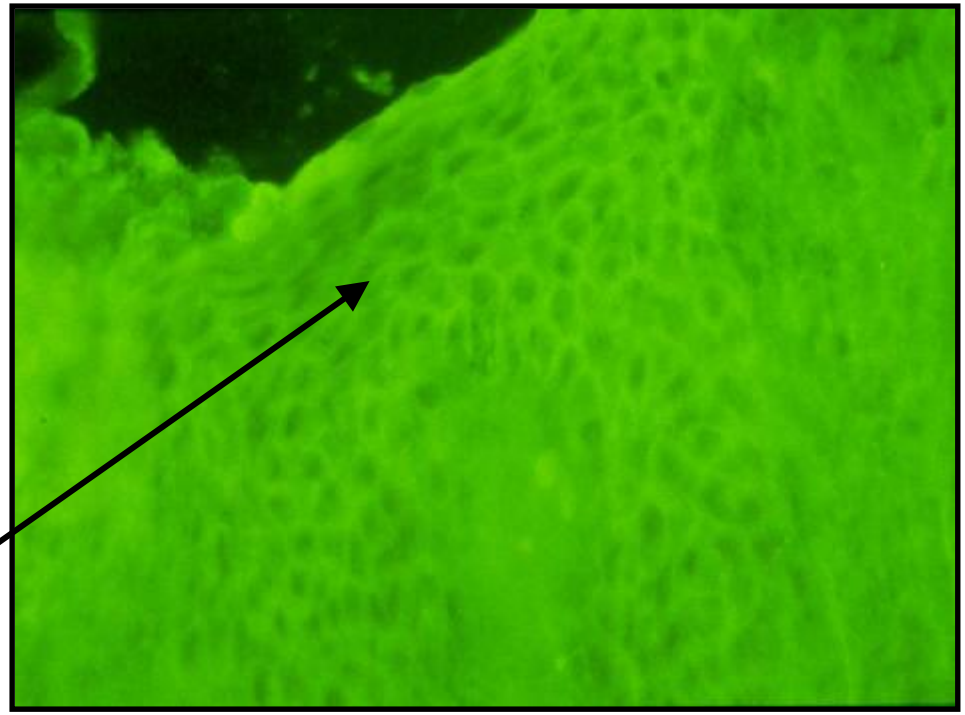


- Suprabasal bulla with acantholysis
- Tombstone appearance
- Cavity contains acantholytic cells & few eos / neutrophils
- Dermal mixed inflam.

Pemphigus vulgaris - IMF

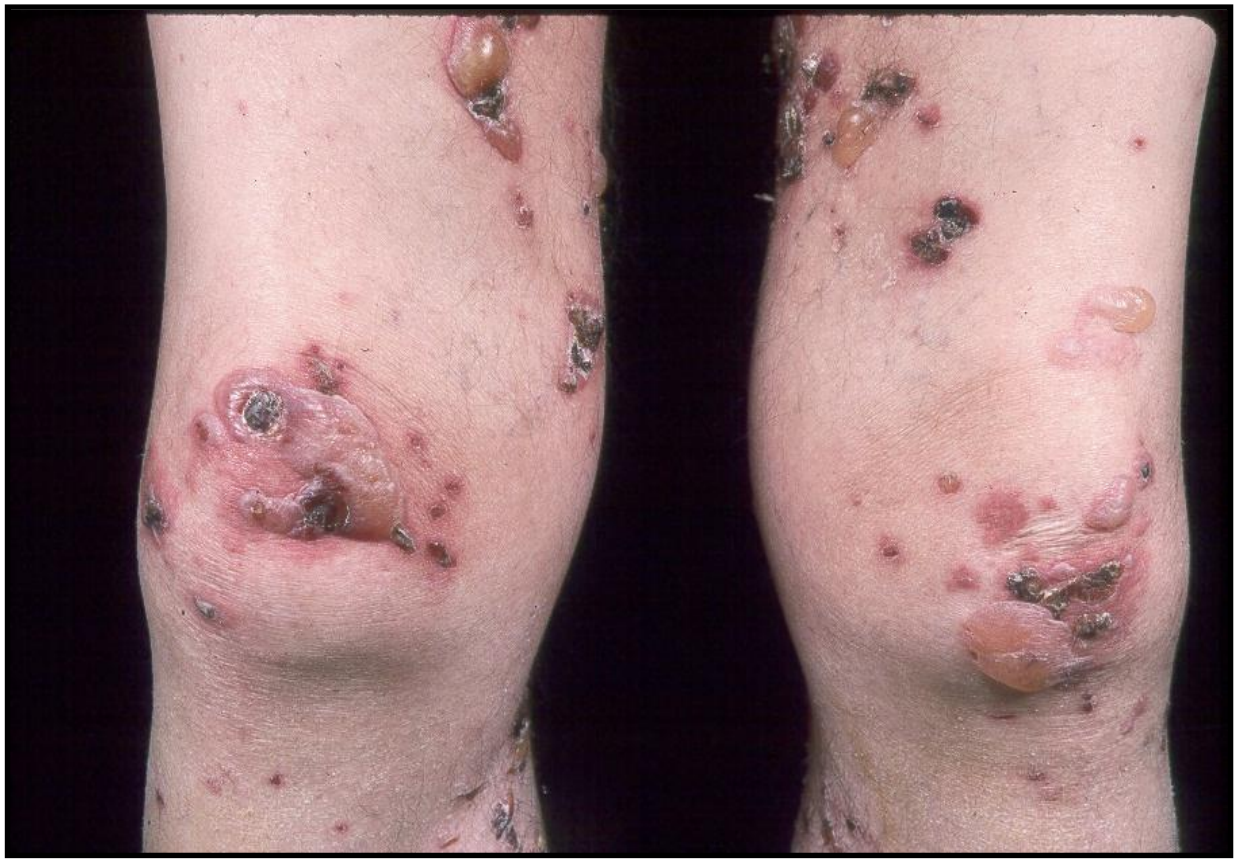


IgA, IgM, IgD - negative



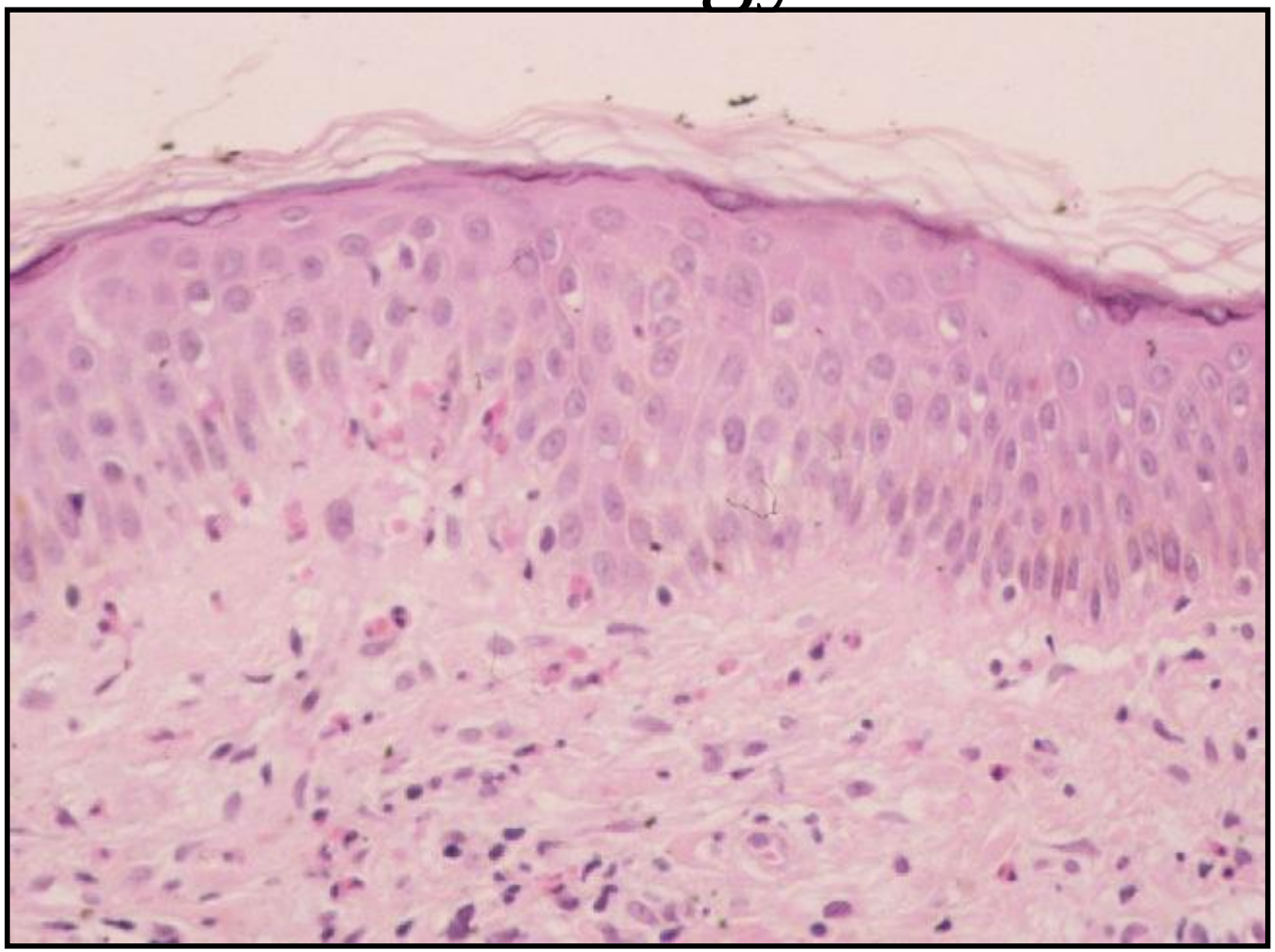
IgG, C3 positive - intracellular

Bullous pemphigoid

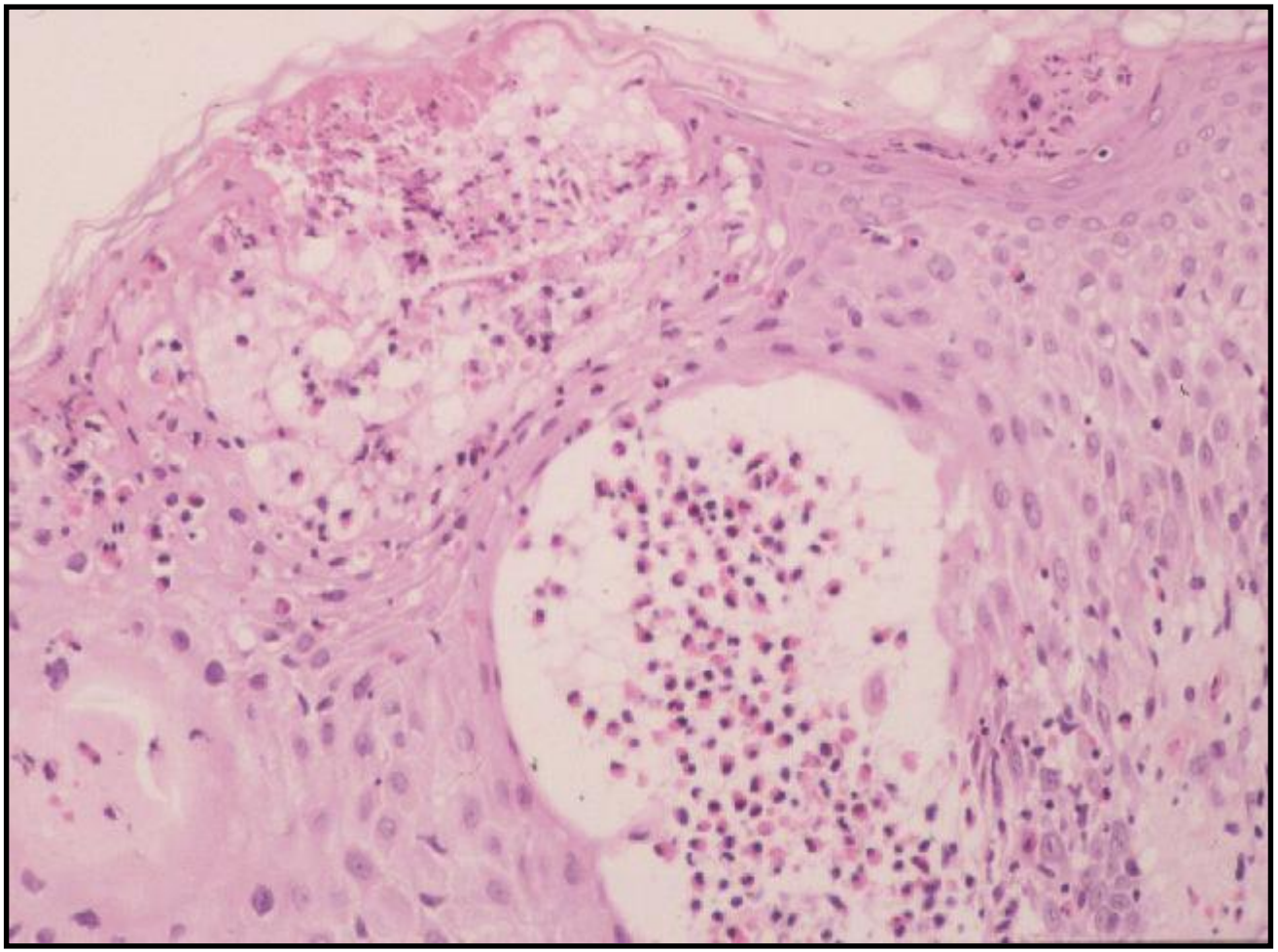


- Tense bullae
- Lower abdomen, groin, flexor arms and legs
- Oral in 10-40% but other mucosal is rare

Bullous pemphigoid – early histology

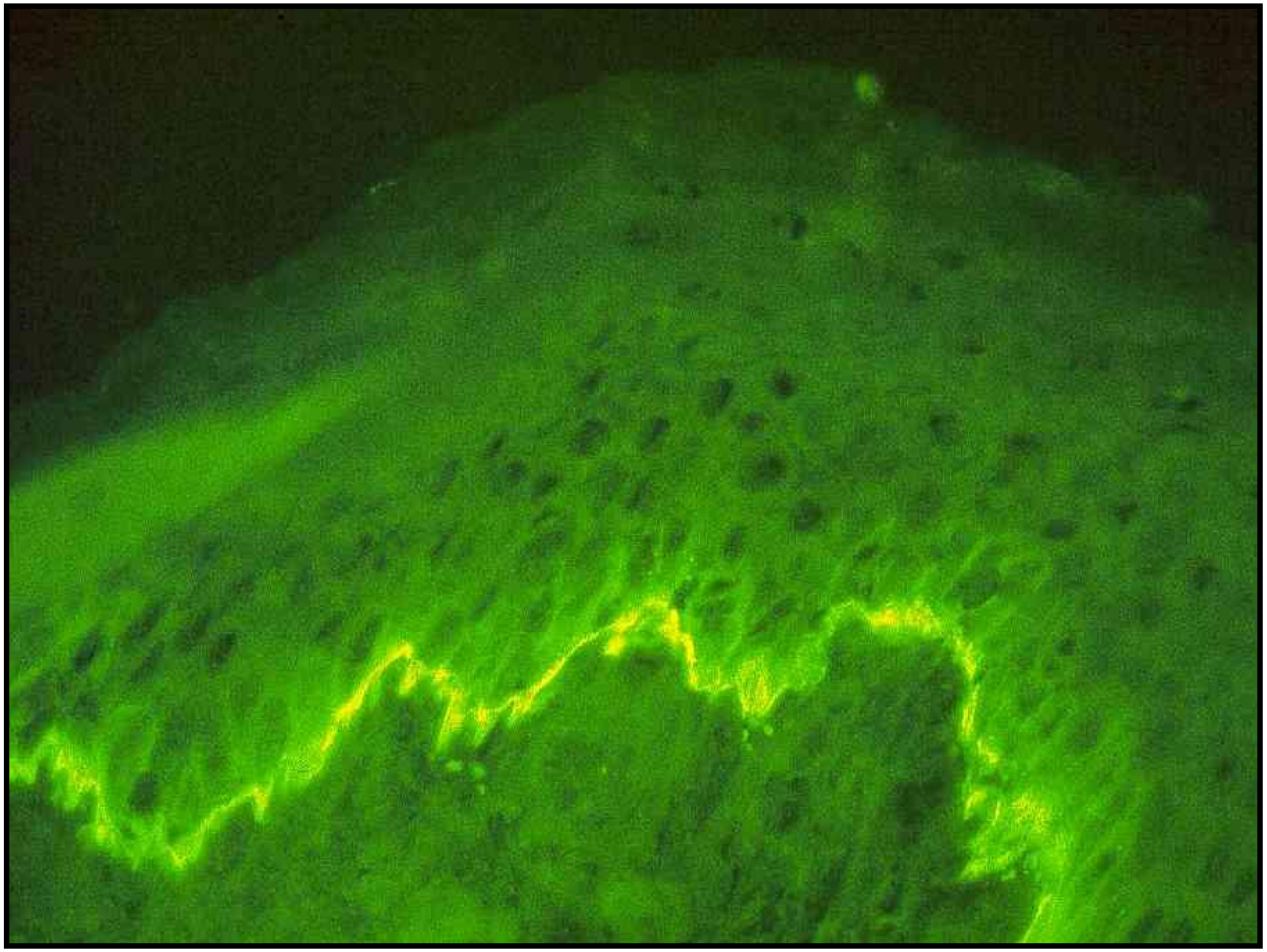


Bullous pemphigoid -Histology



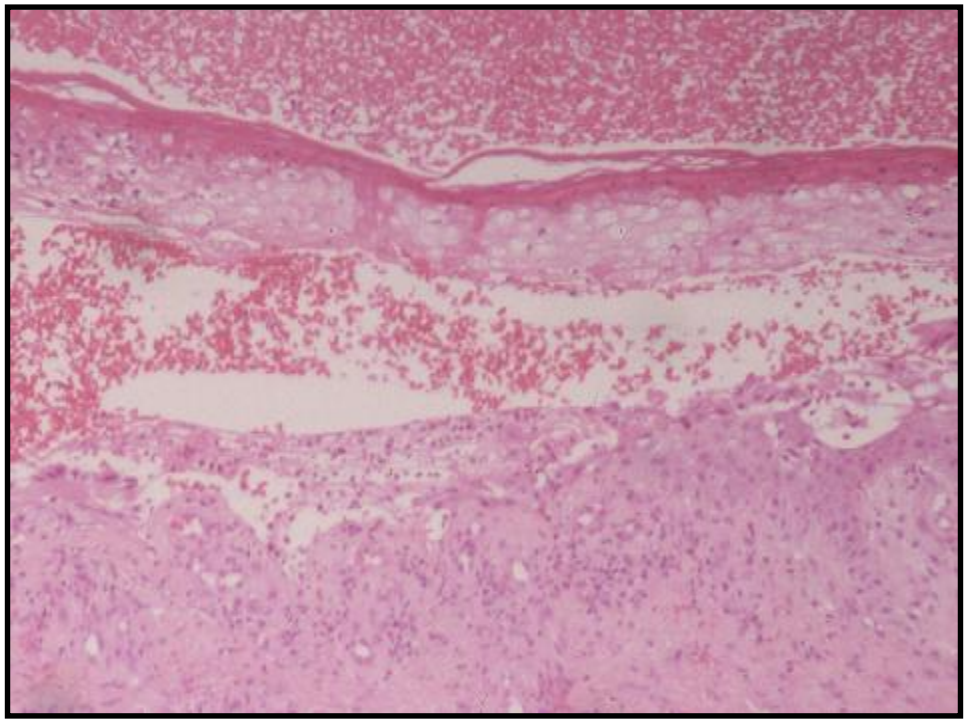
- Subepidermal blister
- Eosinophils + neutrophils

Bullous pemphigoid - IMF



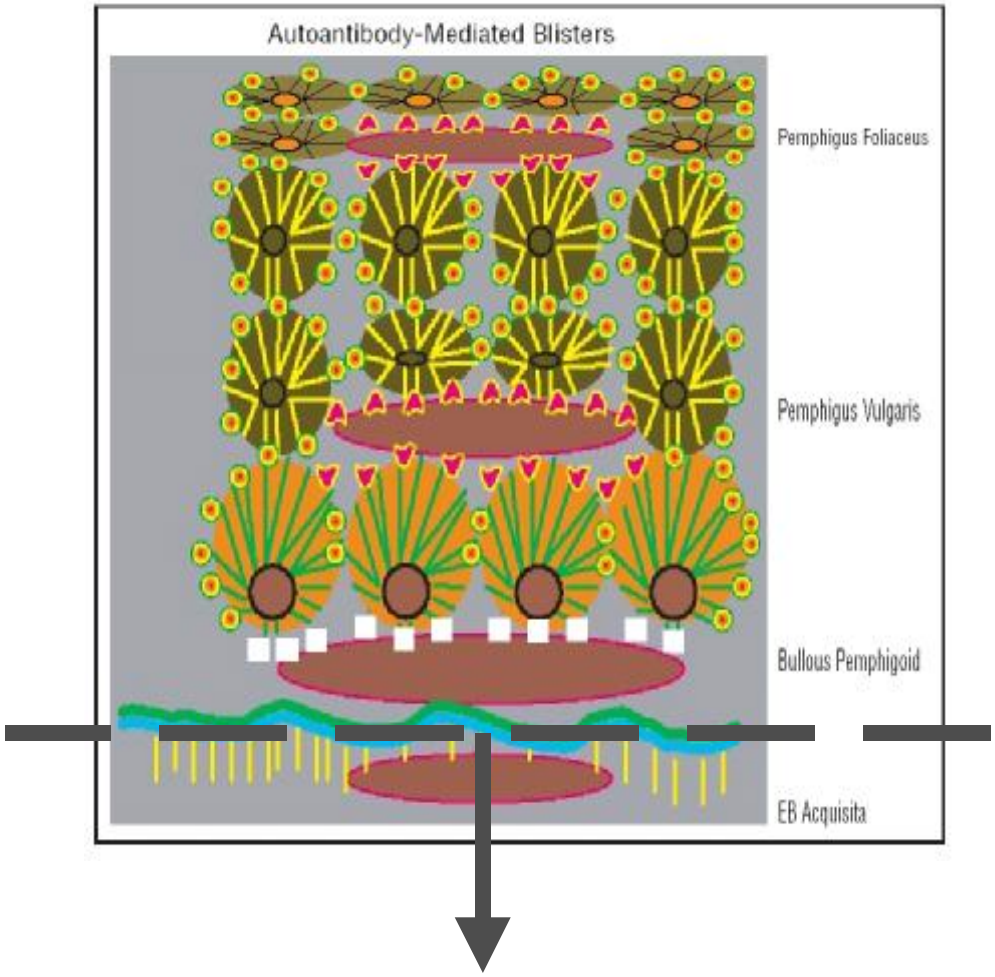
- Linear IgG and C3 at BMZ

Epidermolysis bullosa acquisita



- Rare, non-inherited
- Non-inflammatory bullae
- Heal with scars
- Mid adult life
- Antigen = Type VII collagen (anchoring fibrils)

Split skin immunofluorescence



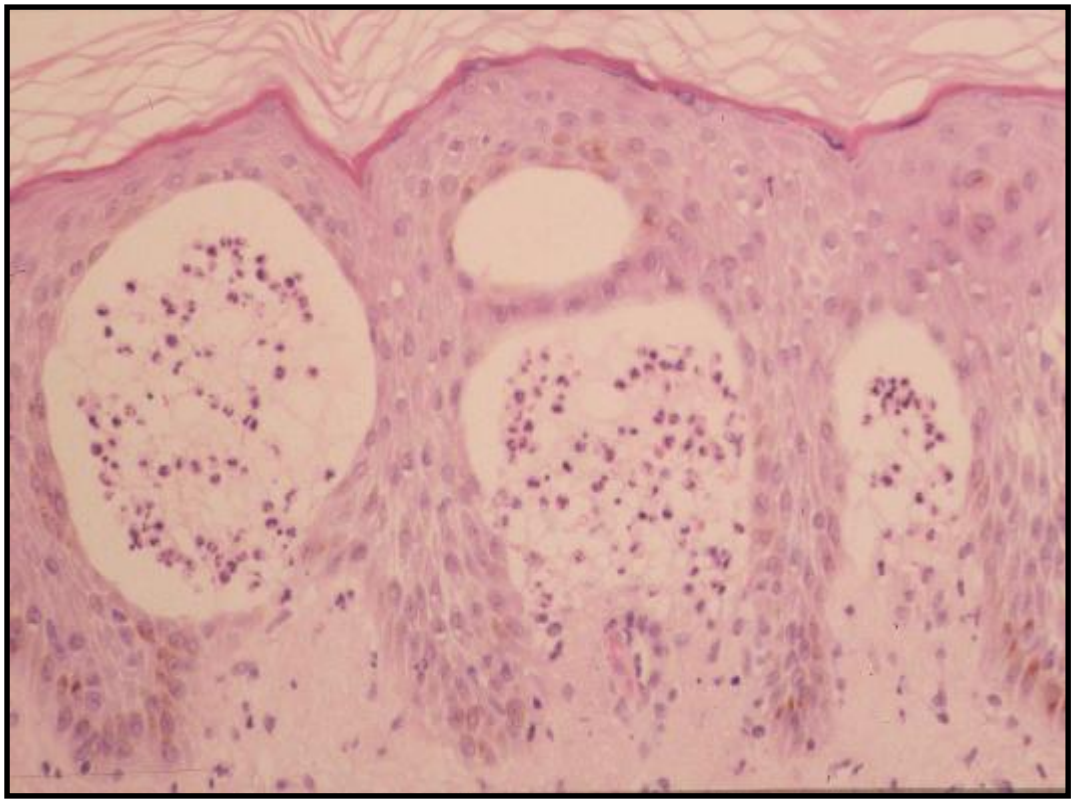
- Incubate in 1mol NaCl
- Induce split in LL
- Immunofluorescence
- Divide
  - BP (roof)
  - EBA (floor)
- Specialised service (St John's)

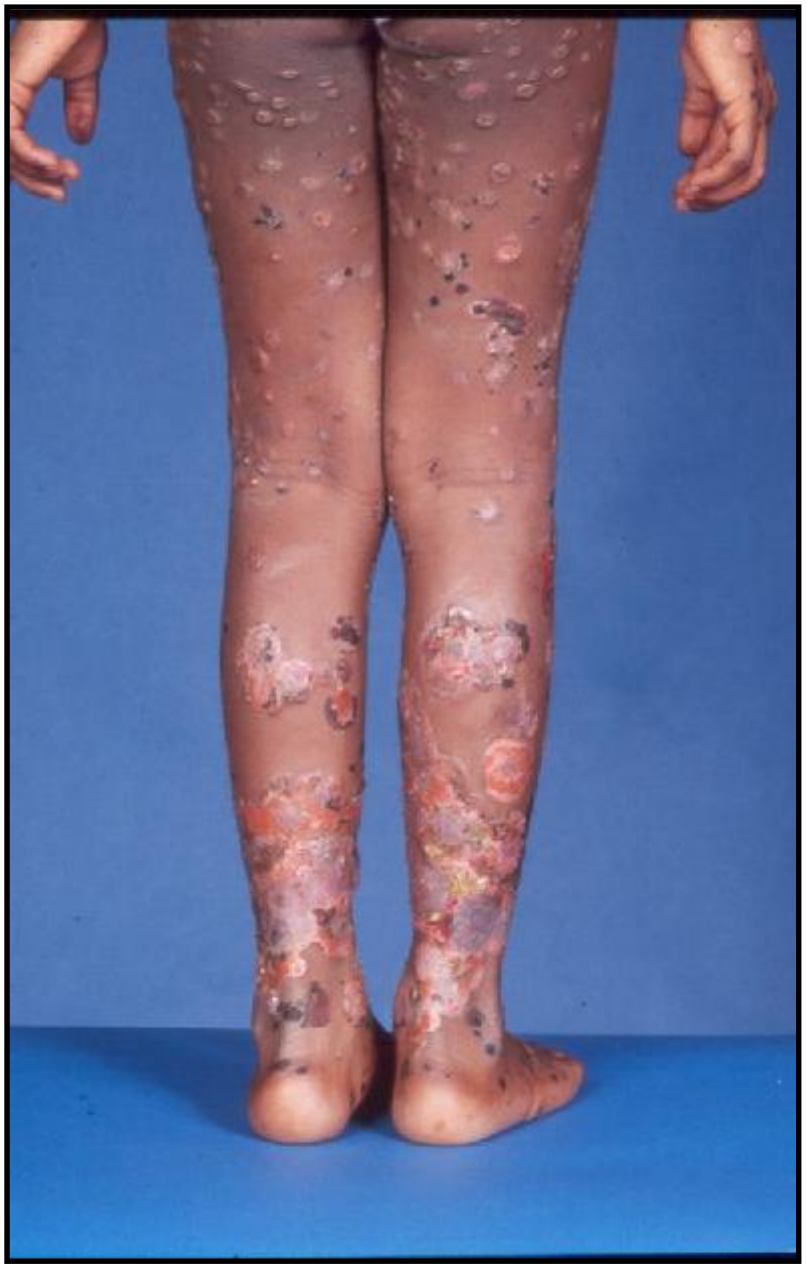
Pemphigoid gestationis (herpes gestationis)

- 1/50,000 pregnancies
- 2nd or 3rd trimester
- Periumbilical then spread
- Histology same as BP
  - Subepidermal blisters with eos and neutrophils
- DIF : C3 (+/- IgG) BMZ (roof)
- Placental matrix antigen
- Diagnosis relies on CLINICAL HISTORY

Dermatitis herpetiformis

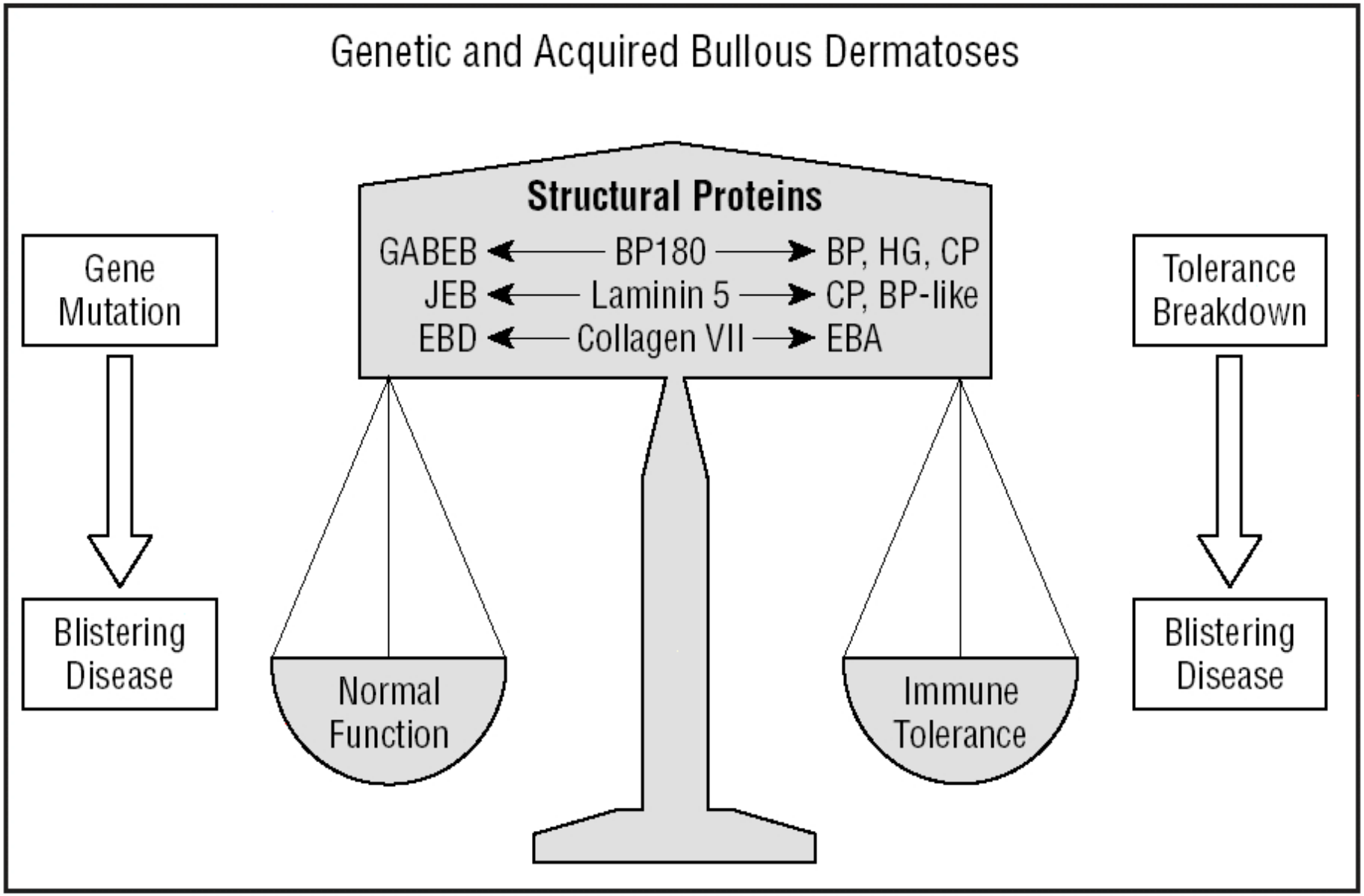
- Clinical
  - Rare, chronic
  - 90% GLUTEN sensitive
  - Extensor surface, symmetrical
- Histology
  - Neutrophils in papillae
  - Granular IgA at dermal papillae on IMF



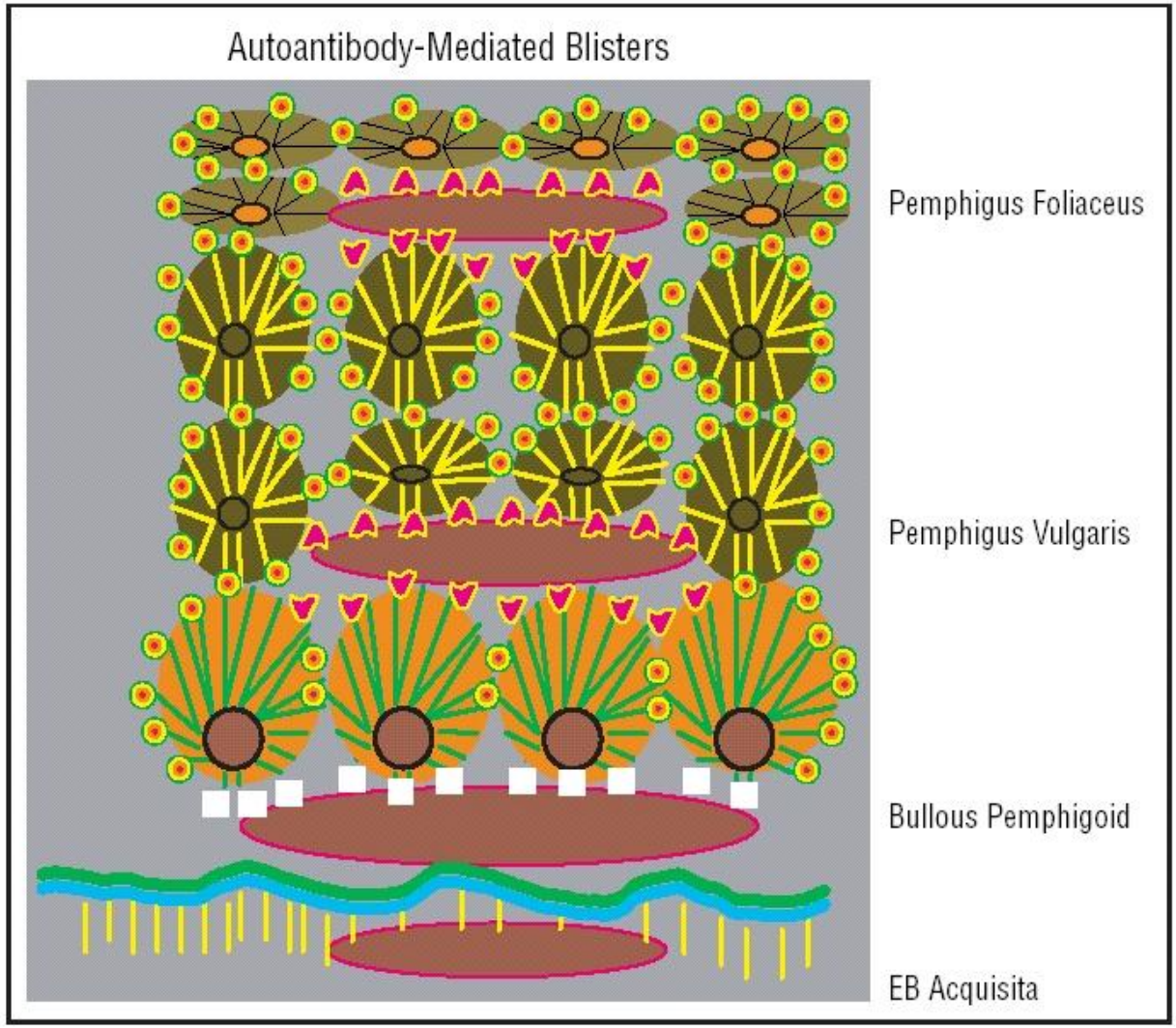


Linear IgA bullous dermatosis

- Rare
- 2 variants
  - Adult linear IgA
  - Chronic bullous dermatosis of childhood
- Linear IgA deposits at BMZ on IMF
- ?Antigen – Type VII coll



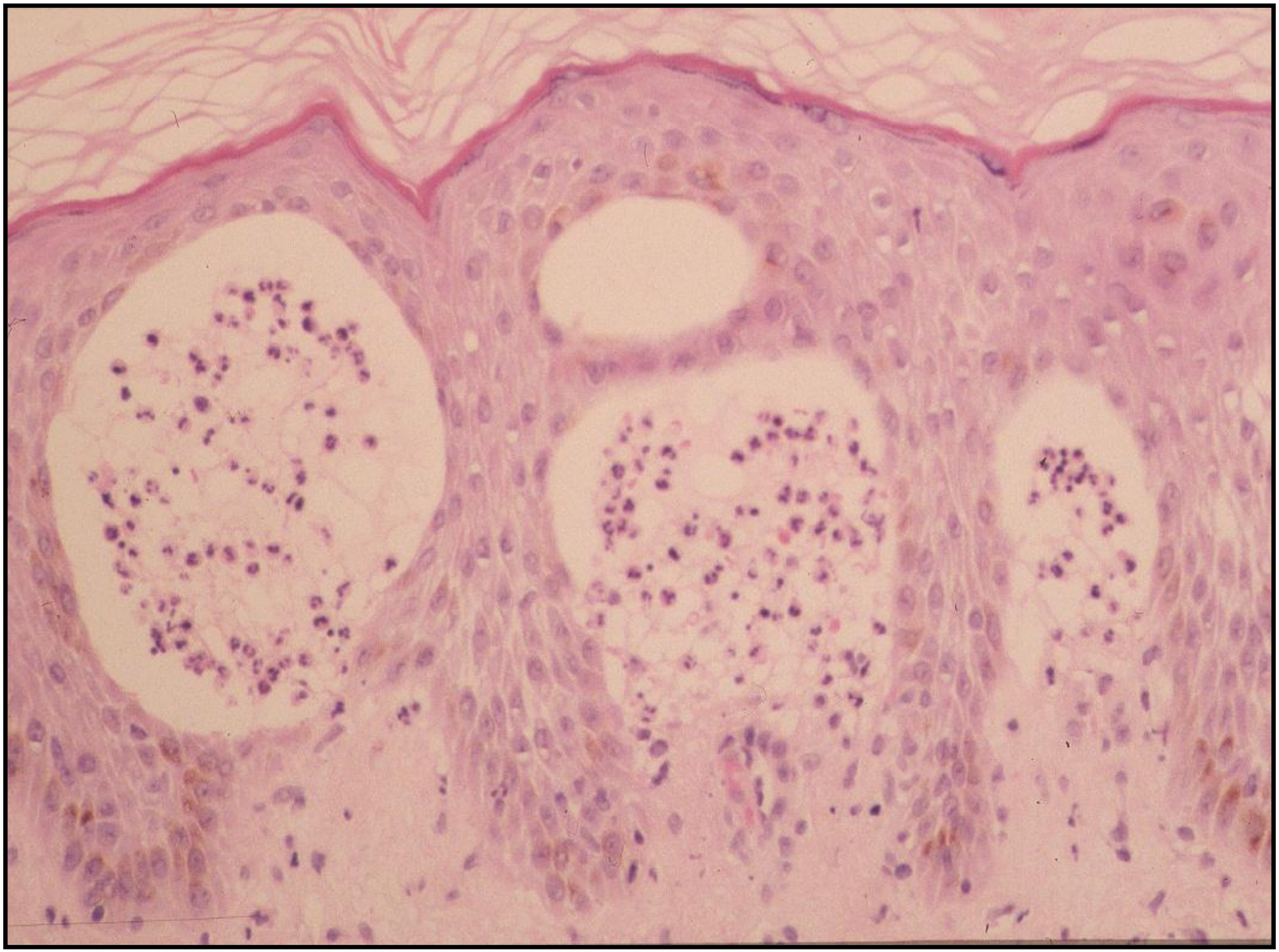
Takehome message…….



Case 1

- 15 male with an itchy, bumpy rash on arms
- History of Coeliac's disease

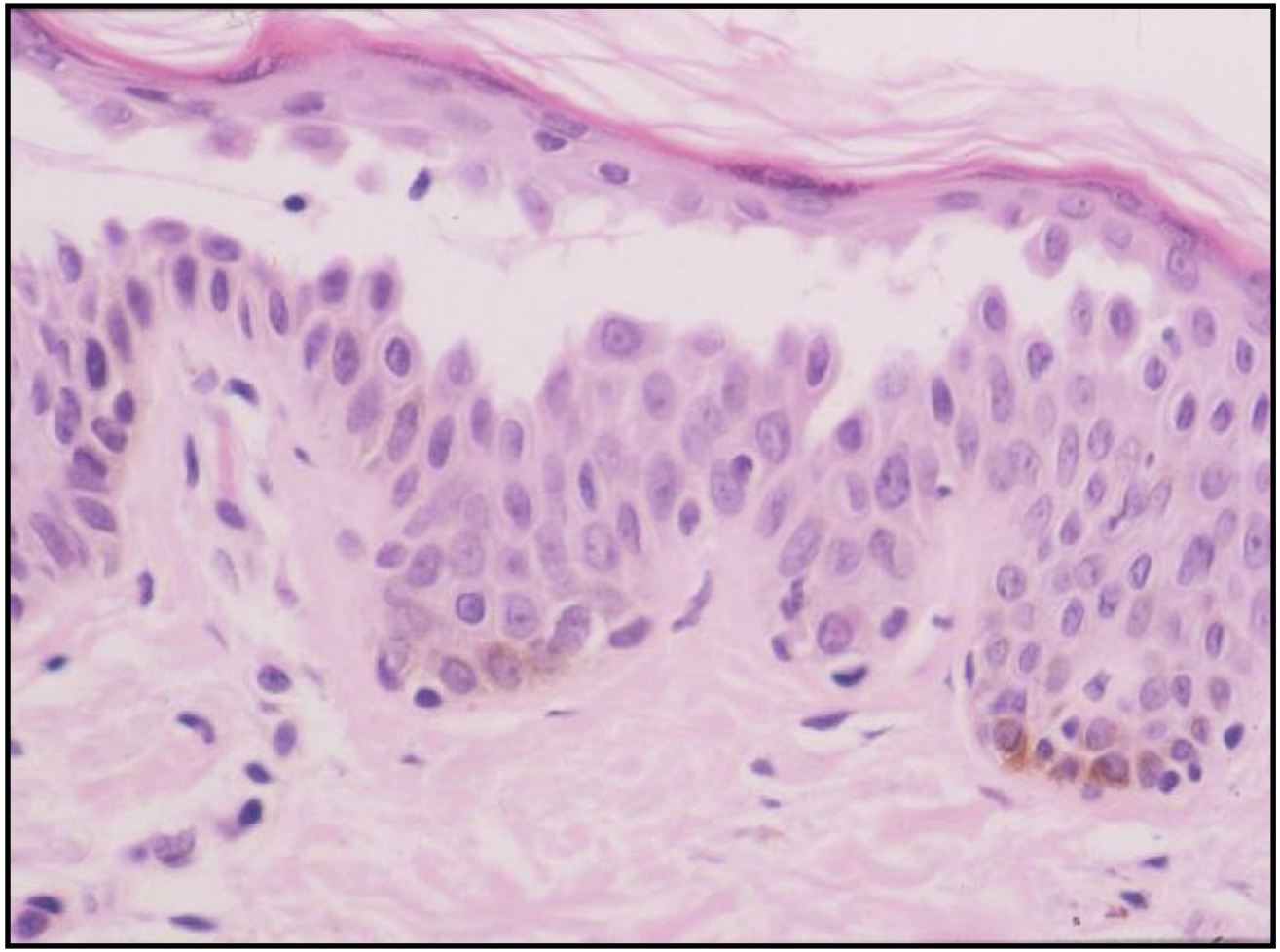
Dermatitis herpetiformis



Case 2

- 68 yr male with scaly blisters (site not stated)

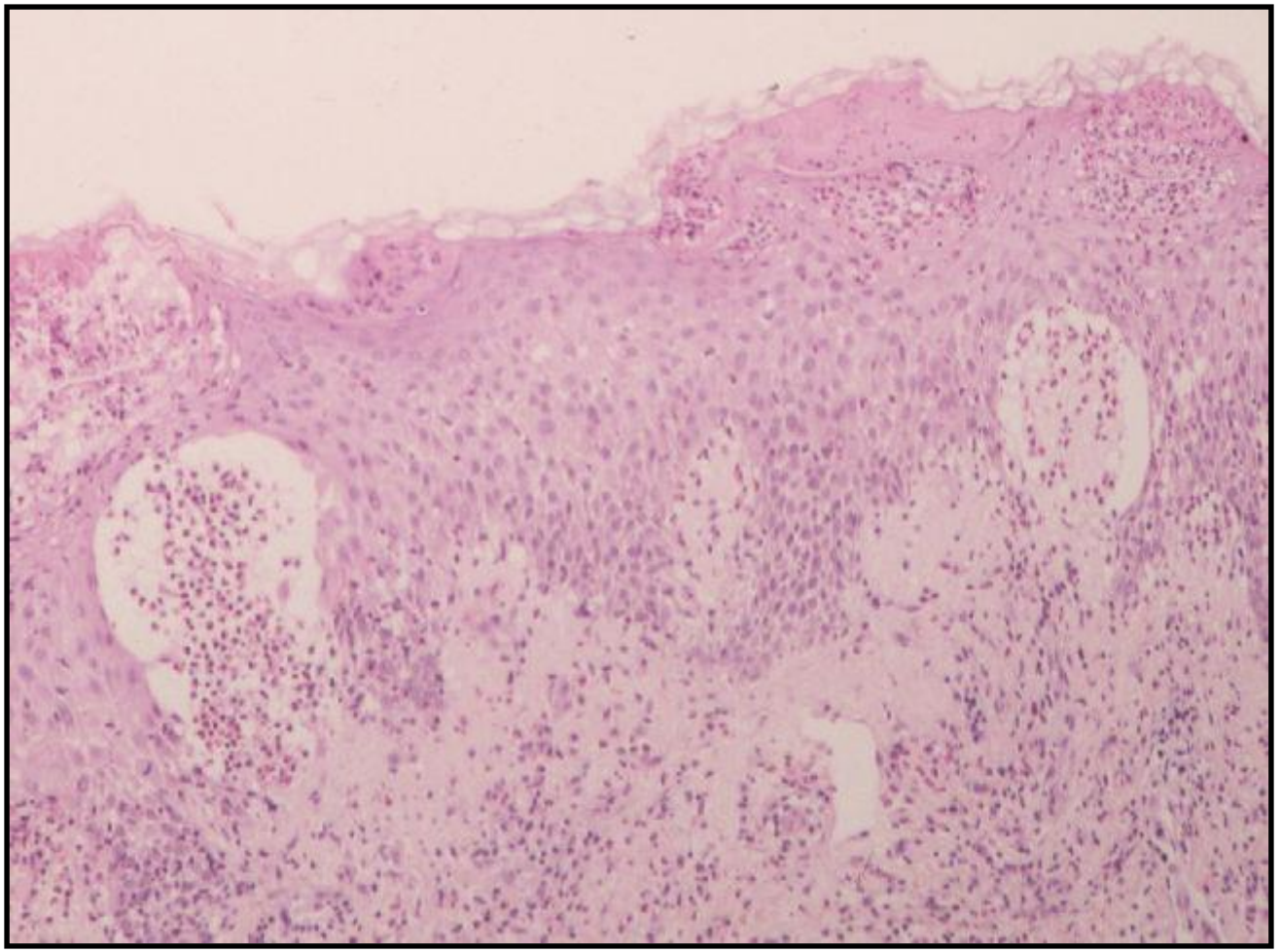
Pemphigus foliaceus



Case 3

- 71 yr male with a blister on left forearm, very itchy.

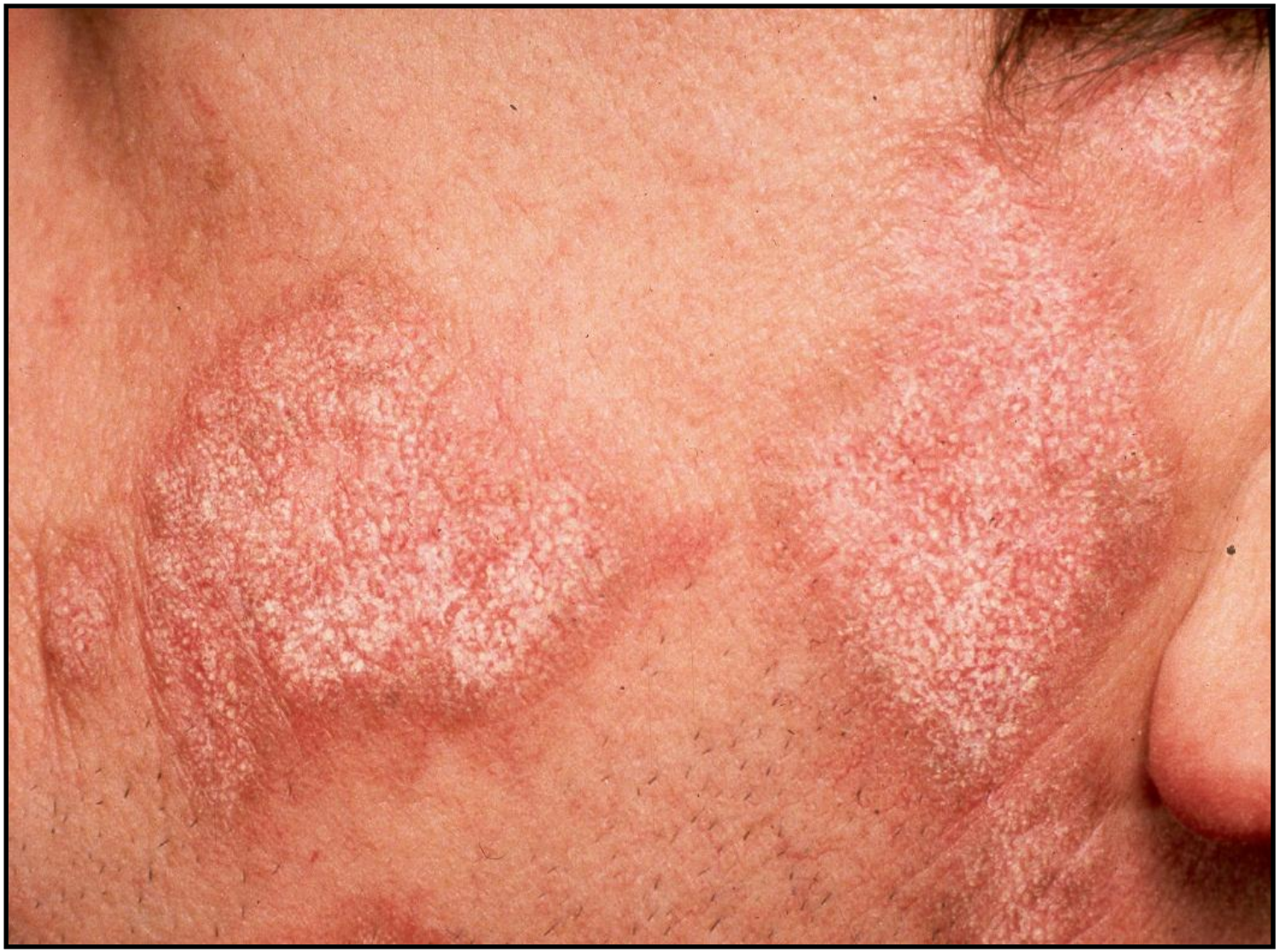
Bullous pemphigoid



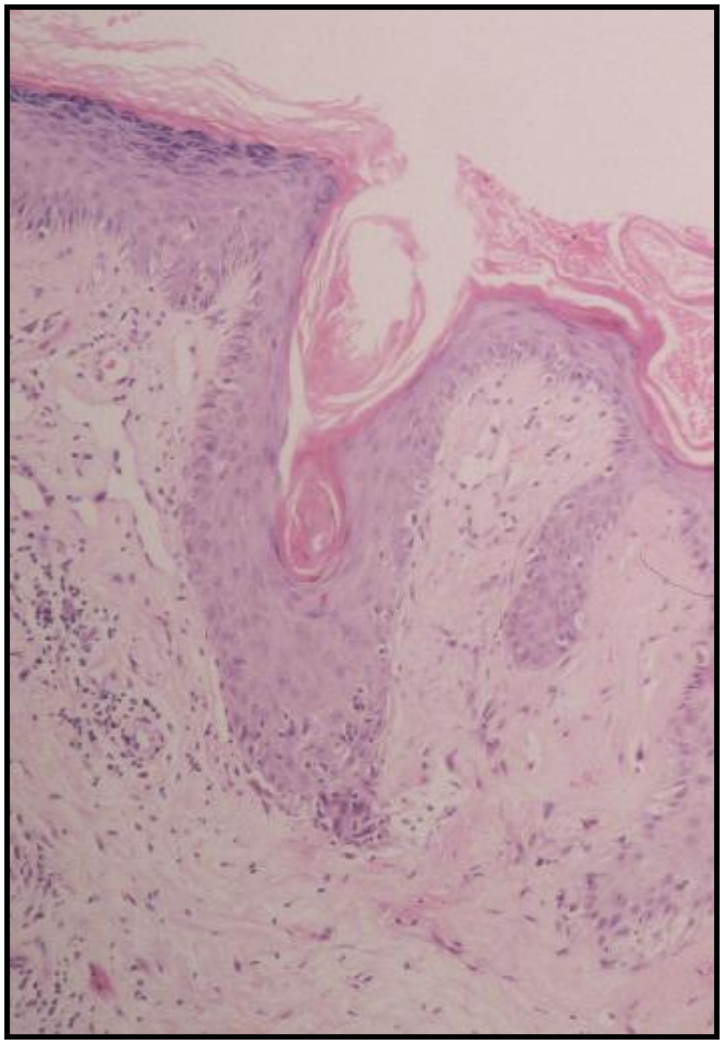
Case 4

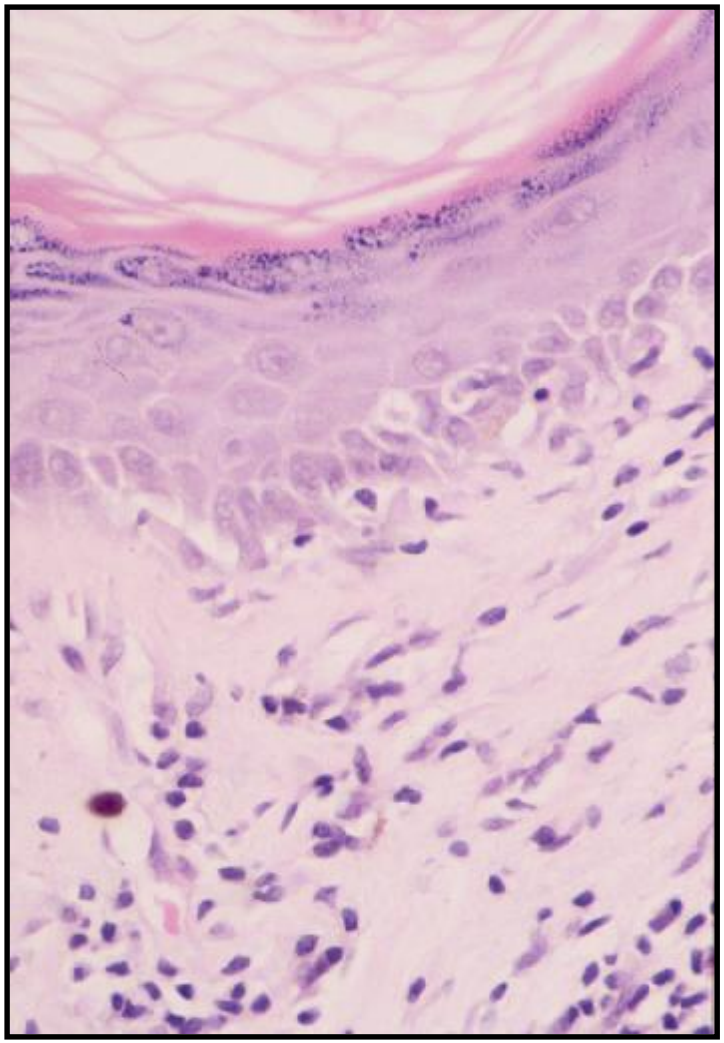
- 46 yr female scaly plaque behind left ear

Case 4



Discoid LE

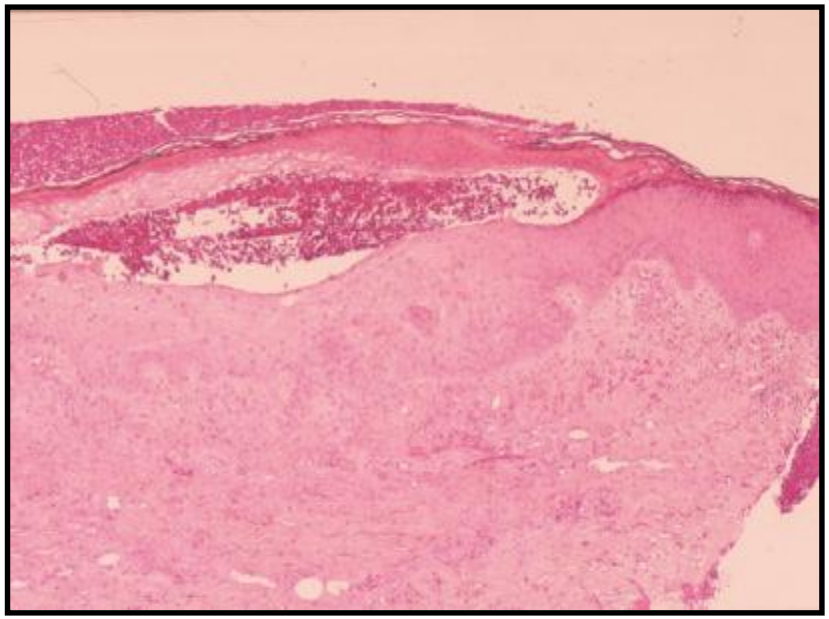


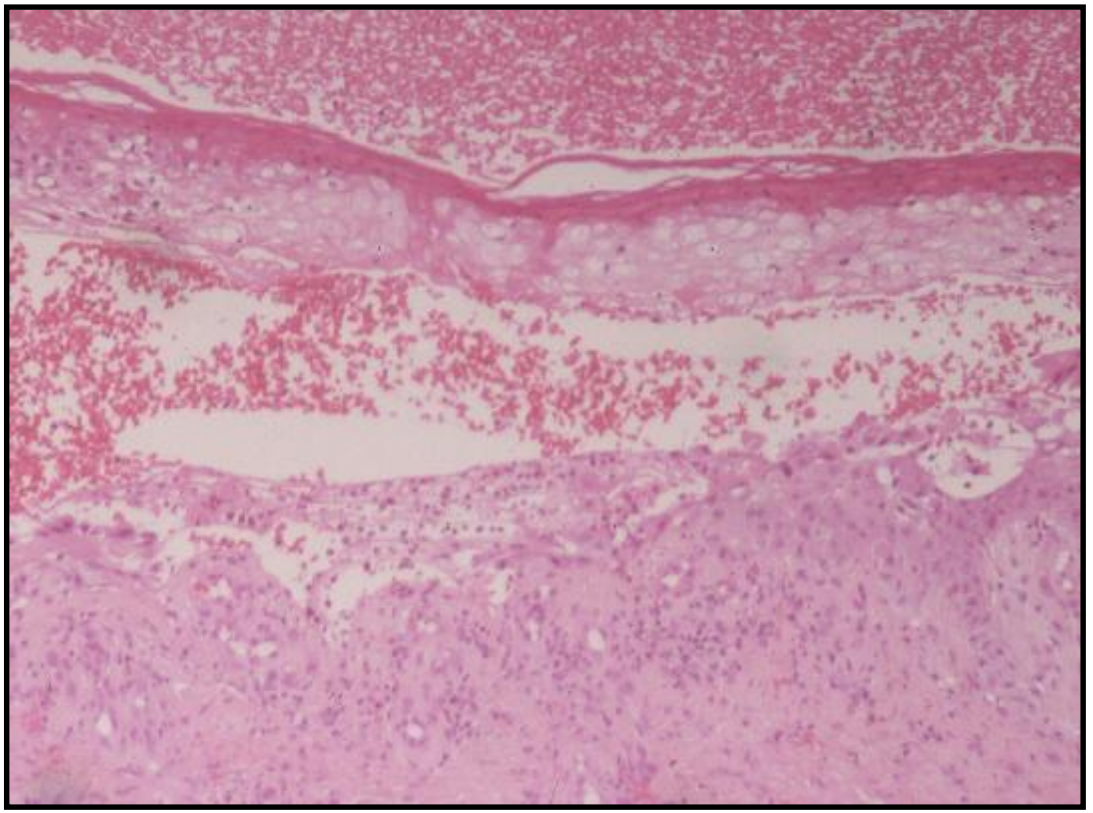


Case 5

- 75 yr male, widespread erythematous itchy eruption that blistered.

Epidermolysis bullosa aquista

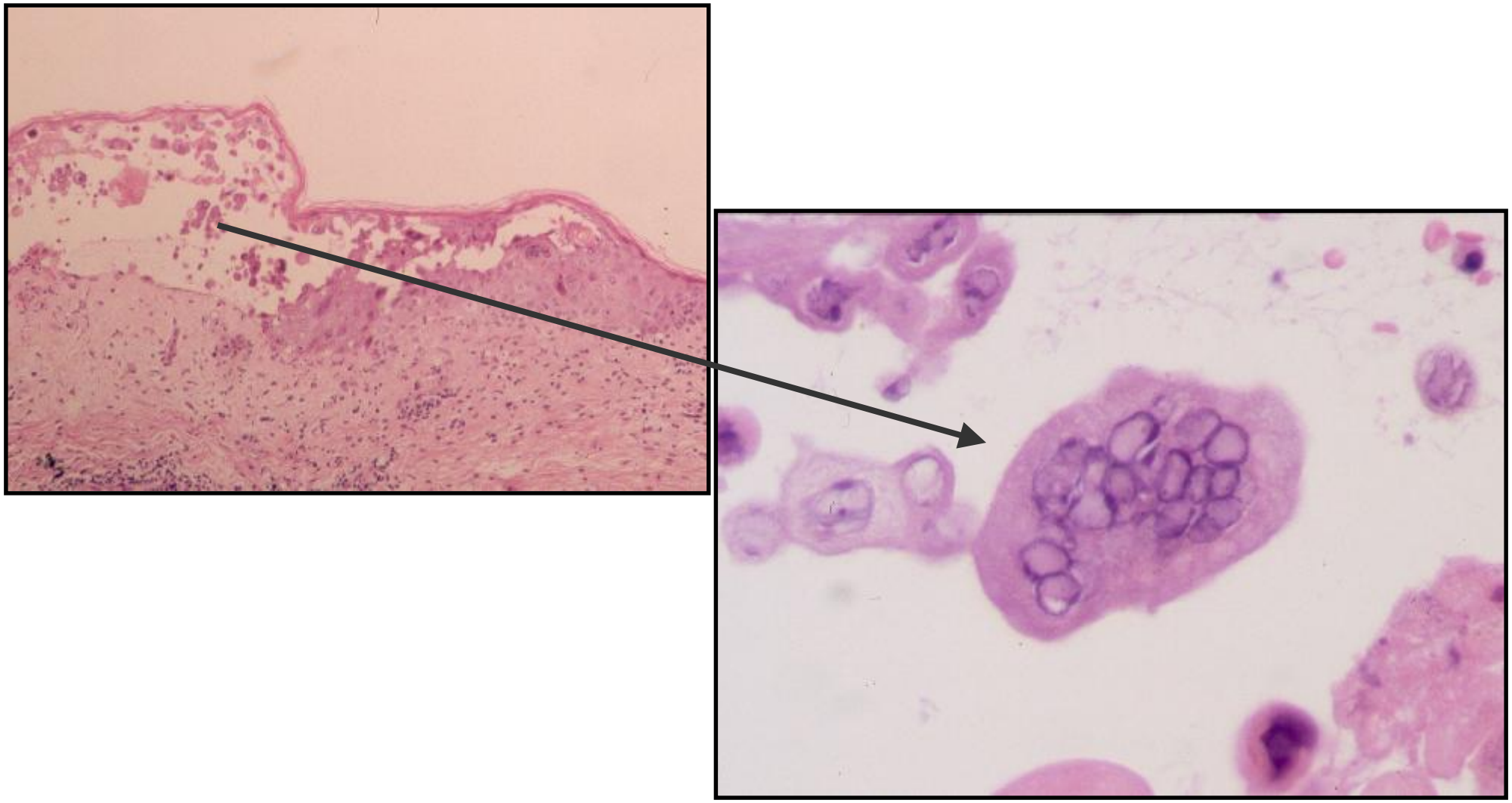




Case 6

- 74 yr female, renal failure, purpuric rash on arms and chest.

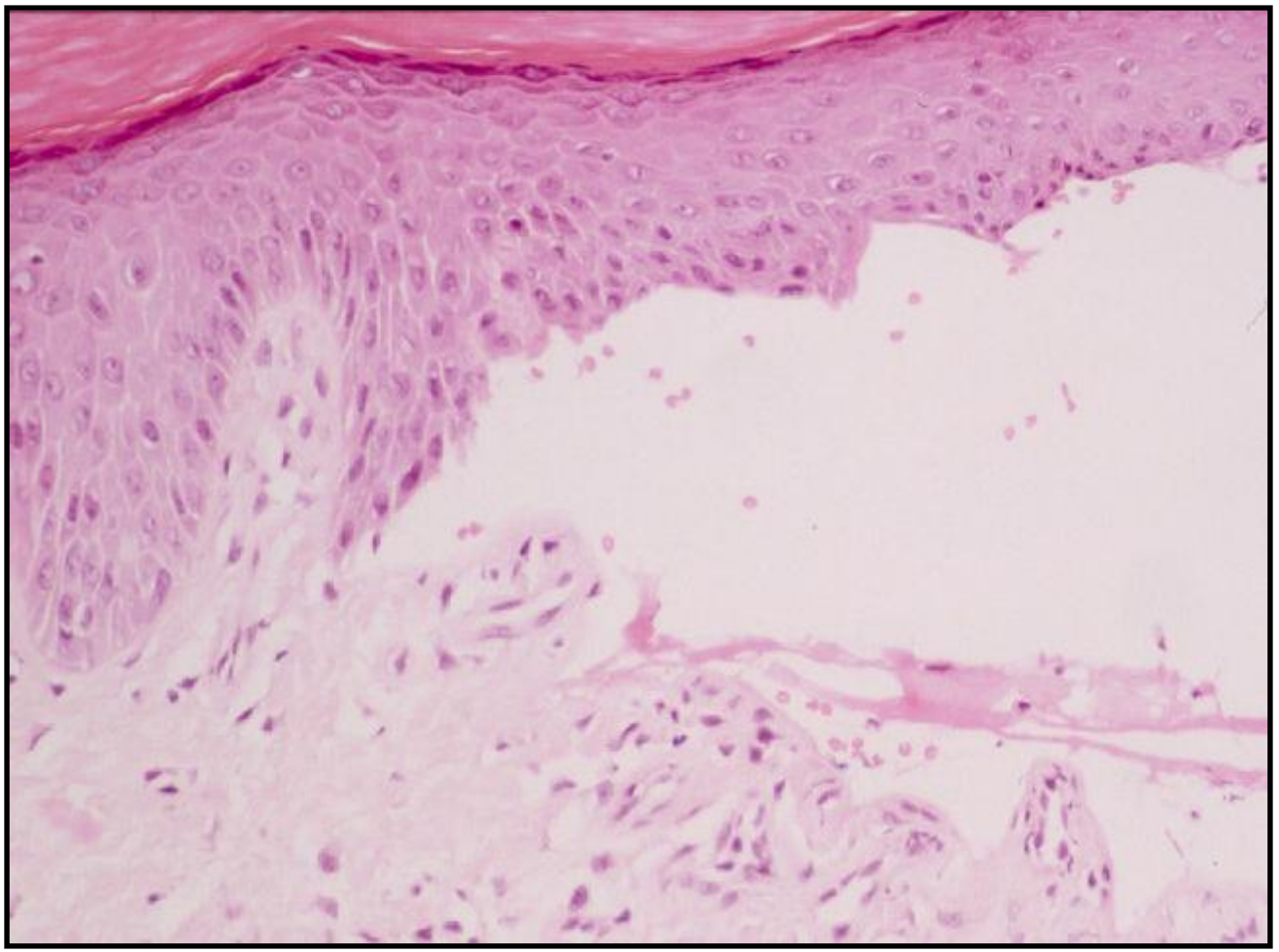
Herpes virus



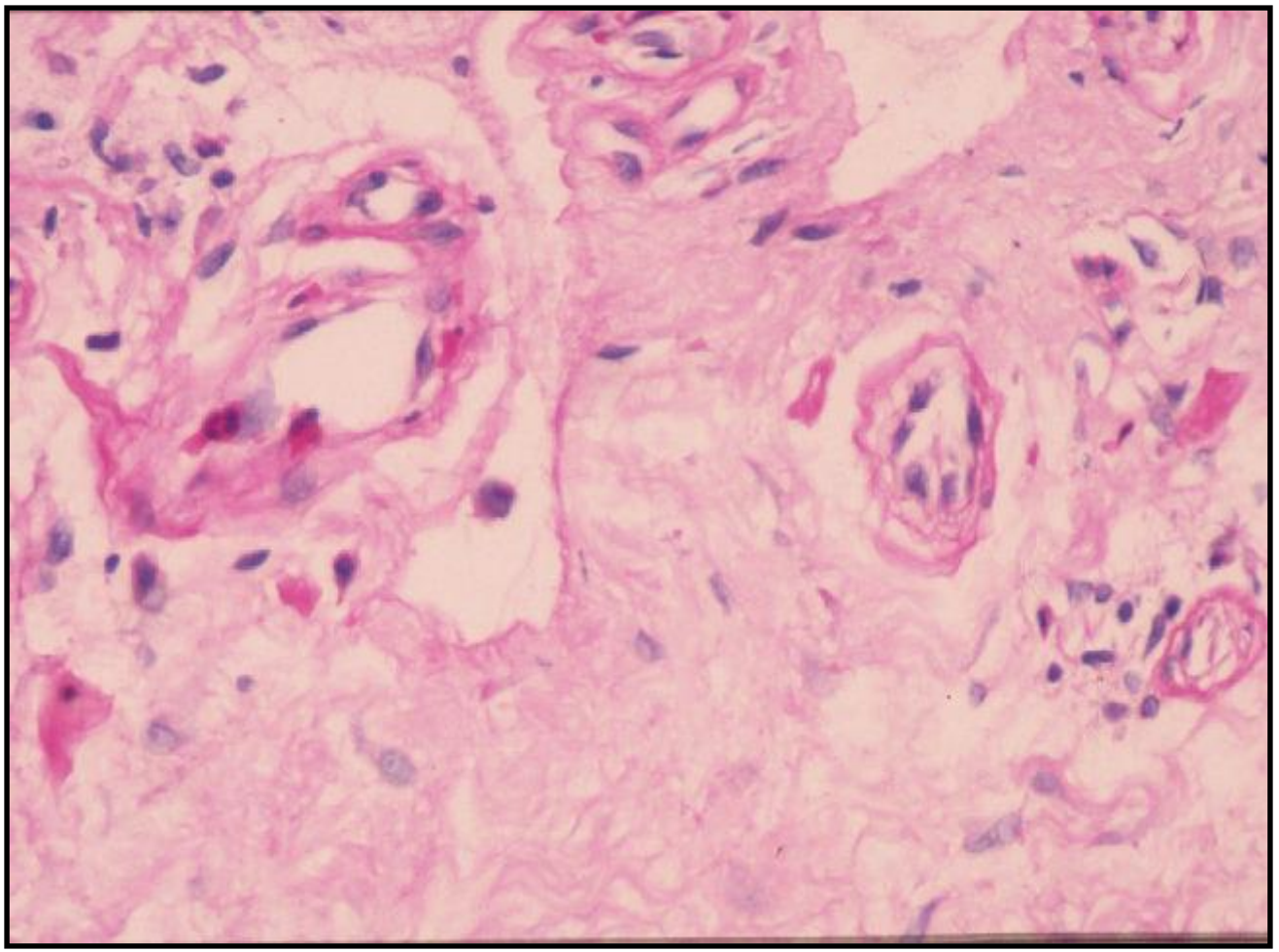
Case 7

- 63 yr male, blistering rash on hands

Porphyria cutanea tarda



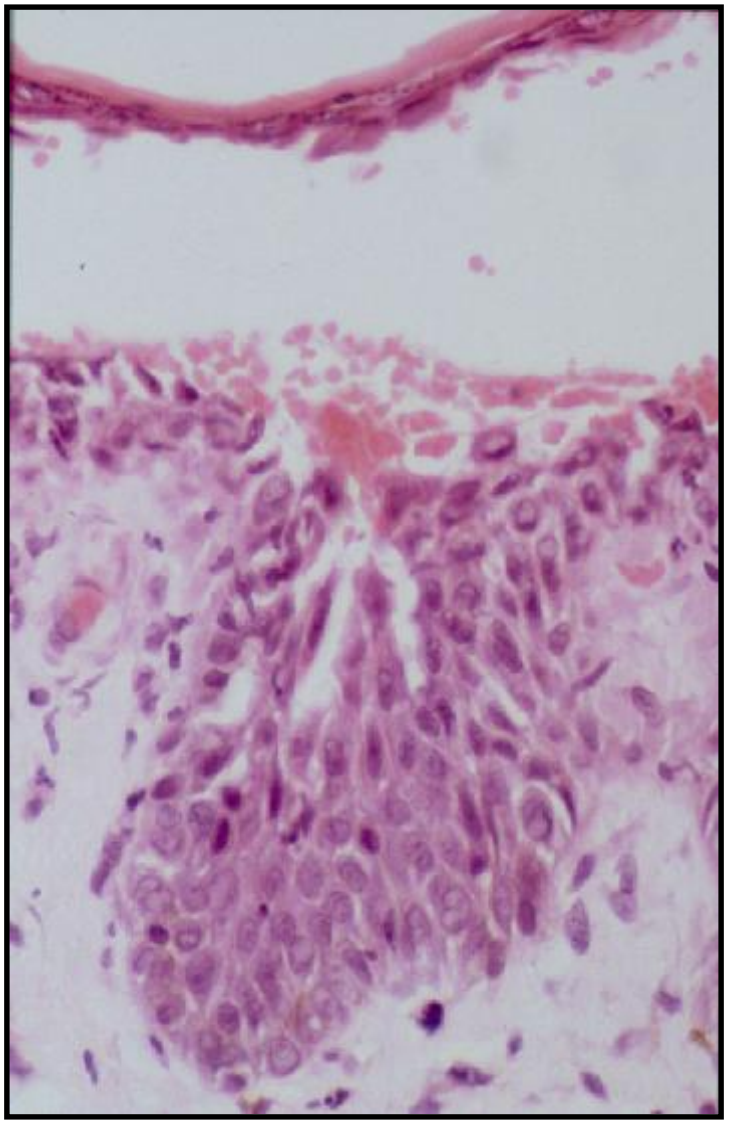
Porphyria cutanea tarda



Case 8

- 81yr female, eroded lesions on right thigh. Mucous membranes are clear.

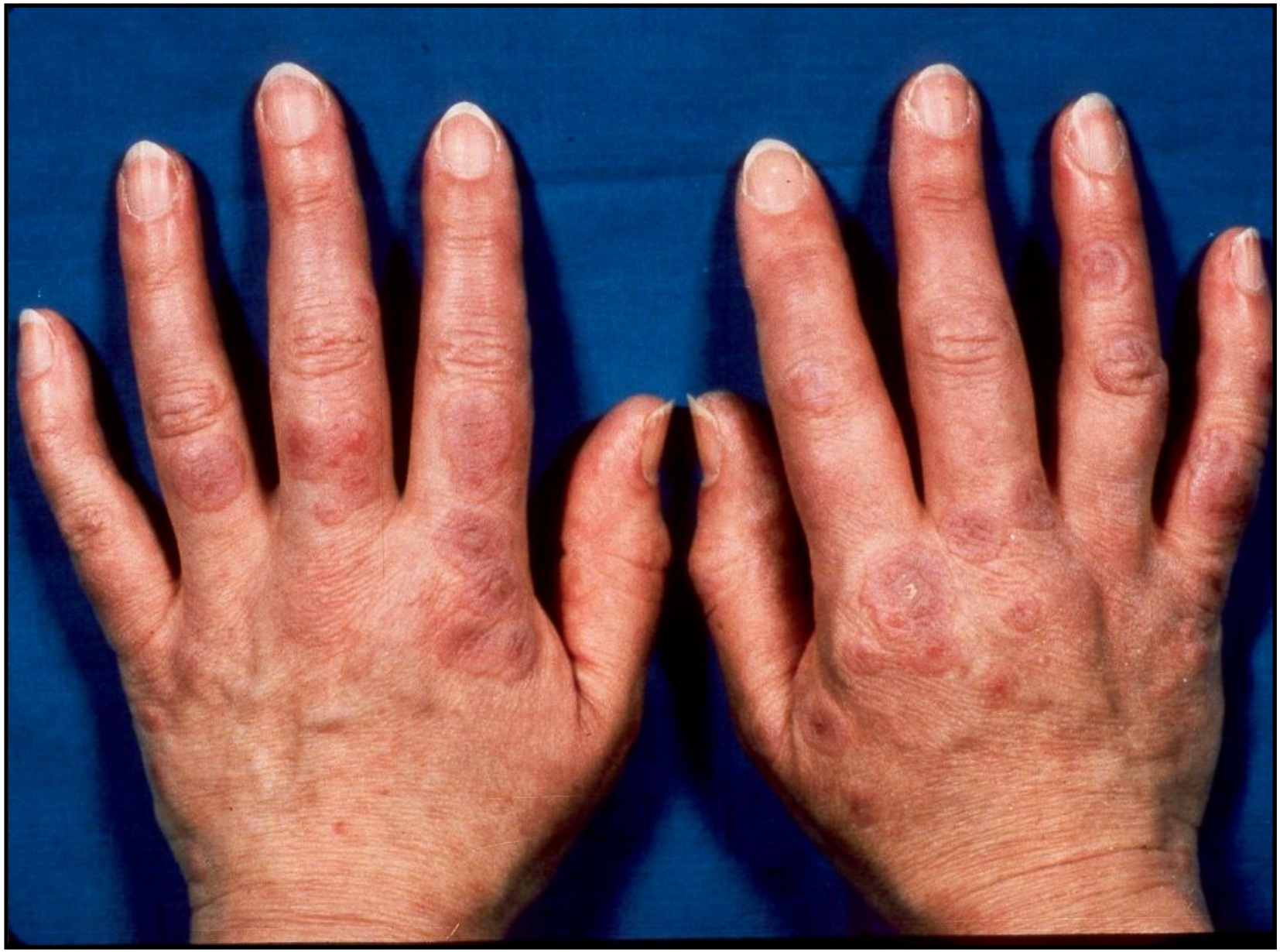
Pemphigus vulgaris



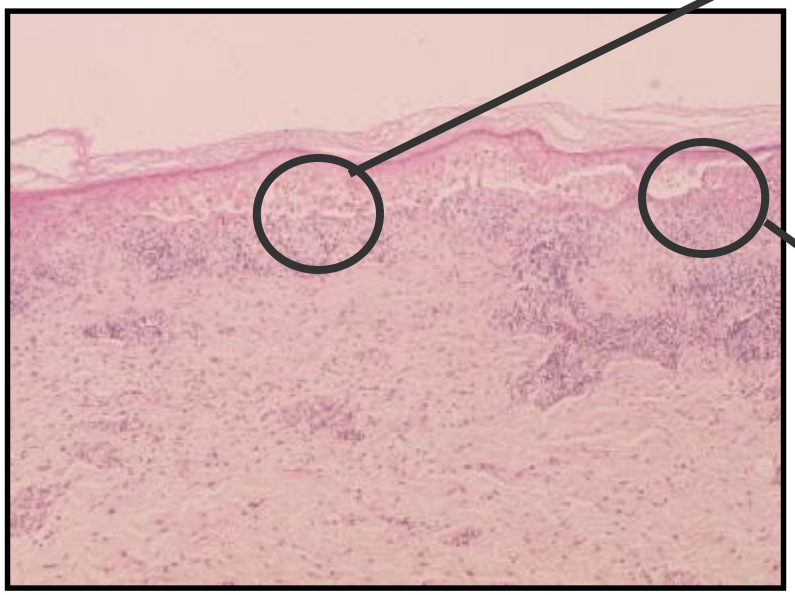
Case 9

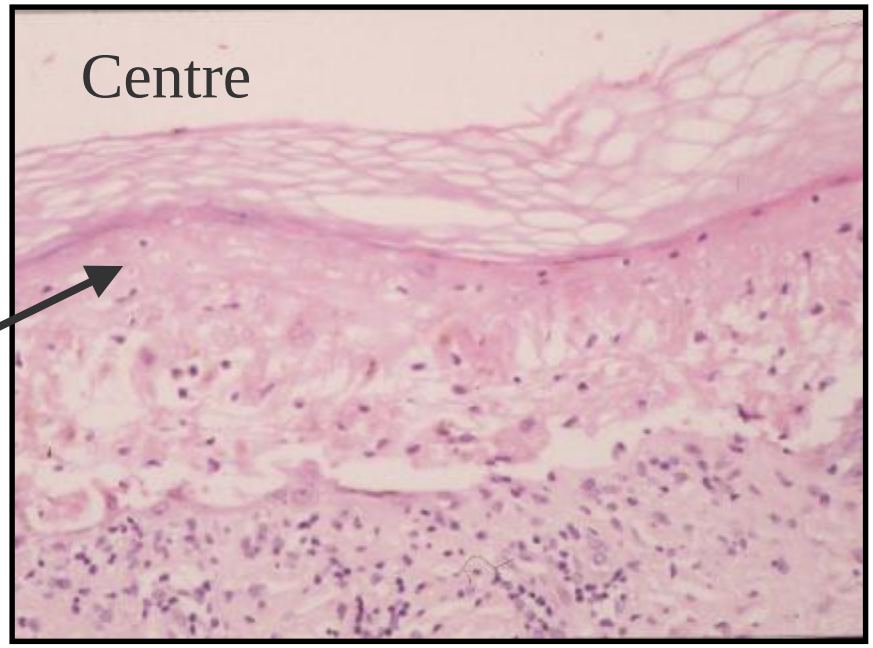
- 46 yr male, blister (site not stated).

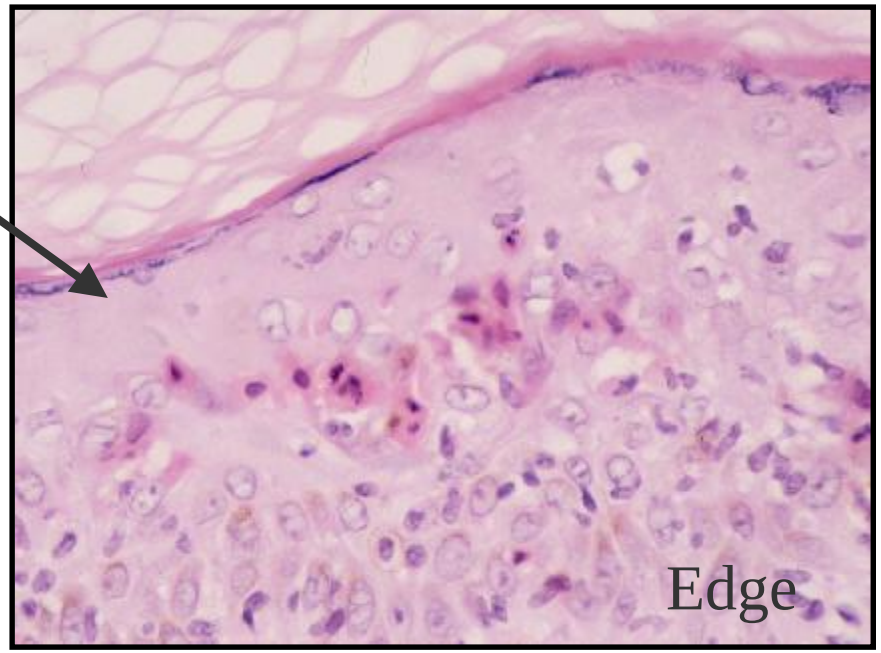
Case 9



Erythema multiforme



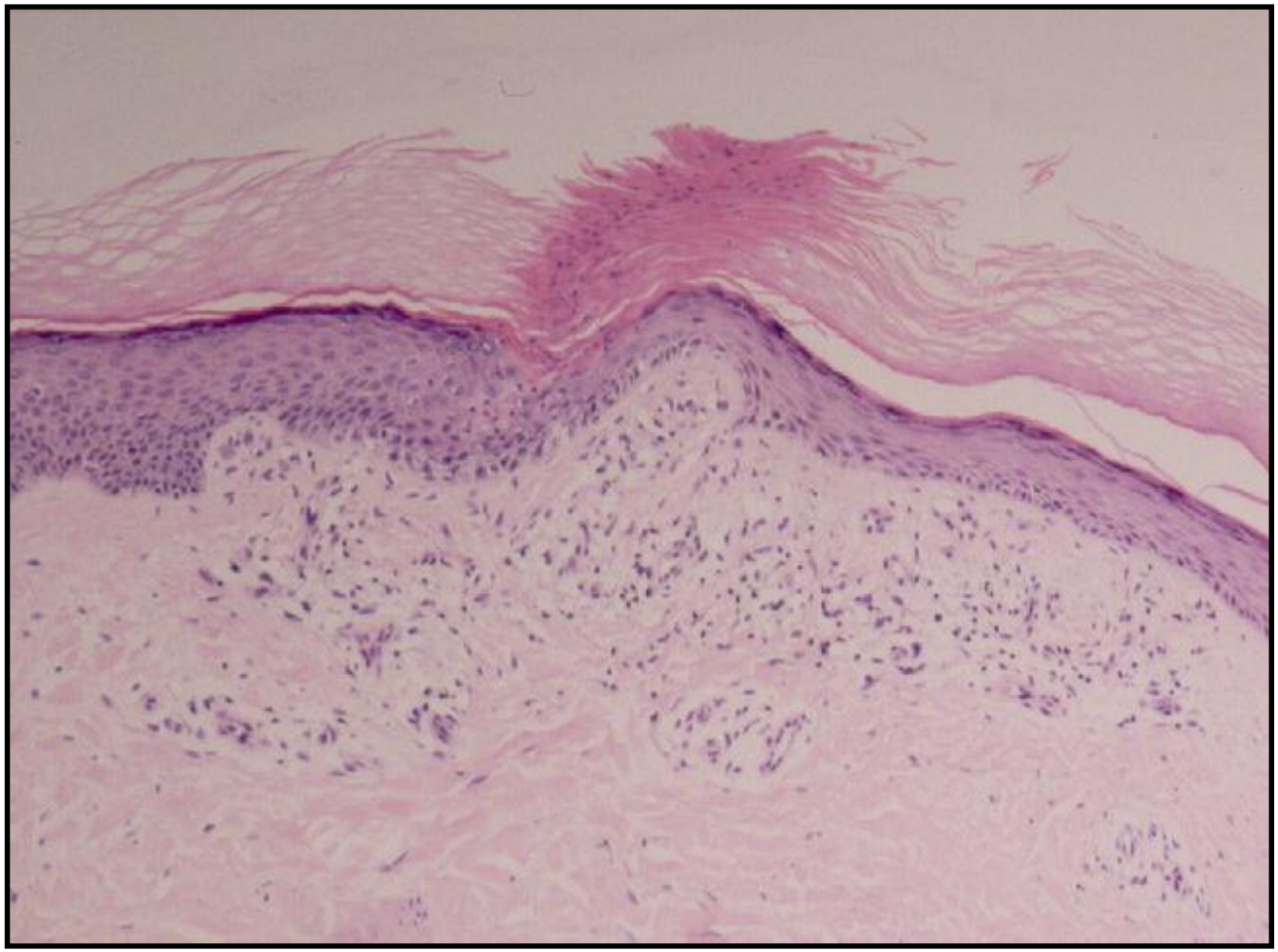




Case 10

- 31 yr female, scaly rash (site not stated)

Porokeratosis



- Two main clinical subtypes
  - Disseminated superficial actinic (DSAP)
  - Porokeratosis of Mibelli
- Cornoid lamella
- Loss of granular layer beneath

References

- Weedon – Skin pathology
- Diaz et al 2000 End of the century overview of skin blisters. Arch Dermatol 136, p106-112