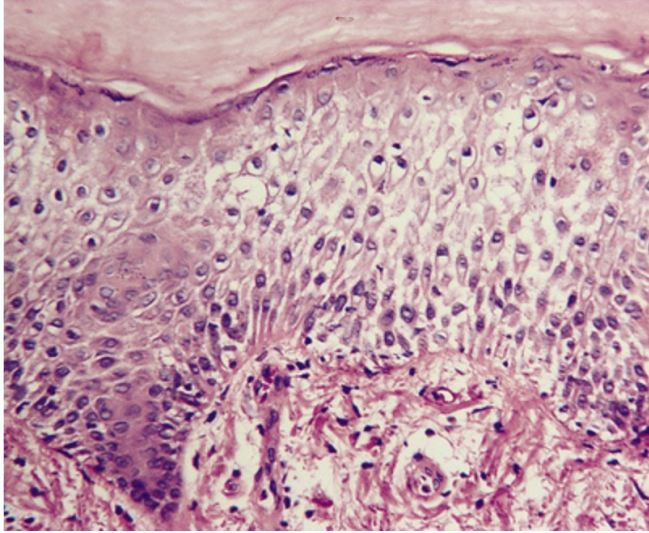


# Vesiculobullous Reactions

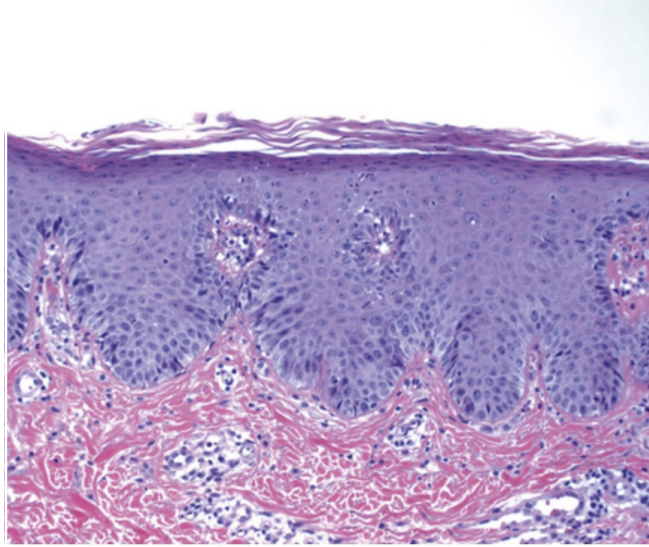
Soheil Sam Dadras MD-PhD

# Tissue reaction patterns



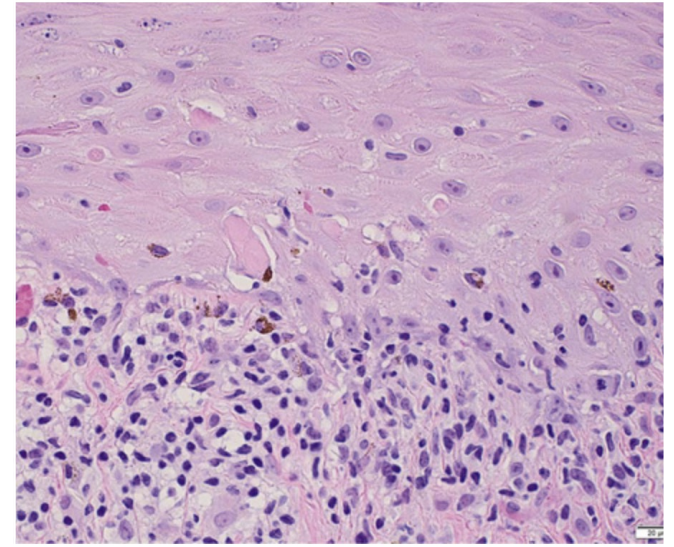
Atopic dermatitis

Spongiotic



Psoriasis

Psoriasiform

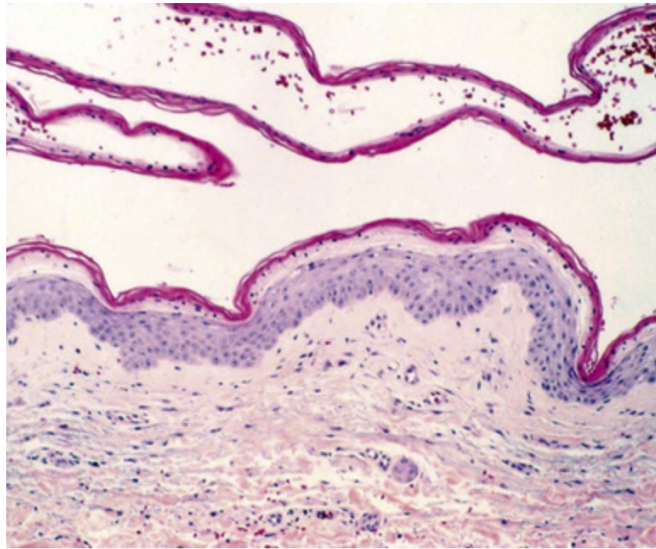


Lichen planus

Lichenoid

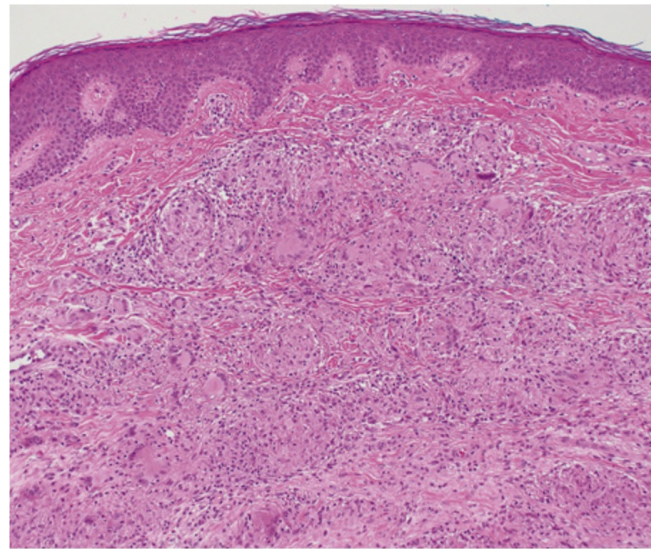


# Tissue reaction patterns



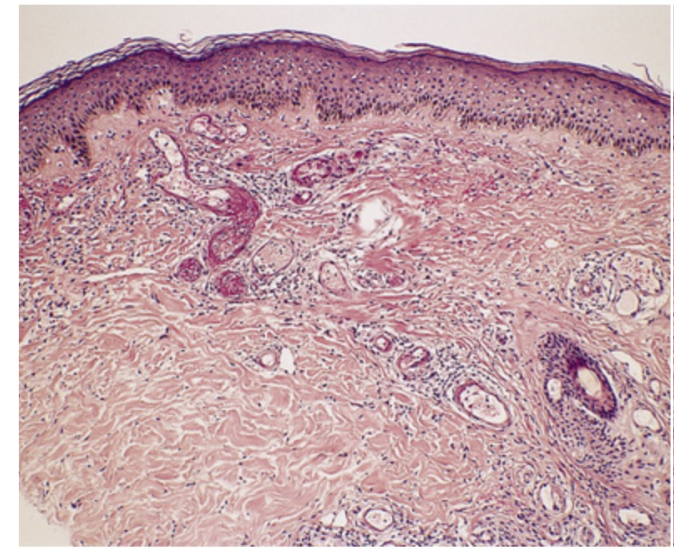
Bullous pemphigoid

Vesiculobullous



Granuloma annulare

Granulomatous



Atrophie blanche

Vasculopathic

# Blistering disorders (epidermis or mucosa)

## Vesicles (vesiculum)

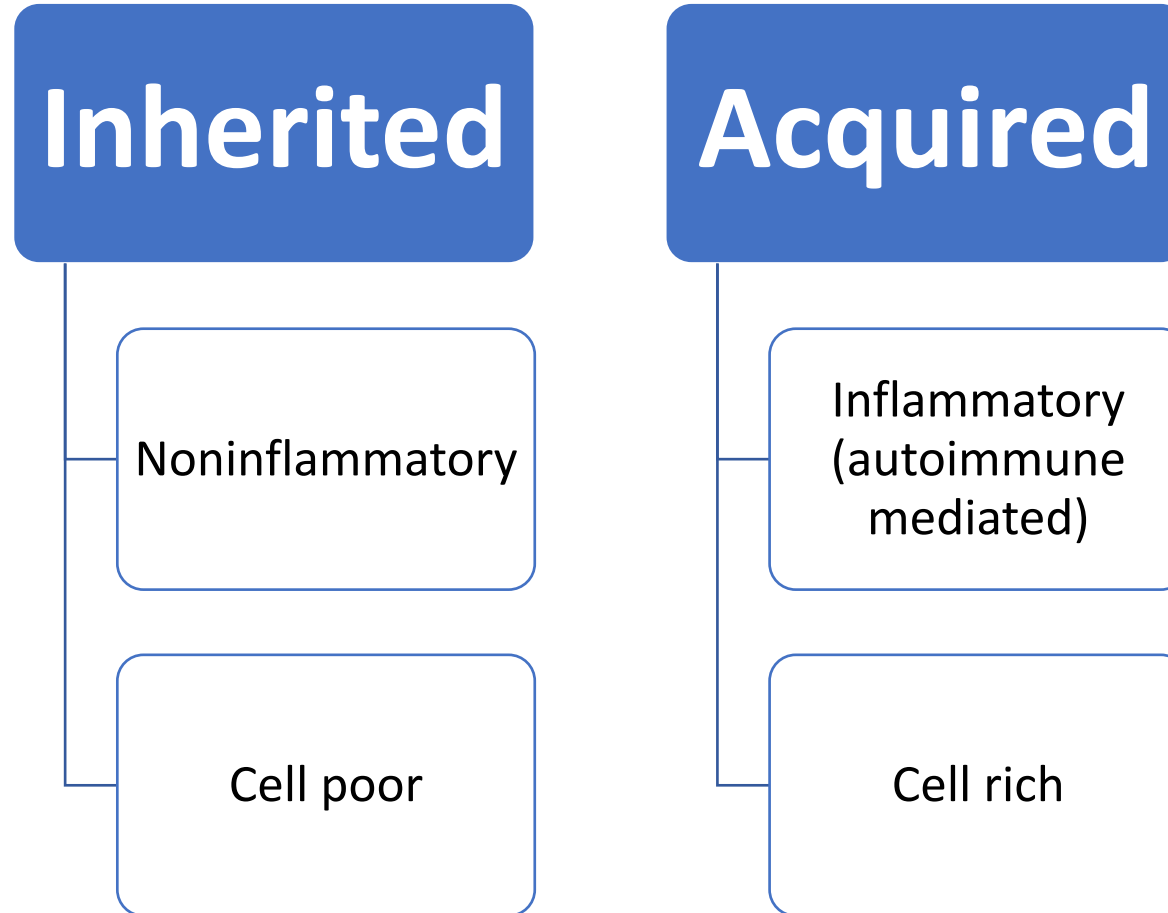
- Bladder
- > 0.5 cm
- Biopsy perilesional (normal skin) for DIF

## Bullae

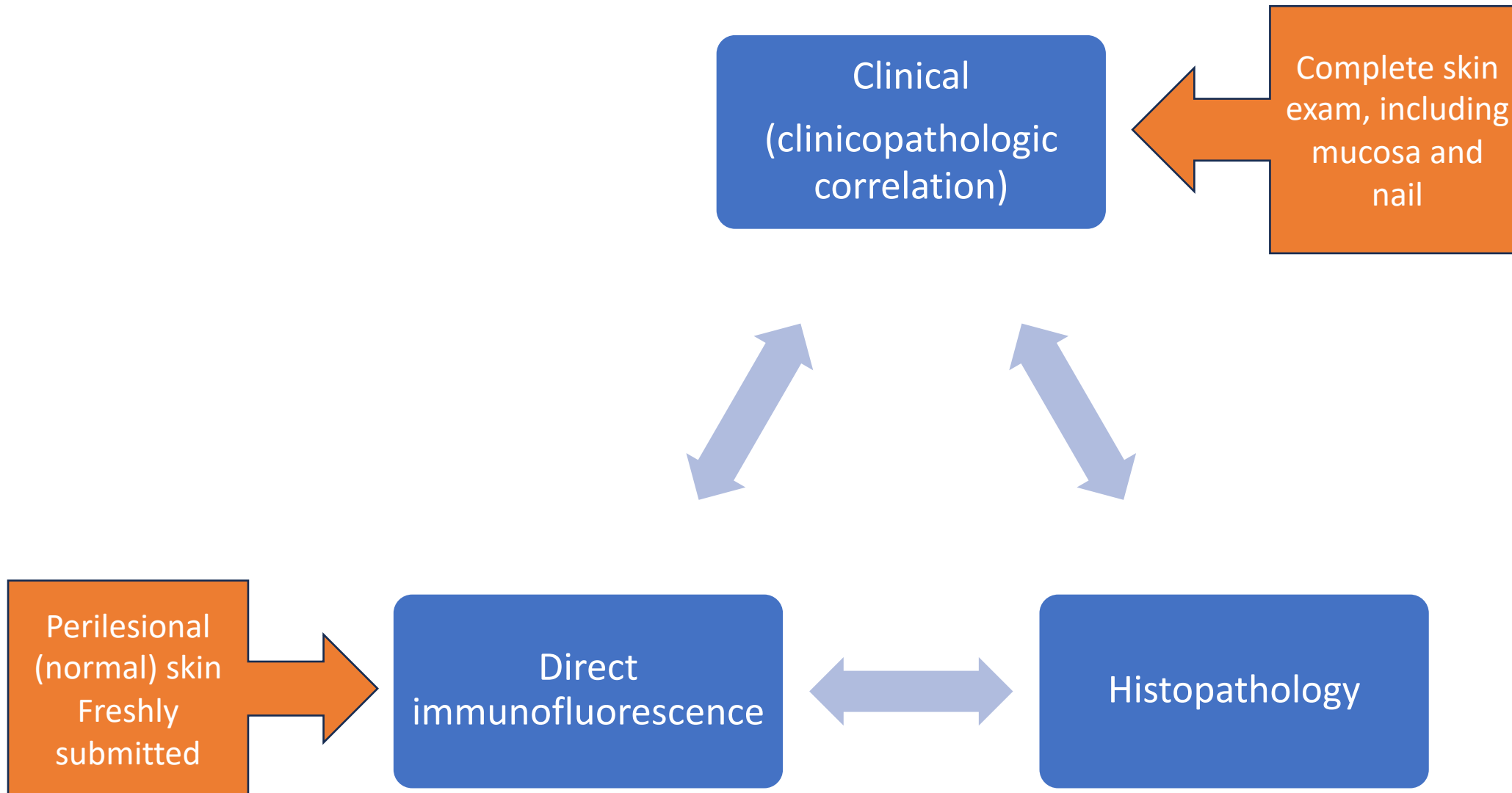
- Bubble
- < 0.5 cm
- Biopsy perilesional (normal skin) for DIF



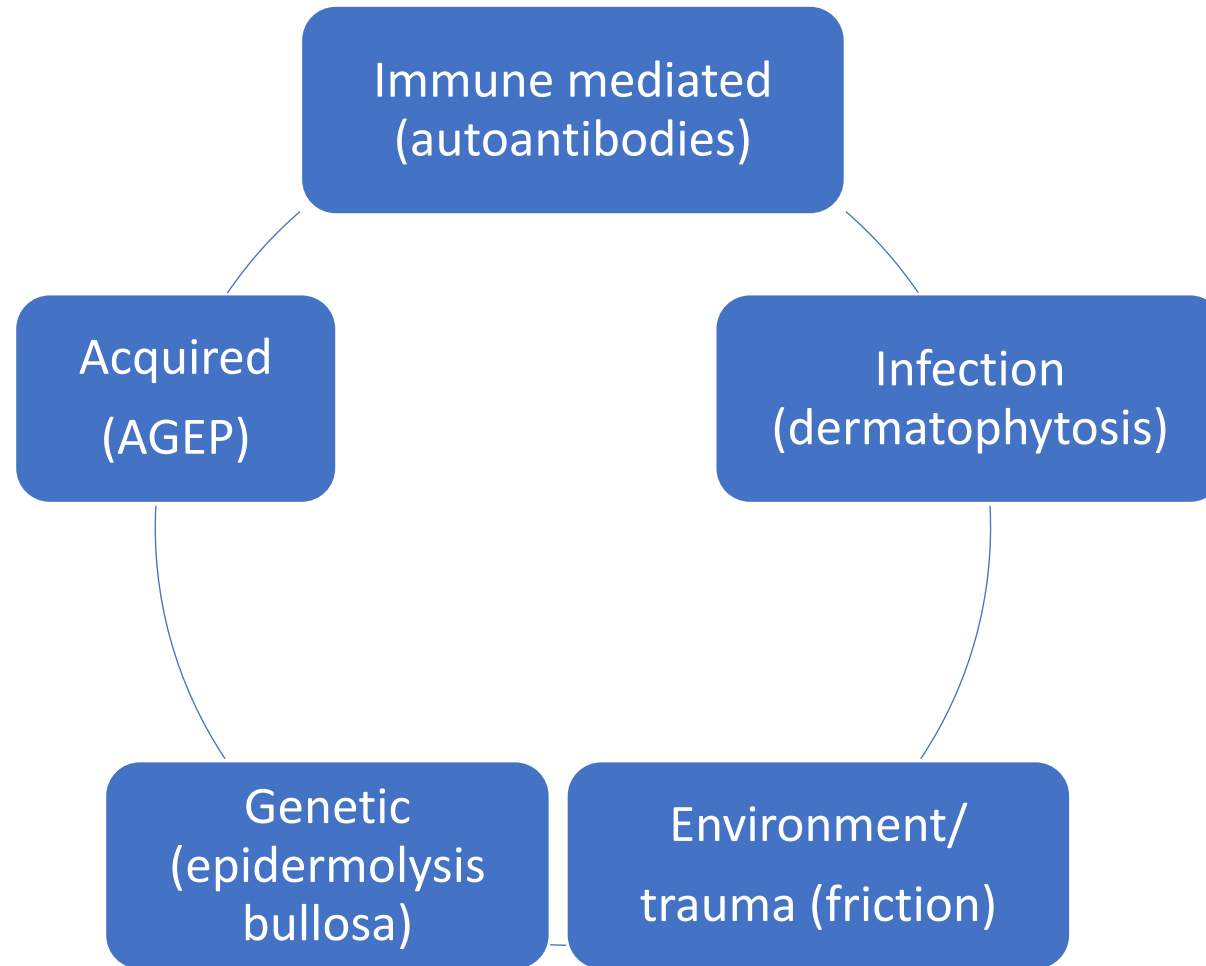
# Vesiculobullous reactions generalized



# The key to making accurate diagnoses in vesiculobullous disorders

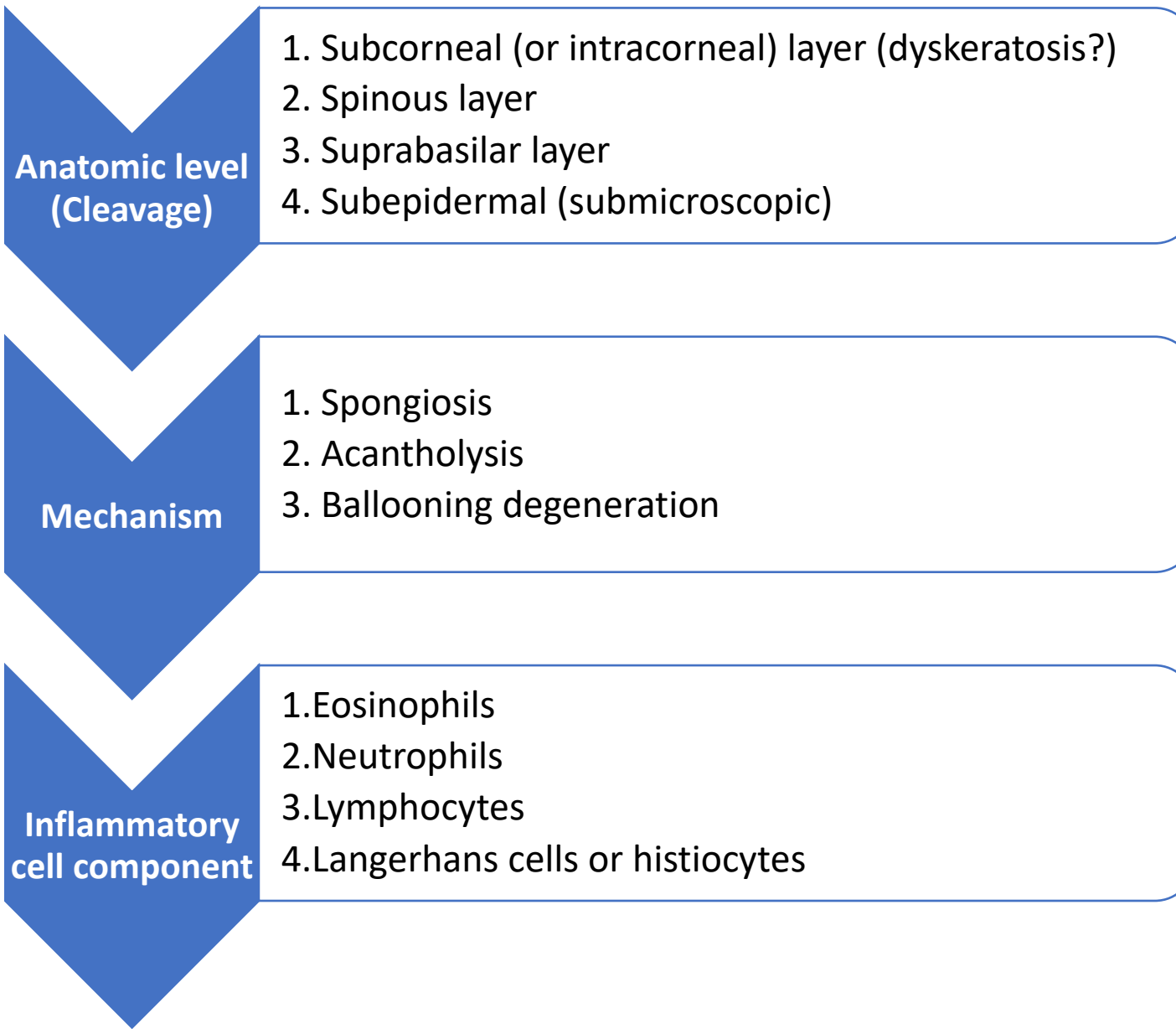


# Causes of vesiculobullous reactions



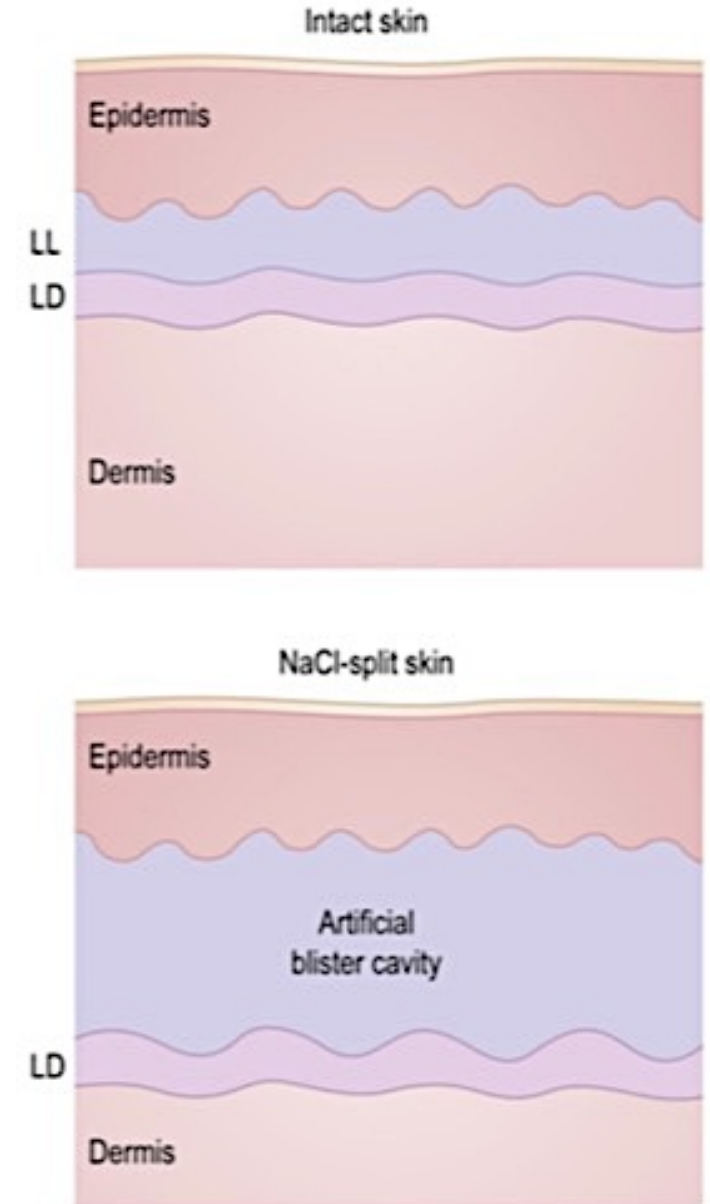


# Assessment of morphology in blistering disorders

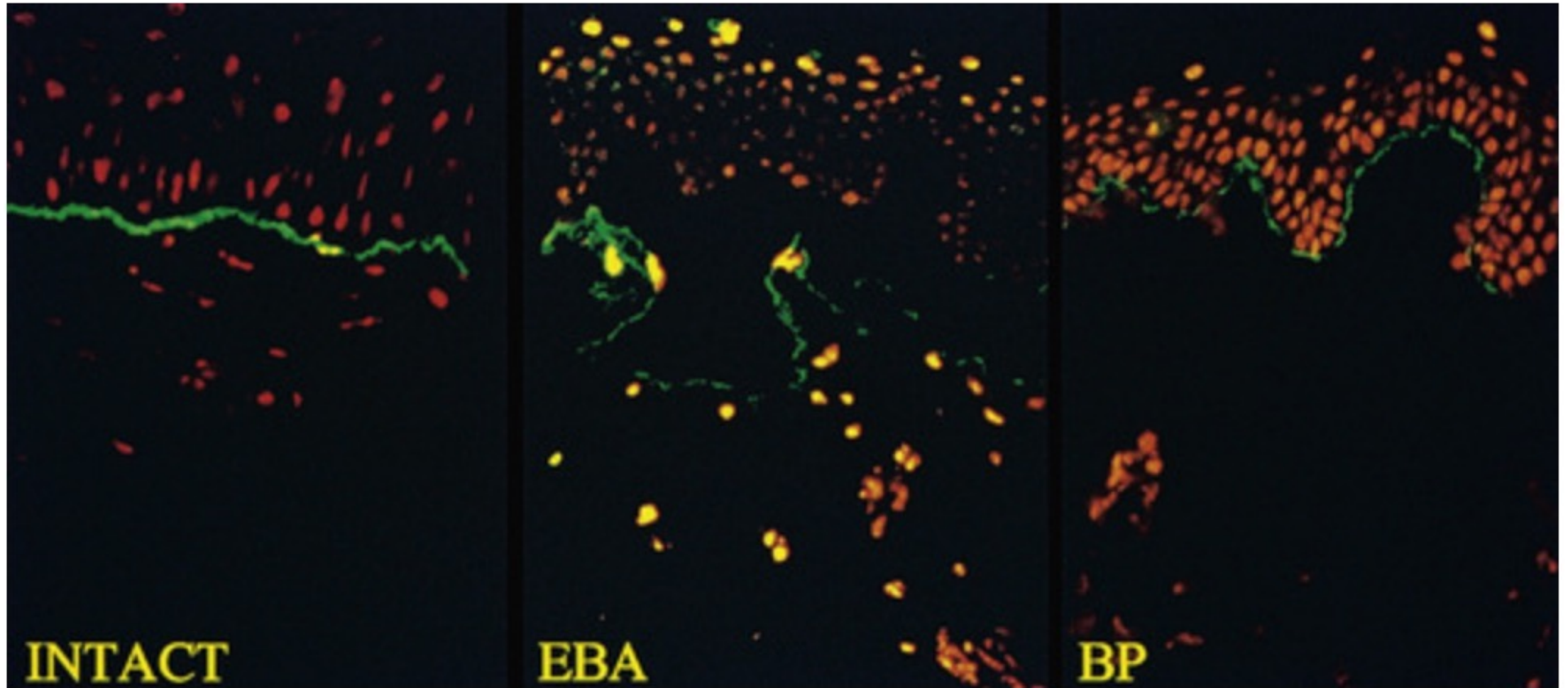


# Special techniques in characterizing blistering disorders

- Electron microscopy (submicroscopic)
- Split-skin immunofluorescence
  - Indirect immunofluorescence by 1M NaCl for 48 hours at 4°C
  - Artificially splits through lamina lucida
- Immunohistochemical mapping by collagen IV
- Direct immunofluorescence (DIF)
  - Perilesional skin
  - Freshly submitted in Zeus or Michel's solution
  - IgG, IgA, IgM, C3 and fibrinogen



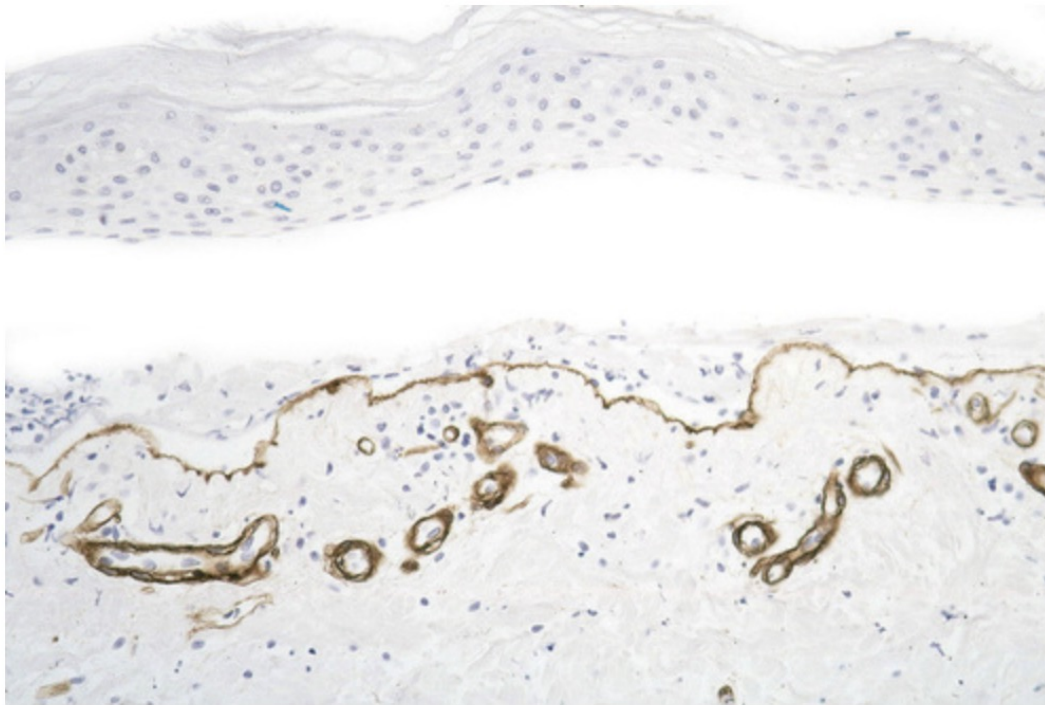
# Split-skin immunofluorescence



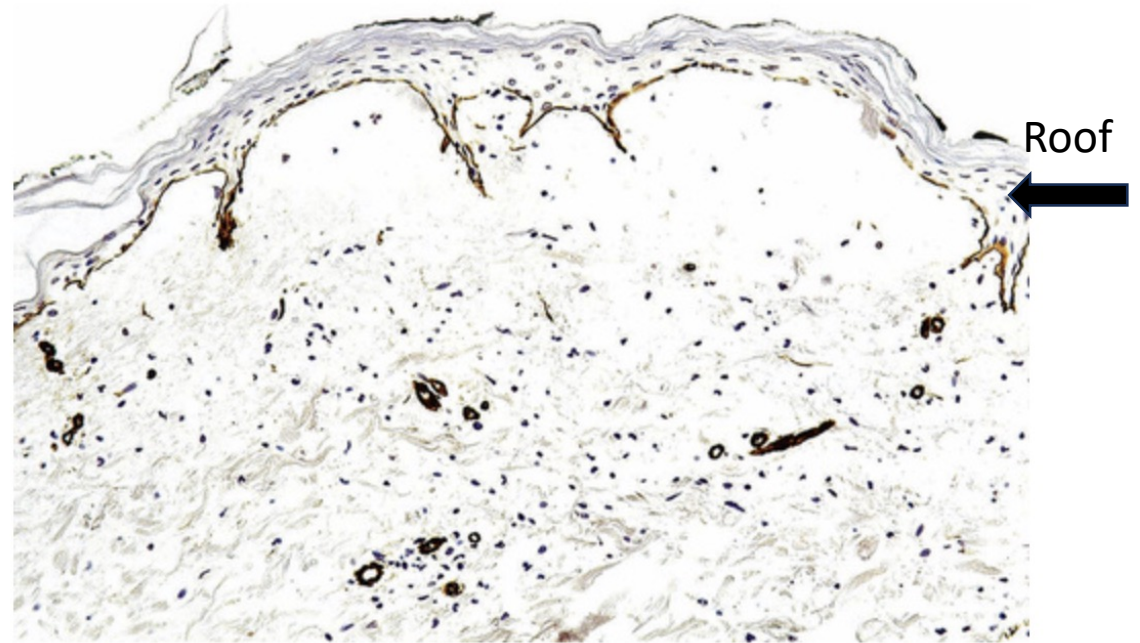


# Immunohistochemical mapping by collagen type IV

**Bullous pemphigoid**



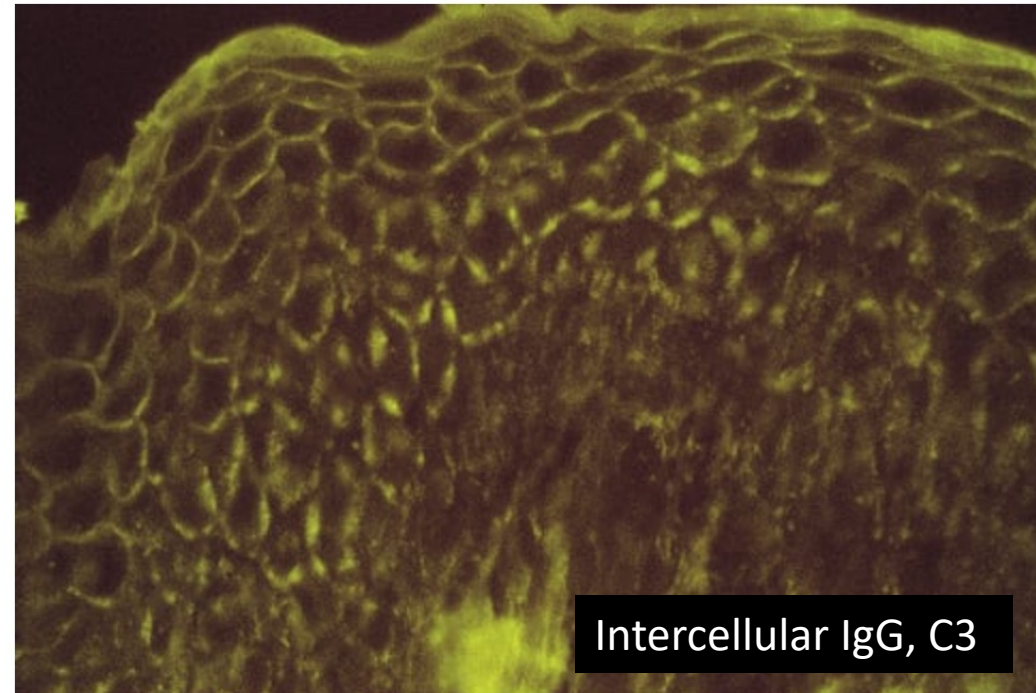
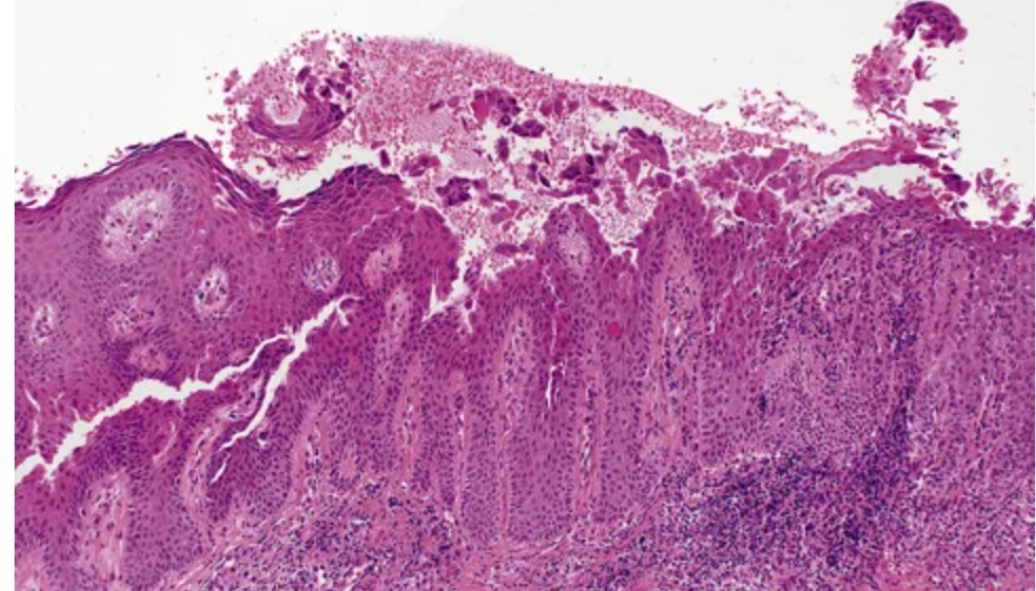
**Epidermolysis bullosa acquisita**



# Intracorneal and subcorneal blisters

- Superficial pemphigus disease group
  - Variants: foliaceous, erythematous, and herpetiform
- Acute generalized exanthematous pustulosis (AGEP)
- Impetigo
- Staphylococcal scalded skin syndrome
- Dermatophytosis
- Subcorneal pustular dermatosis

Denuded stratum corneum and Dyskeratosis

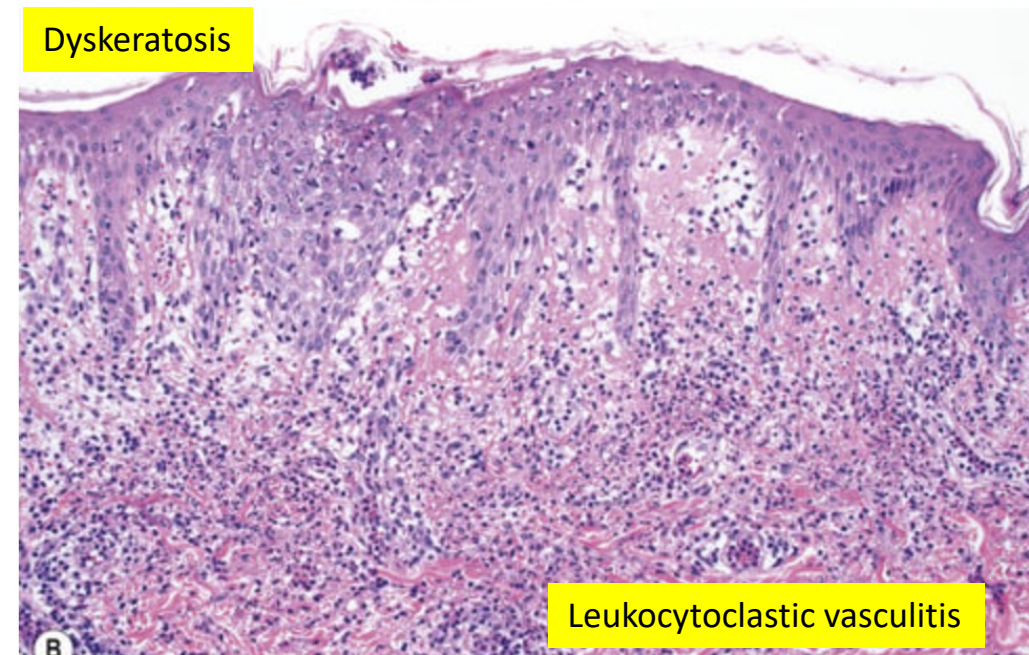
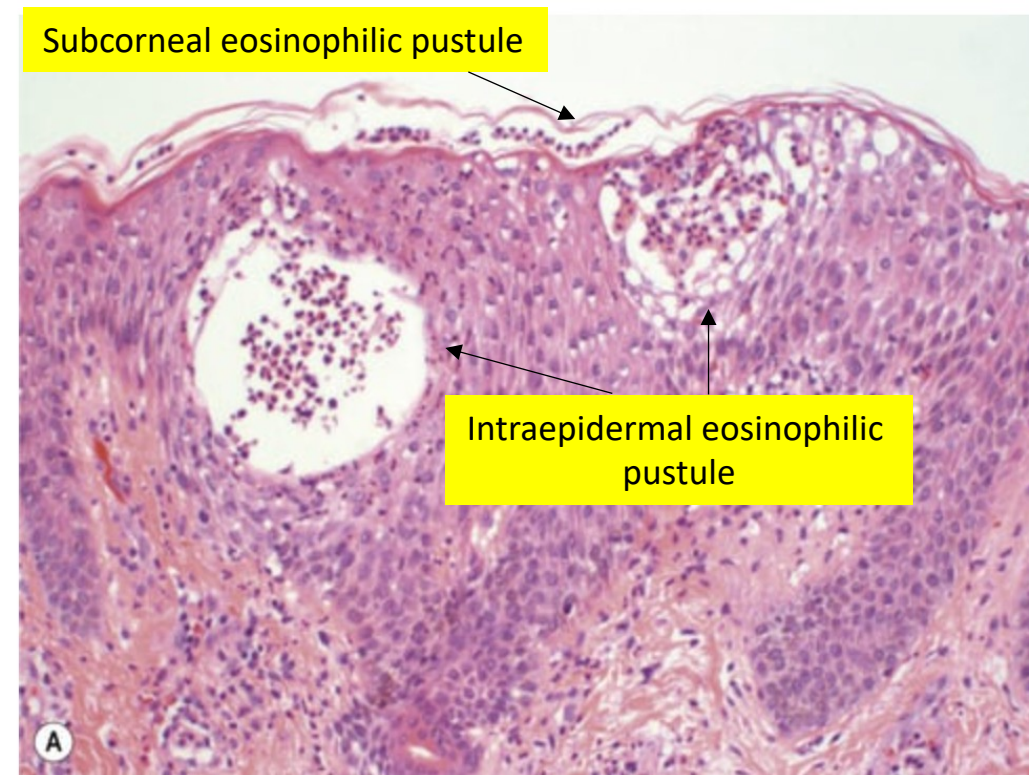


Intercellular IgG, C3



# Acute generalized exanthematous pustulosis (AGEP)

- Rapidly evolving, pustular eruption
- Sterile, miliary pustules on erythematous ground with targetoid appearance
- Develop hours to days after ingestion of beta-lactam, cephalosporin and macrolide drugs
- Histopathology: subcorneal/intraepidermal pustules with eosinophils and neutrophils
  - Dyskeratosis and  $\pm$  Leukocytoclastic vasculitis

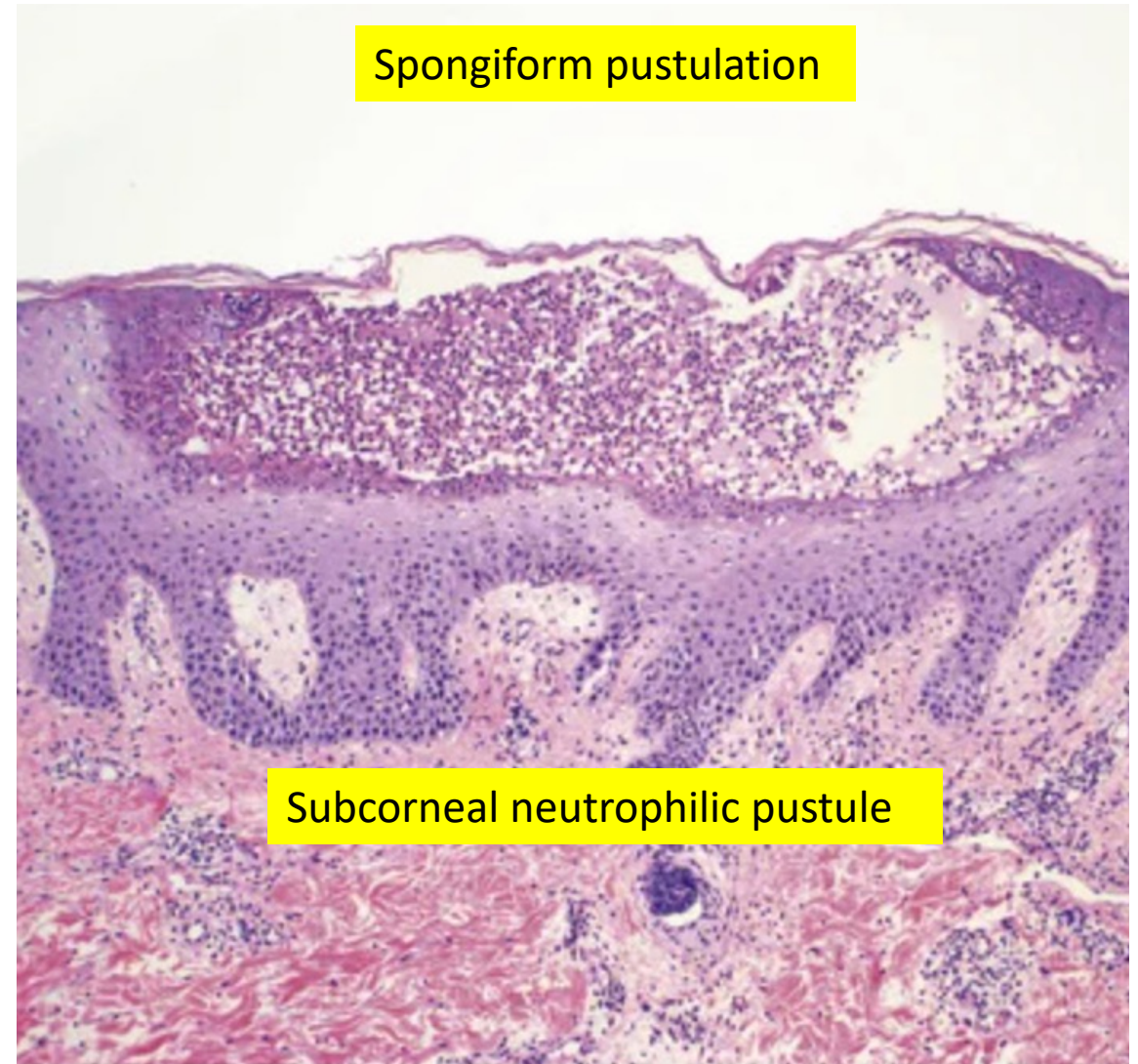




# Subcorneal pustular dermatosis

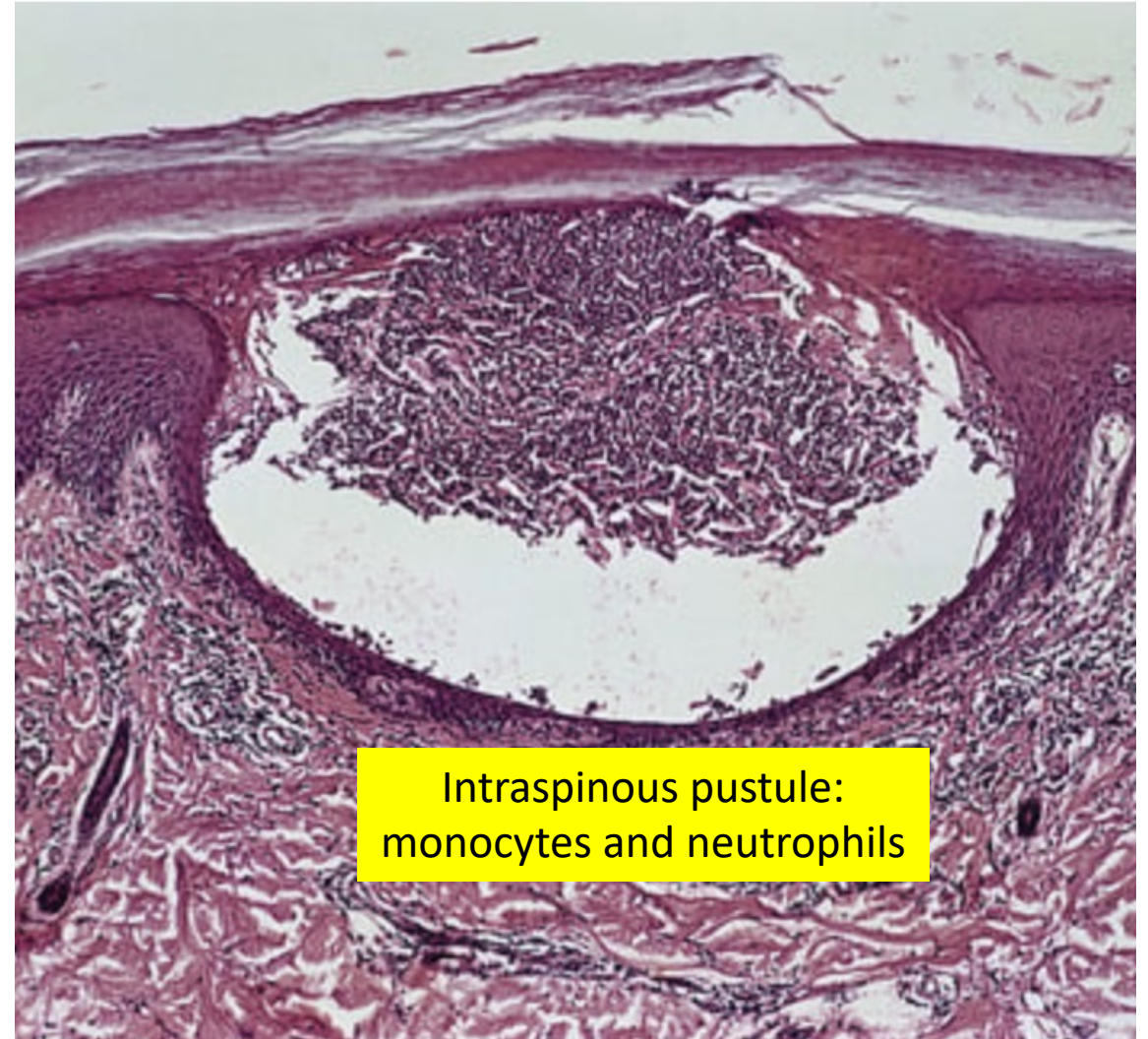
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- Chronic, relapsing vesiculopustular eruption on the trunk, intertriginous areas, and limbs (flexor surface)
- Unknown pathogenesis
- Associated monoclonal gammopathy (IgA or IgG)
  - IgA pemphigus
- DIF negative



# Intraepidermal blisters

- Anatomic level of separation: spinous layer (not subcorneal or superbasilar)
- Spongiotic blistering disorders
  - Acrodermatitis enteropathica
  - Acrokeratosis paraneoplastica
  - Palmoplantar pustulosis
- Viral blistering disorders
  - Herpes, hand, foot and mouth, disease, milker's nodule, and orf
- Friction blister



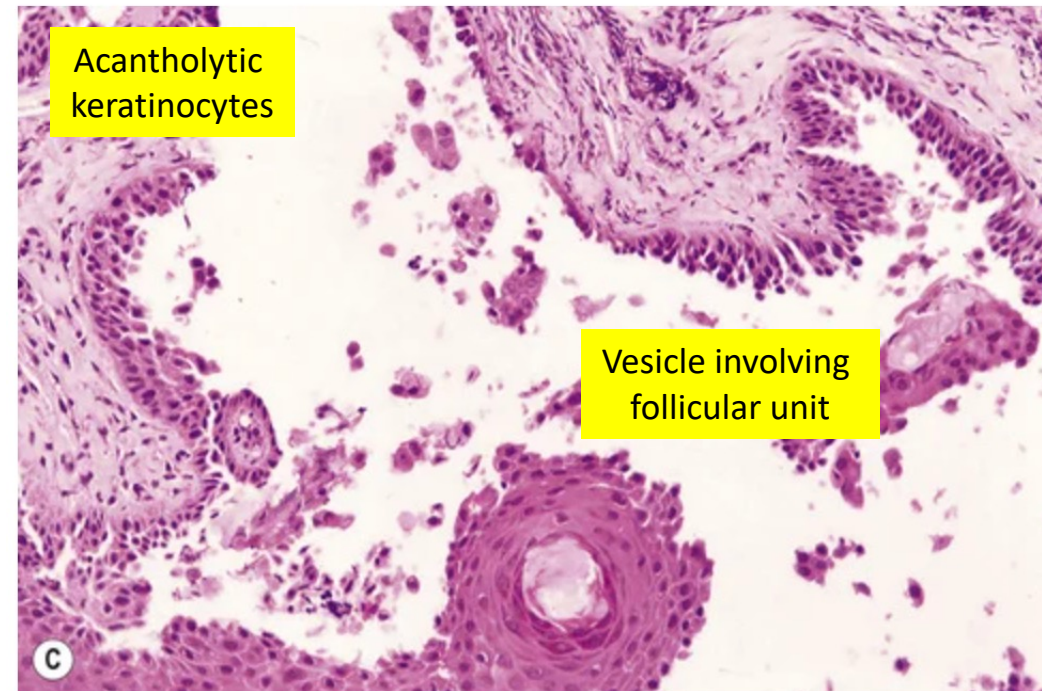
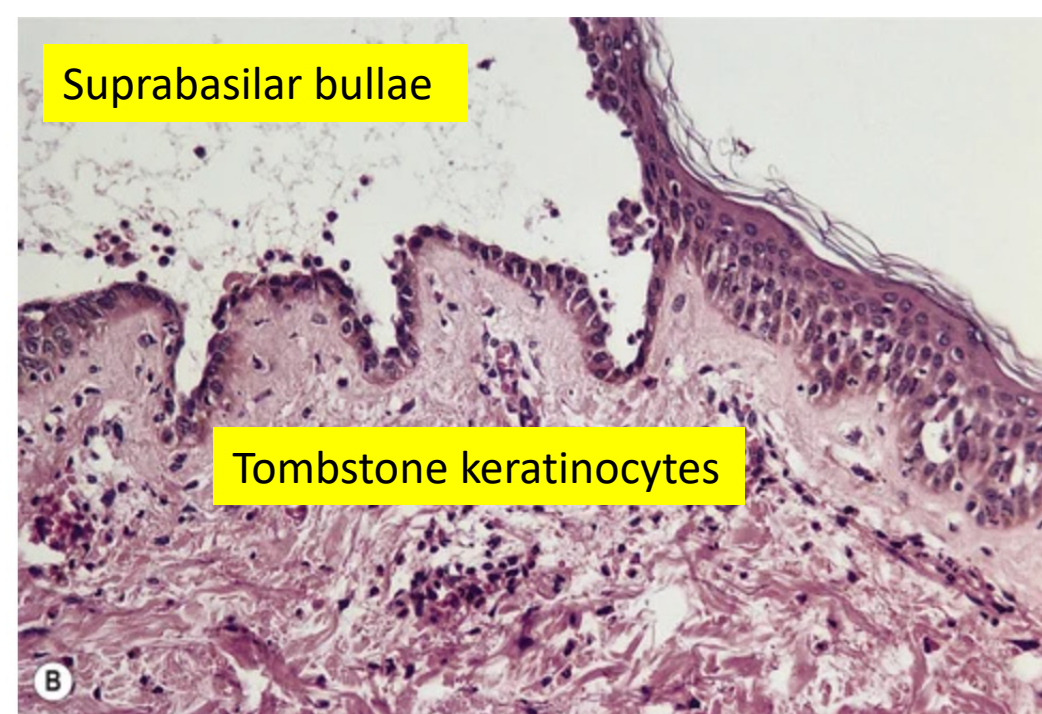
Intraspinous pustule:  
monocytes and neutrophils

Palmoplantar pustulosis



# Suprabasilar blisters

- Above the basilar keratinocytes
- Pemphigus vulgaris, pemphigus vegetans, Hailey–Hailey disease (familial benign chronic pemphigus), Darier's disease, Grover's disease (transient acantholytic dermatosis), and acantholytic actinic keratosis
- Superbasilar bullae with acantholysis
- Tombstone sign: Basal keratinocytes lose their intracellular bridges, but remain attached to the dermis

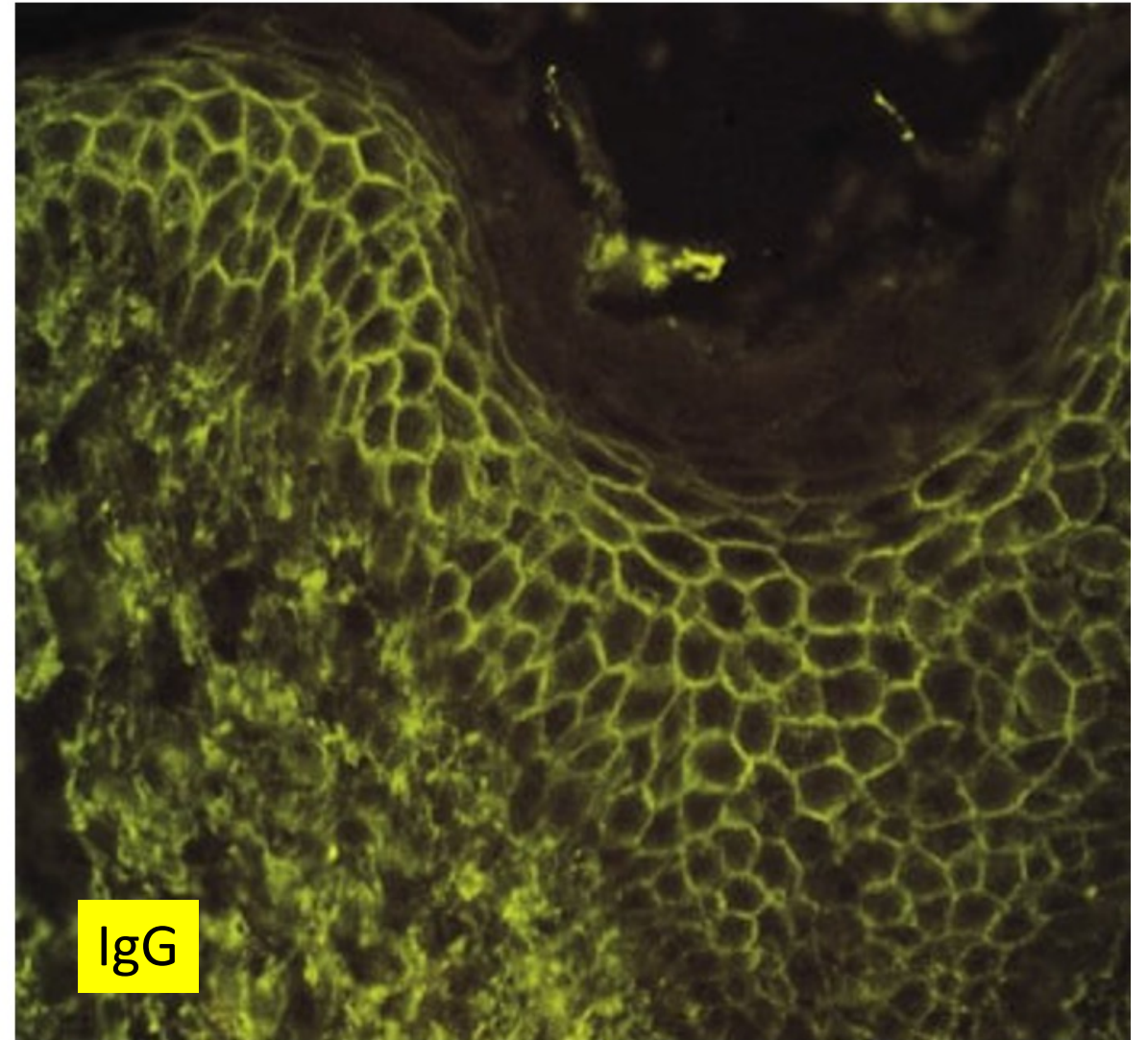




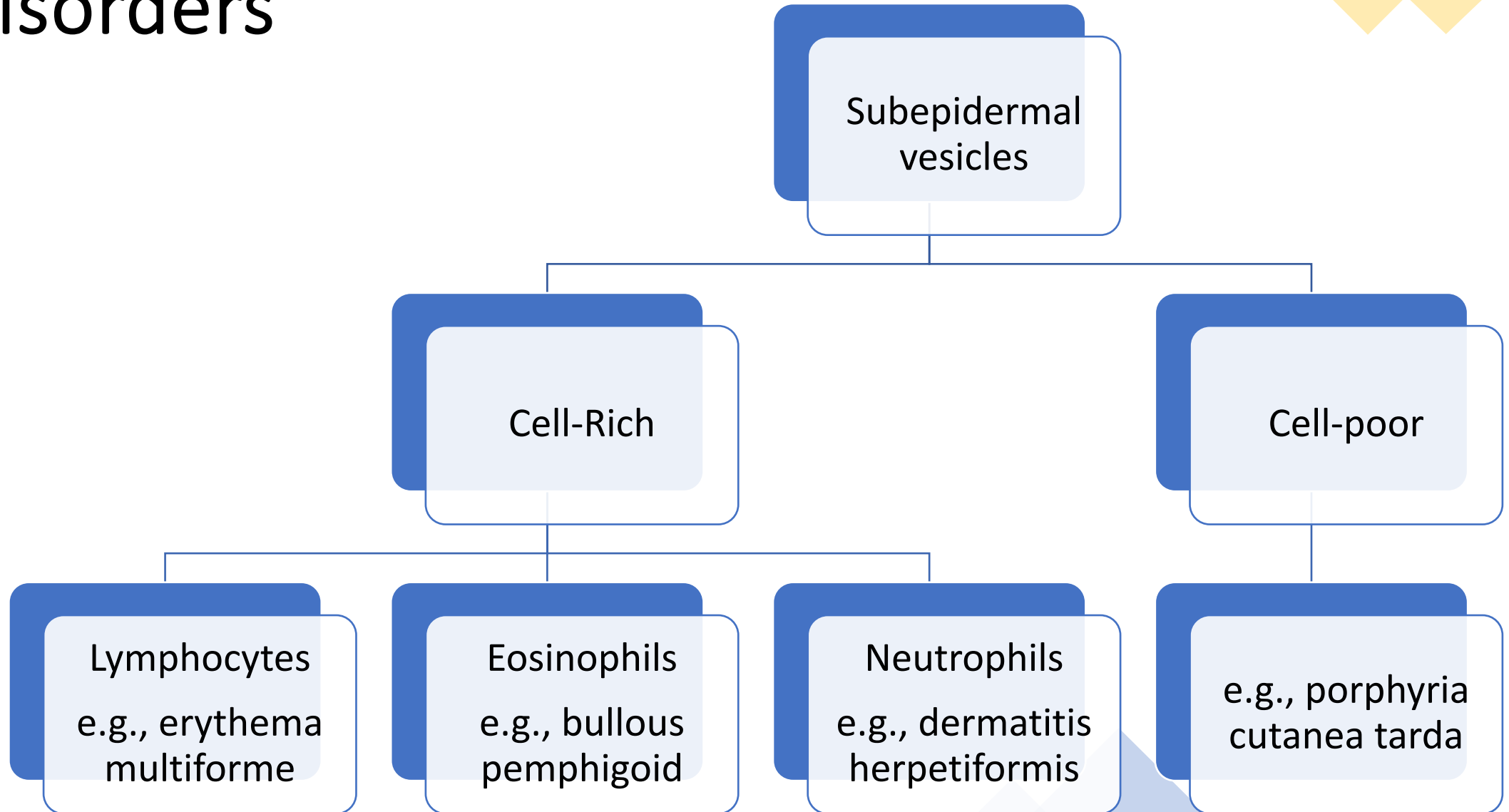
# Pemphigus vulgaris

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- DIF: IgG net-like intercellular pattern
- Lower layers of keratinocytes
- Can show follicular reaction
- Circulating intercellular antibodies in 80-90% of patients
- Antibodies directed against desmoglein 3, disrupting cell-cell adhesion
- Monkey esophagus as substrate



# Classification of subepidermal blistering disorders



## Porphyria cutanea tarda



Preservation of dermal papillae (festooning)

Cell-poor vesicle

Hyaline material (PAS+ DR) in BM or around BVs

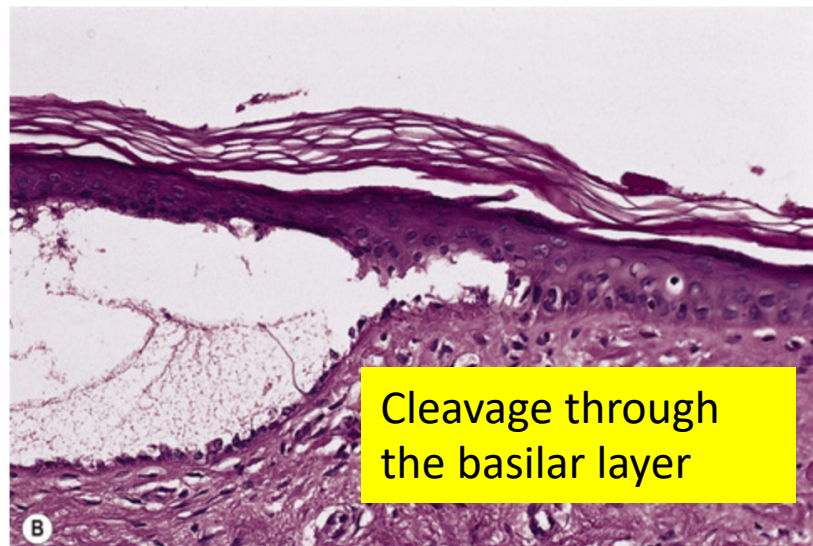
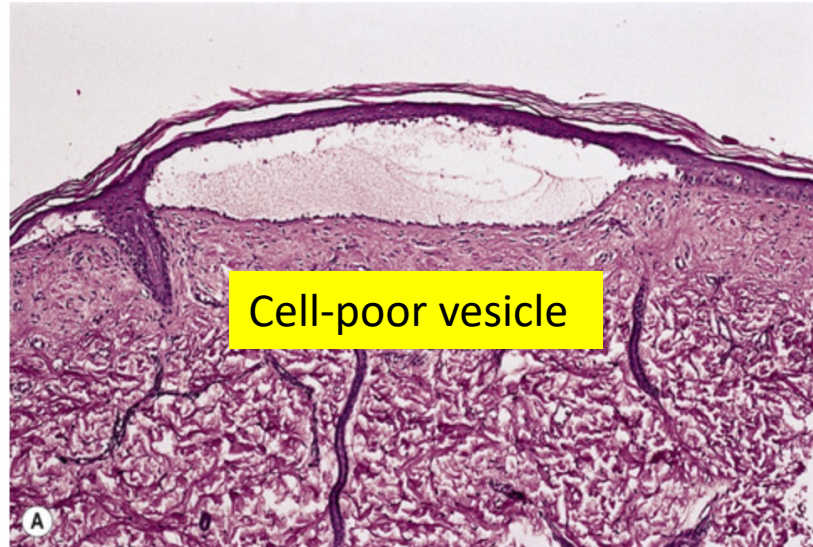
## Subepidermal blistering disorders

- Subepidermal blisters with little inflammation
  - Epidermolysis bullosa, porphyria cutanea tarda, cell-poor variant of BP, burns, toxic epidermal necrolysis, suction blisters, blisters over scar or solar elastosis, amyloid and IgM deposits, and bullous drug reactions



# Epidermolysis bullosa

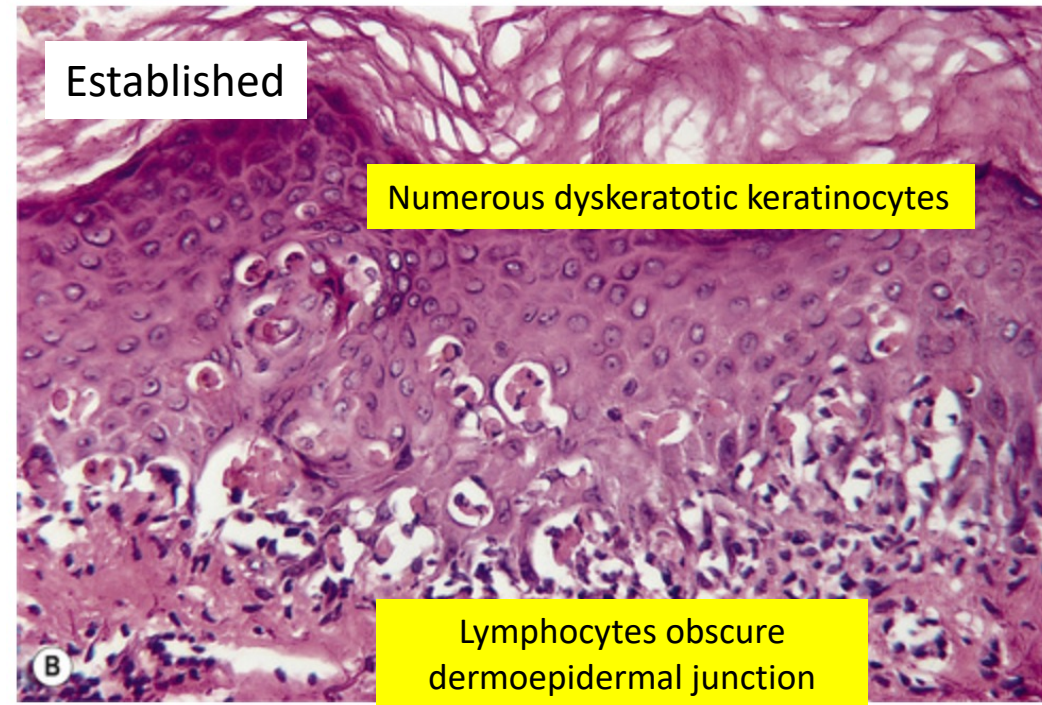
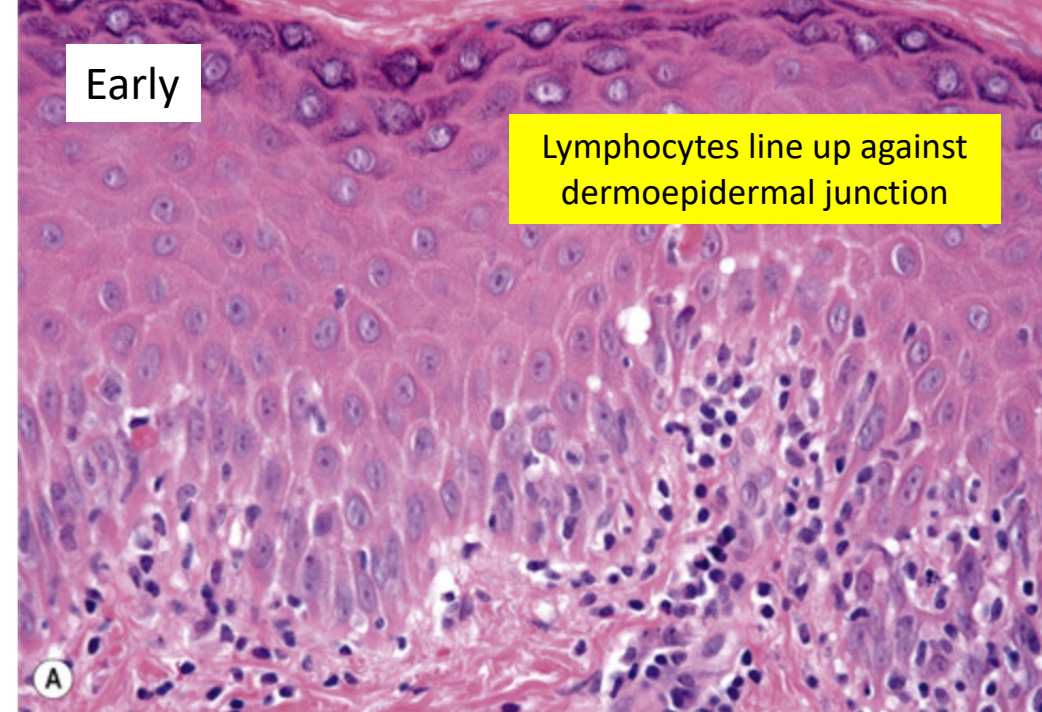
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- Inherited (autosomal dominant), heterogenous group
- Development of blisters/erosions after minor trauma (mechanobullous disorder)
- Epidermolysis bullosa simplex (EBS)
  - One of the major subgroups
  - Intraepidermal cleavage through the basilar keratinocytes
  - Defects in keratin 5 and 14 (assembly, structure and function)

# Erythema multiforme

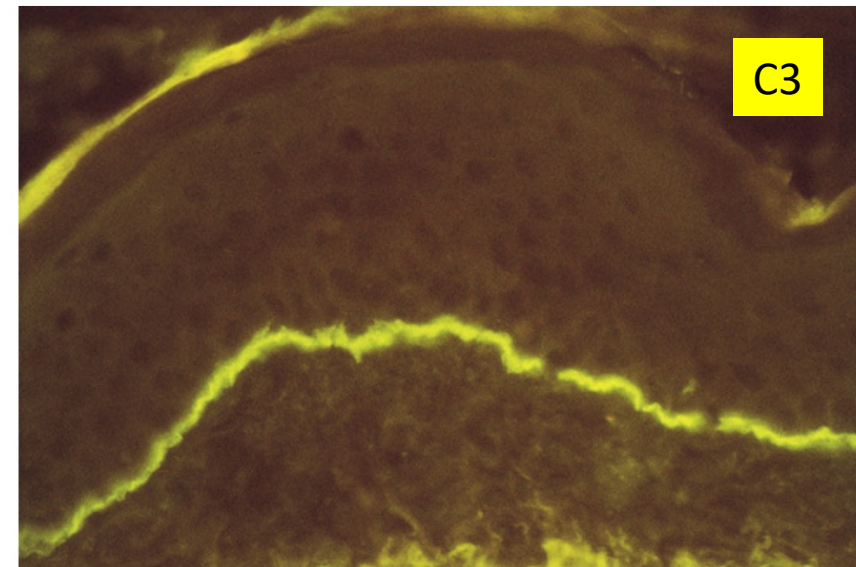
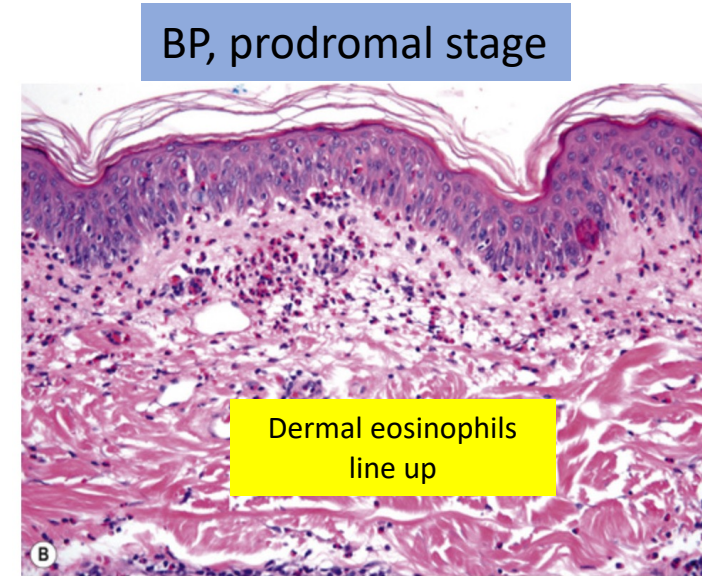
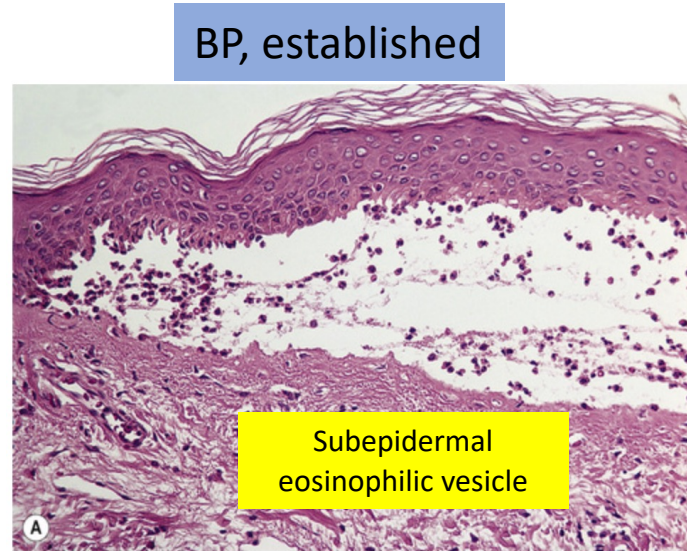
- Self-limited, episodic
- May involve the mucous membranes
- Pleomorphic eruption of erythematous macules, papules, urticarial plaques, and vesicles
- Stevens-Johnson/toxic epidermal necrolysis syndrome with systemic symptoms and involvement of internal organs
- Subepidermal blisters with lymphocytes (cell-rich)





# Subepidermal blisters with eosinophils

- Eosinophils are conspicuous and major component of the inflammation in vesicles and dermis
  - Bullous pemphigoid, pemphigoid gestationis, and arthropod bite reactions, and bullous drug reactions
- Dermatitis herpetiformis (older lesion), cicatricial pemphigoid, and Wells' syndrome

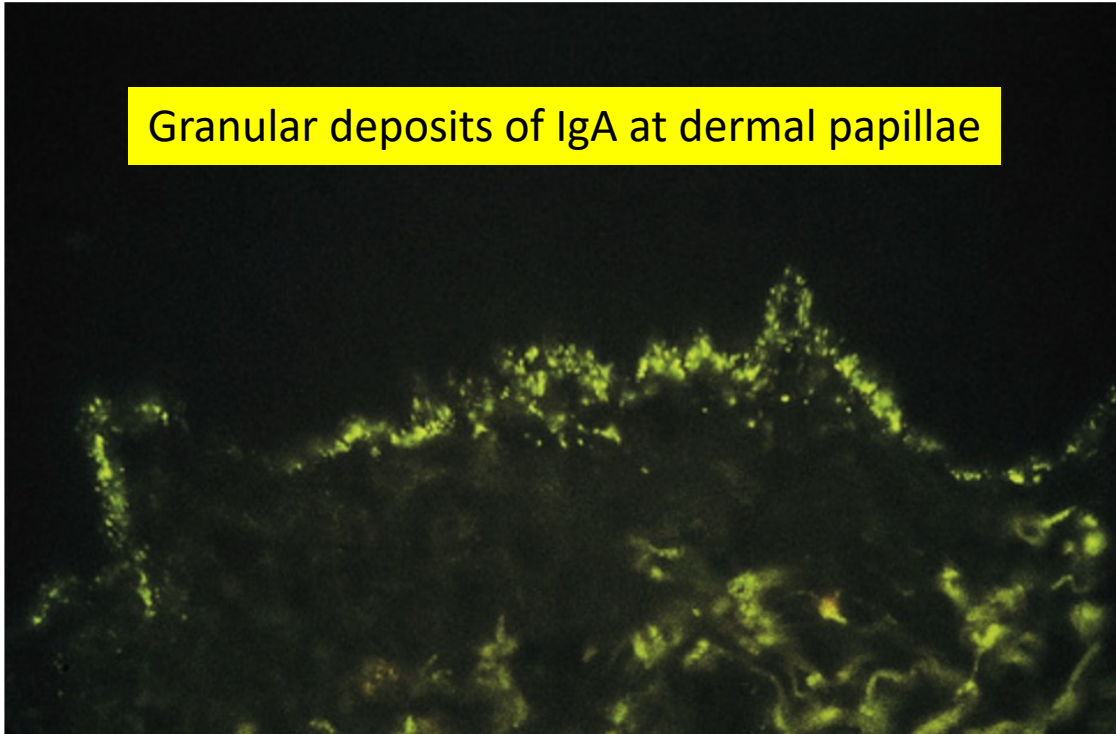


DIF on relational skin: linear C3 and IgG

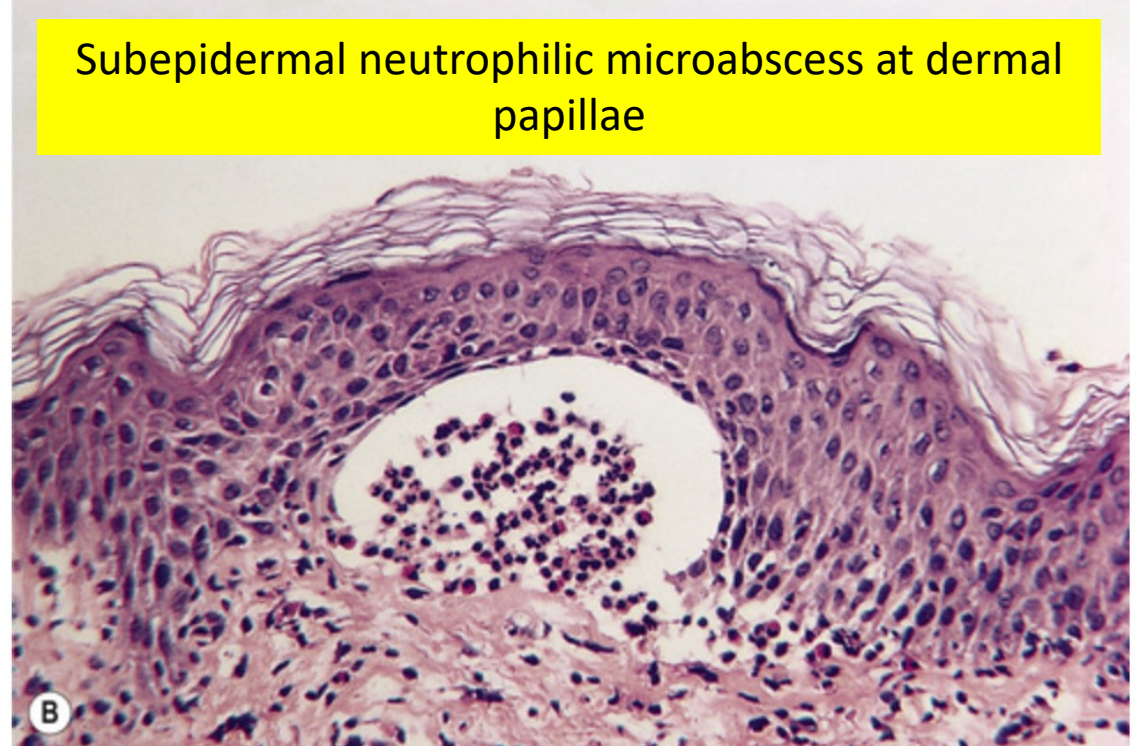
# Dermatitis herpetiformis

- High incidence of gluten-sensitive enteropathy
- Autoantibodies to transglutaminase
- Herpetiform grouping of papulovesicles
  - on extensor elbows, knees, and scalp

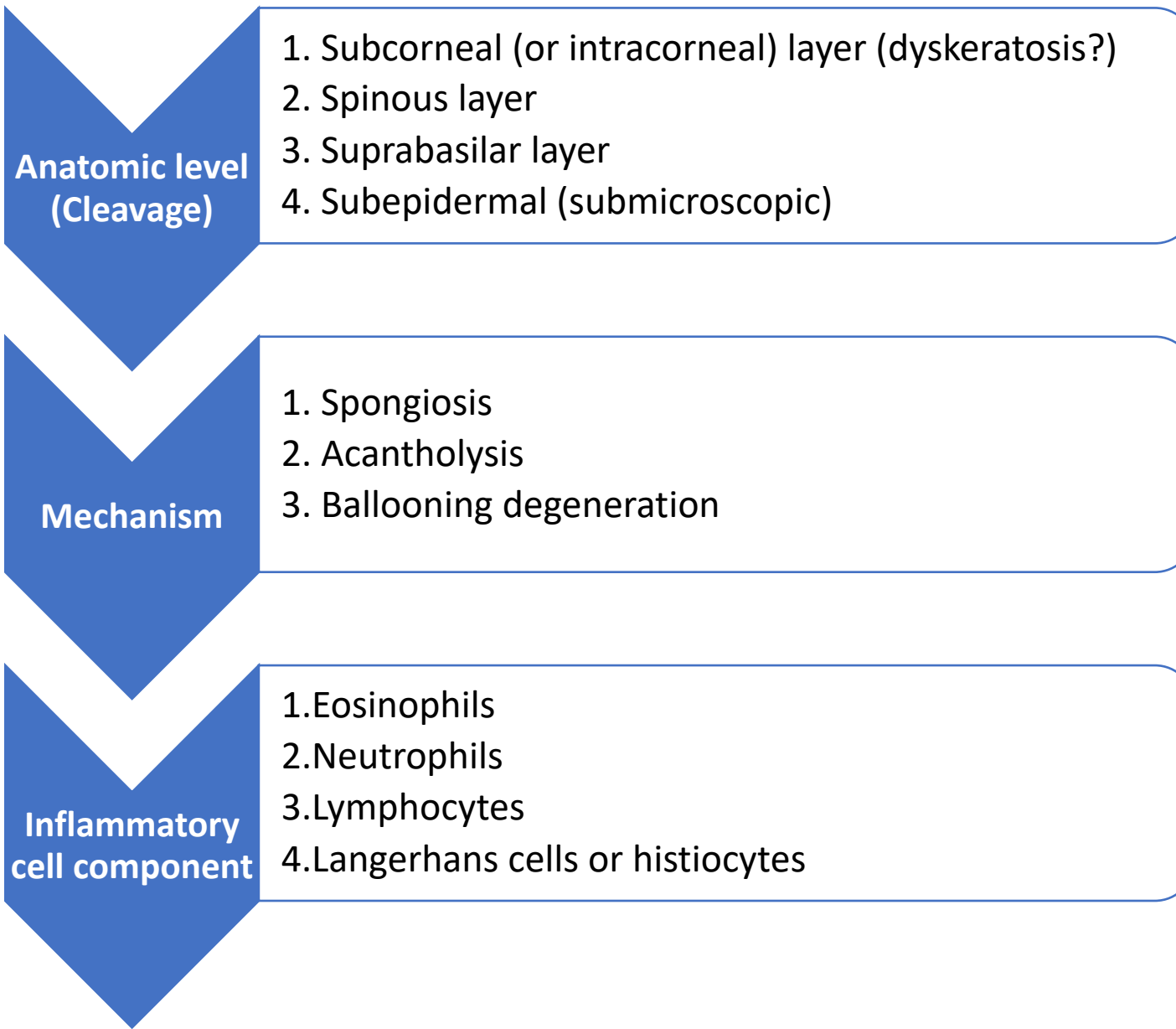
Granular deposits of IgA at dermal papillae



Subepidermal neutrophilic microabscess at dermal papillae



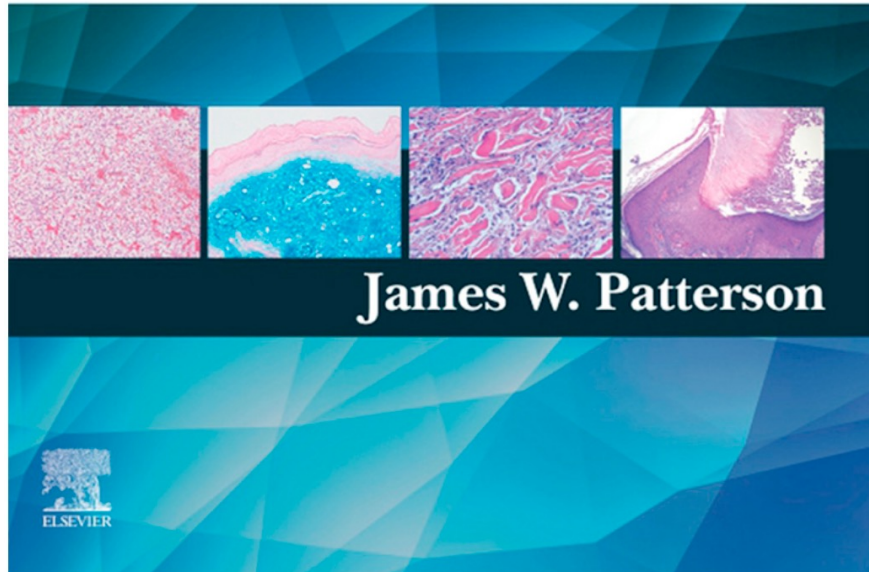
# Assessment of morphology in blistering disorders







Weedon's  
SKIN PATHOLOGY



# References

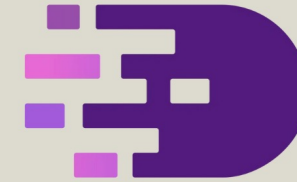
- Weedon's skin pathology
- McKee's pathology of the skin



# Digital Skin Pathology

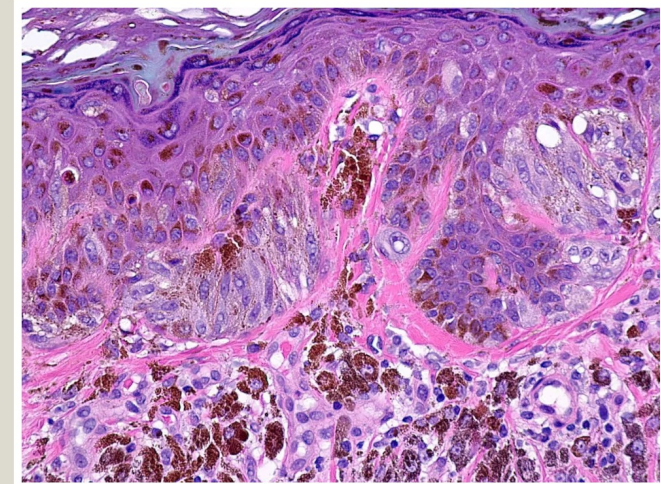
<https://digitalskinpathology.com/>

- Meet the challenges of the growing needs for dermatopathology knowledge
- Learn Dermatopathology based on actual real-life cases
- Residents of Dermatology and Pathology
- Dermatology PAs and NPs
- Primary MDs and general surgeons
- <https://digitalskinpathology.com/>



**DIGITAL SKIN PATHOLOGY (DiSK)**  
Learn Histologic Diagnosis Case-By-Case

**DERMATOPATHOLOGY: LEARN HOW TO  
DIAGNOSE SKIN DISEASES DERM PATH  
DIAGNOSTICS**



**Understand your patient's dermatopathology diagnostic report to provide better clinical care** (how to diagnose skin diseases). derm path diagnostics