

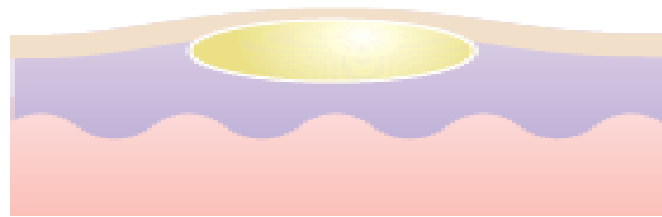
Bullous Skin Disorders (BSD)

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INTRODUCTION

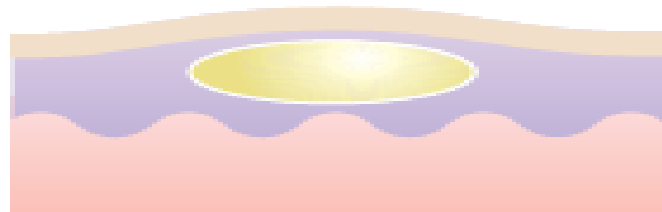
- BSD are skin conditions characterised by **blister** formation.
- A **blister** is an accumulation of fluid between cells of the epidermis or upper dermis.
- Causes of blister could be **genetic, physical, inflammatory, immunologic** and as a reaction to **drugs**.
- BSDs are mostly **autoimmune** .

Location of bullae



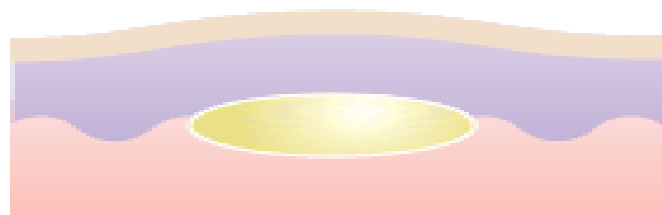
Subcorneal bulla

Bullous impetigo
Miliaria crystallina
Staphylococcal
scalded skin syndrome



Intra-epidermal bulla

Acute eczema
Viral vesicles
Pemphigus
Miliaria rubra
Incontinentia pigmenti



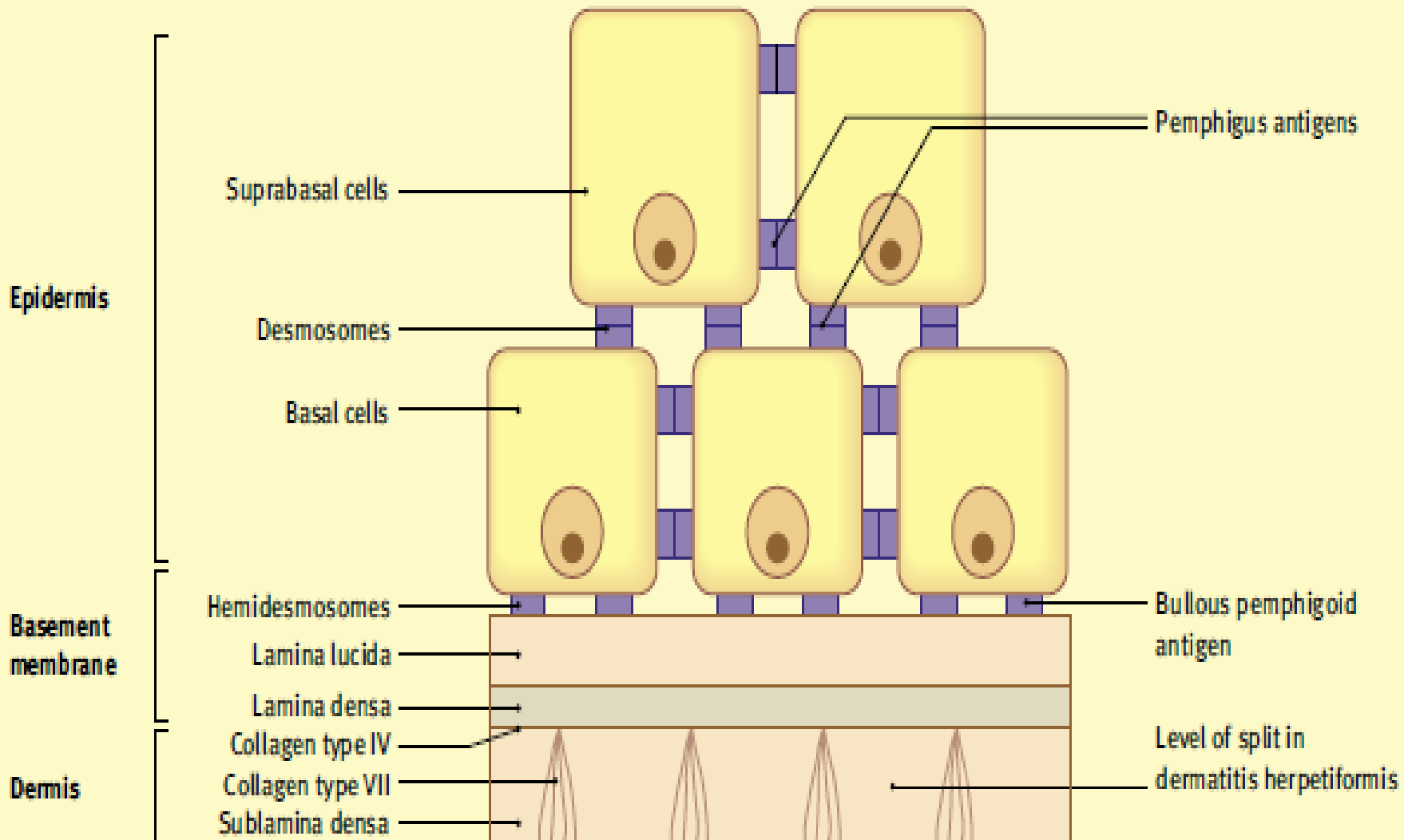
Subepidermal bulla

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

PATHOPHYSIOLOGY

- The keratinocytes of the epidermis are tightly bound together by **desmosomes** and intercellular subs to form a barrier of high tensile strength and stability.
- Beneath the epidermis lies the **basement membrane zone (BMZ)** , which is a specialised area of cell- extracellular matrix adhesion.
- Specialised structures traversing this zone anchor the epidermis to the dermis.
- The **BMZ** is particularly vulnerable to damage or malformation and is a common site of blister formation

Structure of the epidermis and sites of target antigens/cleavage in bullous diseases



Types:

1. Genetic Blistering Diseases:

- A. Epidermolysis Bullosa B . Hailey-Hailey disease (Benign familial pemphigus)

2. Immunobullous Diseases:

A. Intraepidermal Immunobullous Diseases:

1. Pemphigus Vulgaris (PV)
2. Pemphigus vegetans .
3. Pemphigus foliaceus
4. Pemphigus erythematosus
5. Paraneoplastic P

B. Subepidermal Immunobullous Diseases:

1. Bullous Pemphigoid
2. Linear IgA disease
3. Dermatitis Herpetiformis
4. Pemphigoid Gestations
5. Epidermolysis Bullosa Acquisita

IMMUNOLOGIC BULLOUS SKIN Dis.

These includes:

- **Pemphigus**
- **Pemphigoid**
- **Dermatitis Herpetiformis (DH)**
- **Chronic dermatoses of childhood (linear IgA dis.)**

PEMPHIGUS

- is derived from the Greek word *pemphix* meaning bubble or blister.
- A serious, acute or chronic, bullous autoimmune disease of **skin** and **mucous membranes** based on acantholysis.
- It is a severe and potentially life threatening diseases.
- **Types includes;**
 - P. vulgaris, vegetans, foliaceus, erythematosus, and paraneoplastica

Epidemiology

- occur worldwide.
- PV incidence varies from 0.5-3.2 cases per 100,000.
- more common in **Jewish** and people of **Mediterranean descent** or Indian origin
- Common in the **middle age** groups(40-60 yrs of life)
- men and women equally affected

AETIOLOGY

- It is an **autoimmune dis.** in which pathogenic IgG antibodies binds to antigens within the epidermis
- The main Ags are desmoglein 1 and 3 (3 in PV & 1 in PF).
- Both are adhesion molecules found in the desmosomes
- The Ag-Ab reaction interferes with adhesion, causing the keratinocytes to fall apart (acantholysis)

CLINICAL FEATURES

PV : is characterized by **flaccid blisters** of the **skin** and **mouth** .

- The blisters rupture easily to leave widespread painful erosions.
- **Most** patients develop the mouth lesions **first**.
- **Mouth ulcers** that persists for **months** before **skin lesions** appears on the trunk, flexures and scalp
- Shearing stress on normal skin(sliding pressure) can cause **new erosion** to form(+ve Nikolsky sign).

Mouth ulcers in PV { appear 1st in most cases }





+ ve Nikolski's Sign

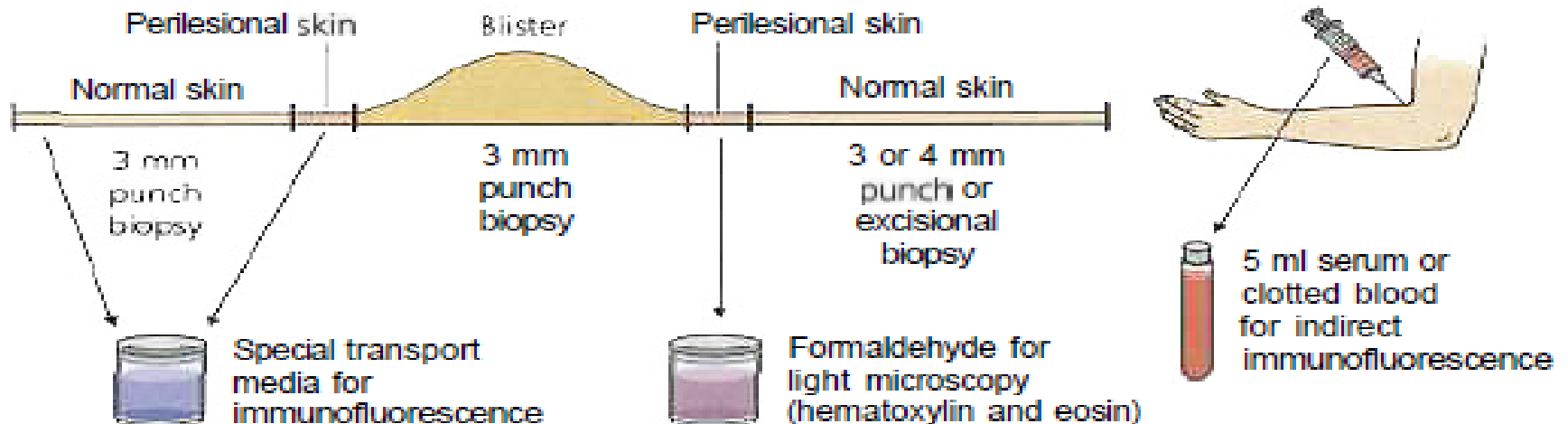


Nikolsky Sign : Dislodging of epidermis by lateral finger pressure in the vicinity of lesions, which leads to an erosion.

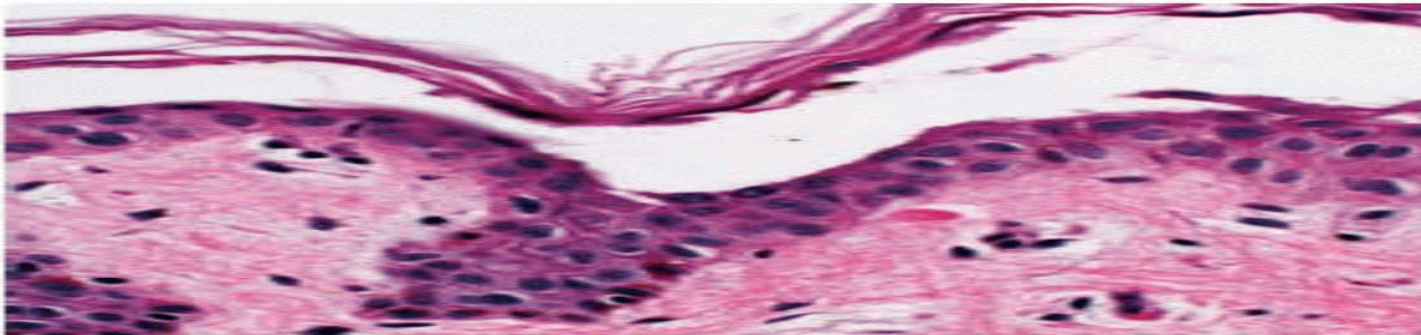
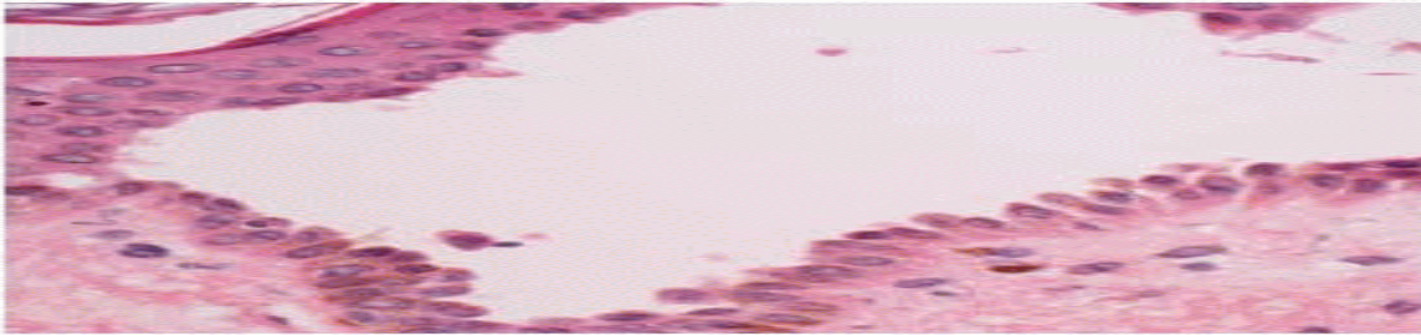
Shearing stresses on normal skin can cause new erosions to form

Diagnosis

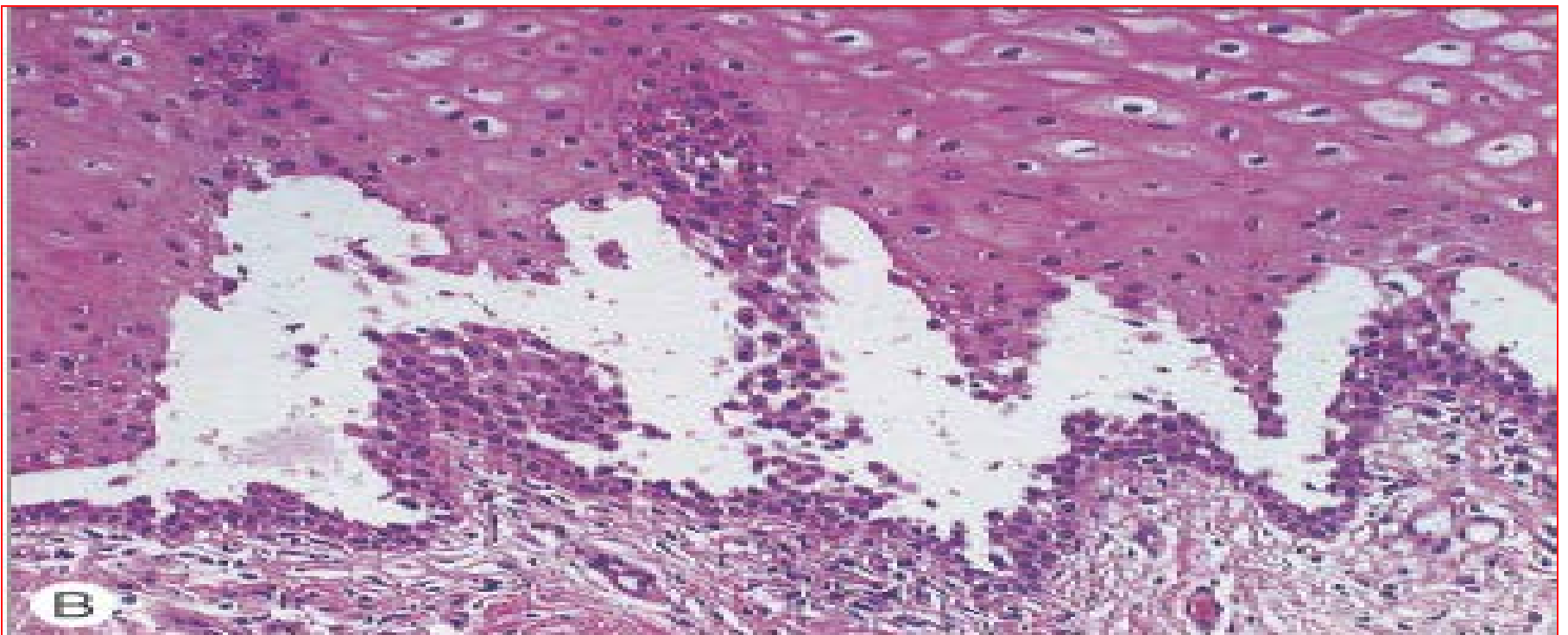
- **Clinical evaluation**
- **Histopathologic by Light microscopy**
- **Immunofluorescent examination.** is a laboratory technique for demonstrating the presence of tissue bound and circulating antibodies
- **Electron microscopic examination ;(EM) NOT routinely done**



Pemphigus Vulgaris :
Dermatopathology by Light microscopy;
skin Biopsy from the edge of a blister

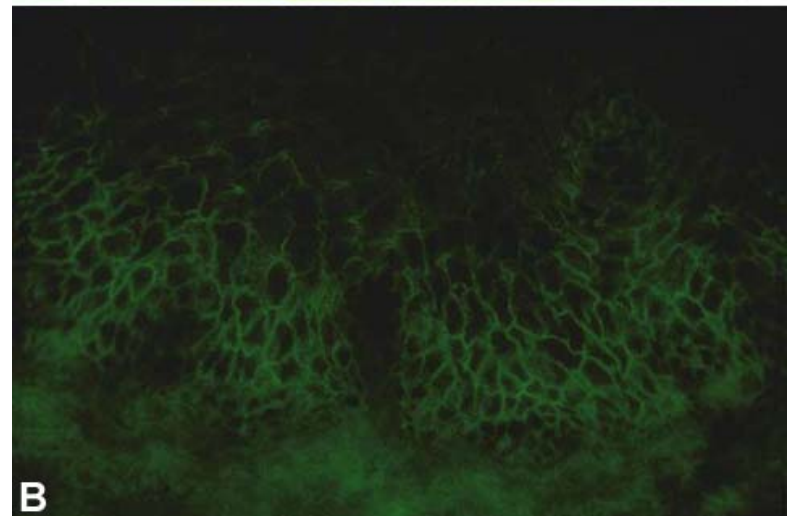
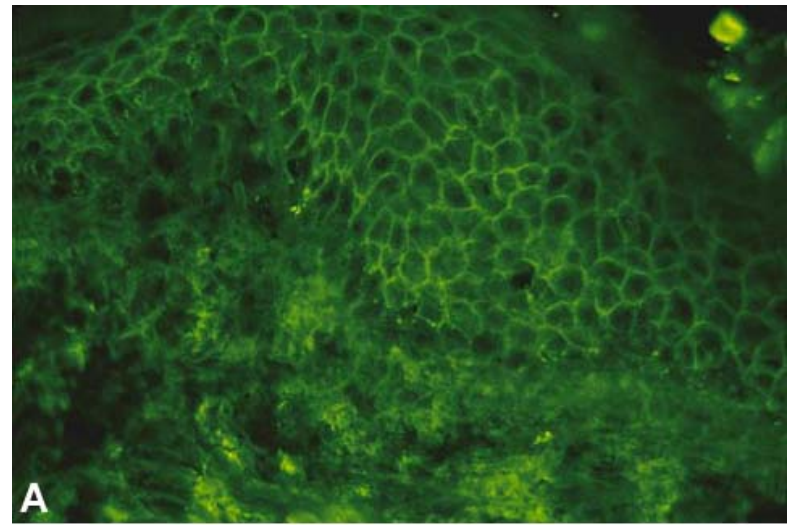


Biopsy shows that the vesicles are intra-epidermal, with rounded keratinocytes floating freely within the blister cavity (acantholysis)



Pemphigus Vulgaris ;Immunofluorescence

- **A) DIF : (skin)** Note deposition of IgG around epidermal cells.
- **B) IDIF: (serum)** using monkey esophagus:
Note binding of IgG antibodies to the epithelial cell surface.



DDx

- Other types of pemphigus
- Bullous pemphigoid
- Dermatitis herpetiformis (DH)
- Bullous impetigo
- EB or Ecthyma
- familial benign pemphigus (Hailey-Hailey disease)

Mouth ulcers:

- **Aphthae**
- **Behcet's dis.**
- **Herpes simplex infection**
- **Bullous lichen planus**

TREATMENT

Systemic steroid ;

2 to 3 mg/kg of prednisolone until cessation of new blister formation and disappearance of Nikolsky sign.

Concomitant Immunosuppressive Therapy(steroid sparing agents)

such as **Azathioprine** , 2–3 mg/kg

Methotrexate , either orally or IM at doses of 25 to 35 mg/week.

cyclophosphamide or mycophenylate mofetil

High-dose intravenous immunoglobulin (HIVIg) ;

(2 g/kg every 3–4 weeks) may help gain quick control whilst waiting for other drugs to work.

Rituximab (Anti-CD20 monoclonal antibody) has been reported to help multidrug resistance, IV , once a week for 4 weeks.

Rx is usually prolong and need regular follow up

Dosage should be dropped only when new blisters stop appearing

COMPLICATIONS

- Side effects of treatment is the leading cause of death
- Areas of denudation become infected and smelly
- Oral ulcers makes eating painful

PARANEOPLASTIC PEMPHIGUS (PNP)

- PNP Lesions combine features of **pemphigus vulgaris** and **erythema multiforme**, clinically and histologically
- Mucous membranes primarily and most severely involved.
- **Associated internal malignancy as;**
- **e,g:** Non-Hodgkin's lymphoma and Chronic lymphocytic leukemia

Drug-induced PV

Drugs can induce PV

Drugs reported most significantly in association with PV are;

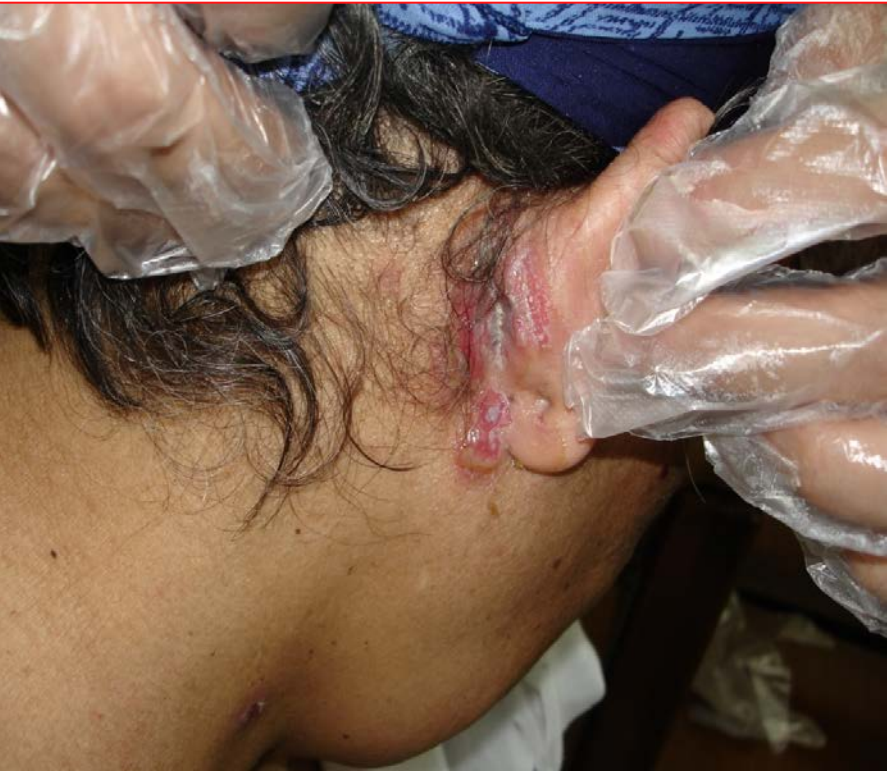
Penicillamine

captopril

Pemphigus vegetans in the axilla, some intact blisters can be seen



Pemphigus Vegetans



Pemphigus Vegetans



BULLOUS PEMPHIGOID

- **an autoimmune blistering disorder**
- **Antibodies binds to normal skin at the BMZ**
- **It is more common than pemphigus**
- **Mainly affect the elderly**
- **Mucosal involvement is rare**

PATHOGENESIS

- **There is linear deposition of Igs & complements against proteins at the dermo-epidermal junction**
- **The IgG antibodies bind to two main antigens, most commonly to BP230 and less often BP180 found in the hemidesmosome and in the lamina lucida.**
- **Complement is then activated , starting an inflammatory cascade.**
- **Eosinophils often participate in the process, causing the epidermis to separate from the dermis**

BULLOUS PEMPHIGOID



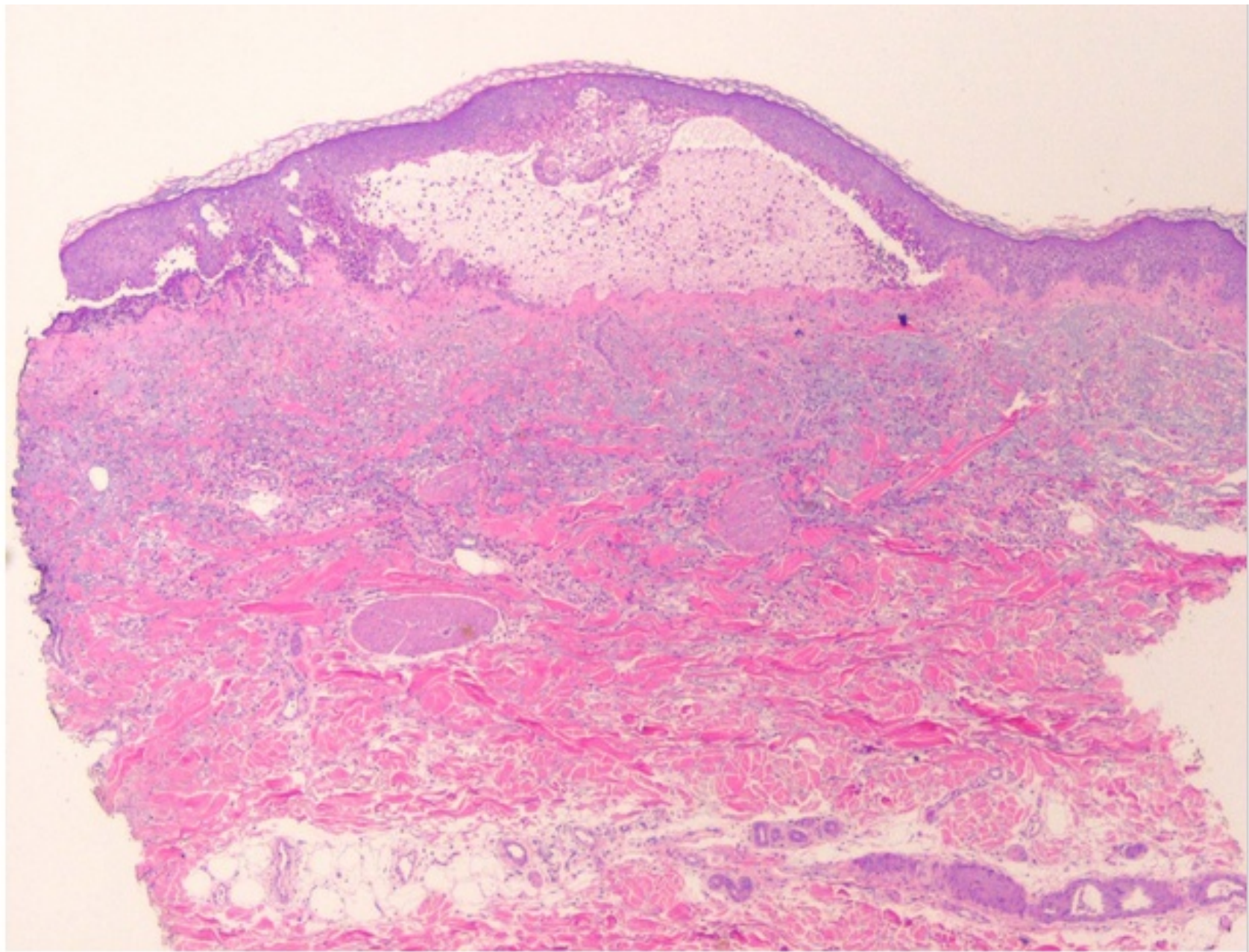


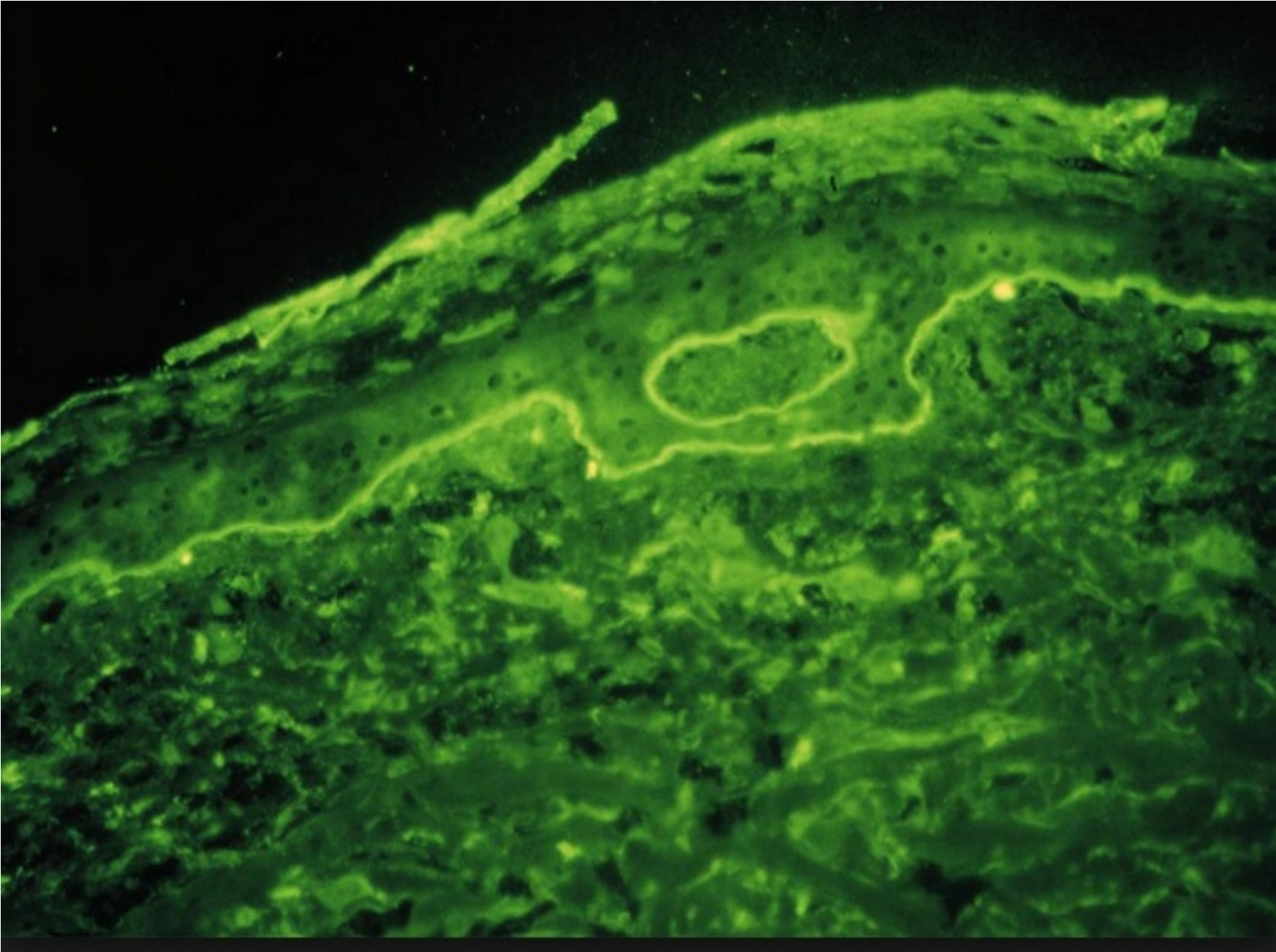
CLINICAL FEATURES

- **Pemphigoid is a chronic, usually itchy, blistering disease, mainly affecting the elderly**
- **Early stages of the dis. is characterised by pruritus**
- **Bullae may be centered on erythematous and urticated base.**
- **Large tense bullae found anywhere on the skin**
- **The flexures are often affected; inner aspect of the thigh, flexure surface of forearms, axillae, groin and lower abdomen**
- **the mucous membranes usually are not.**
- **The Nikolsky test is negative.**

INVESTIGATIONS

- **Skin biopsy** shows a **deeper blister**(than in pemphigus) owing to a subepidermal split through the BM
- **On direct IF**, perilesional skin shows **linear band of IgG and C3 along BMZ**
- **Indirect IF** shows IgG antibodies that reacts with the BMZ in most patients
- **Hematology Eosinophilia (not always)**





DDx

- Epidermolysis bullosa
- Bullous lupus erythematosus
- Dermatitis herpetiformis
- Bullous erythema multiforme

TREATMENT

- In acute phase, **prednisolone** 40-60mg daily is usually needed to control the eruption
- **Immunosuppressive agents** may also be required
- **Dosage** should be reduced as soon as possible to low maintenance, taken on alternate days until treatment is stopped.
- In **very mild cases** and for **local recurrences**, topical glucocorticoid or topical tacrolimus therapy may be beneficial.
- **Tetracycline ± nicotinamide** has been reported to be effective in some cases.
- Treatment can often be withdrawn after 2-3yrs

COMPLICATIONS

- **Complications of systemic steroids and immunosuppressive agents if used on the long term**
- **Loss of fluid from ruptured bullae**

DIFF BTW PEMPHIGUS AND PEMPHIGOID

Pemphigus

- Usually affects the middle age
- Acute and non itchy
- Seen on the trunk, flexures and scalp
- Mouth Blister is common
- Nature of blister is superficial and flaccid
- Circulating Ab is IgG to intracellular adhesion proteins
- Serum Ab Titer correlate with clinical disease activity.
- Acantholysis
- Nikolsky sign is positive

Pemphigoid

- Elderly patients
- Chronic and itchy
- Usually flexural
- Mouth Blister is Rare
- Blister is tense and bloody
- IgG to BM region
- Serum Ab Titer does not correlate with clinical disease activity.
- No acantholysis
- Nikolsky sign is negative

Dermatitis Herpetiformis (DH)

- Intensely itchy, chronic **papulovesicular** eruption distributed symmetrically on **extensor surfaces**.
- It may start at **any age**, including **childhood**; however, the **2nd, 3rd, and 4th** decades are the most common.
- **Skin biopsy** ; If a vesicle can be biopsied before it is scratched away, the histology will be that of a **subepidermal blister**, with **dermal papillary collections of neutrophils** (microabscesses).
- **DIF** ; **Granular IgA** deposits in normal-appearing skin are **diagnostic** for DH.
- Most, if not all, DH patients have an associated **gluten-sensitive enteropathy**.
Course; The condition typically lasts for decades unless patients avoid gluten entirely.
- **Differential diagnosis**; scabies, an excoriated eczema, insect bites or neurodermatitis.
- **RX** ; The rash responds rapidly to **dapsone** therapy
gluten-free diet works very slowly. Combine the two at the start and slowly reduce the dapsone



CHRONIC BULLOUS Disease OF CHILDHOOD

- Chronic blistering dis. which occur in children, usually starts before the age of 5yrs
- Small and large blisters appears predominantly on the **lower trunk, genital area, and thighs**
- May also affects the **scalp** and **around the mouth**
- New blisters form around healing old blisters forming a **CLUSTER OF JEWELS**
- **Course** is chronic and spontaneous remission usually occurs after an average of 3-4 yrs
- **IgA** autoantibodies binds to the BM proteins such as ladinin and laminin in linear form



CLINICAL FEATURES

- **Circular clusters of large blisters like the type seen in pemphigoid**
- **It involves the perioral area, lower trunk, inner thighs and genitalia**
- **Blistering may spread all over the body**



INVESTIGATION

- **Skin Biopsy** will show subepidermal splits
- **Direct IF** reveals **IgA** along the BM of the epidermis in a **linear** pattern

TREATMENTS

- **Oral dapsone 50-200mg daily**
- **Sulphonamides and immunosuppressants**
- **Erythromycine**

Disease	Skin Lesions	Mucous Membranes	Distribution
PV	Flaccid bullae on normal skin, erosions	Almost always involved, erosions	Anywhere, localized or generalized
PF	Crusted erosions, occasionally flaccid vesicles	Rarely involved	Exposed, seborrheic regions or generalized
PVeg	Granulating plaques, occasionally vesicles at margin	As in PV	Intertriginous regions, scalp
Bullous pemphigoid	Tense bullae on normal and erythematous skin; urticarial plaques and papules	Mouth involved in 10–35%	Anywhere, localized or generalized
EBA	Tense bullae and erosions, noninflammatory or BP-, DH- or LAD-like presentation	May be severely involved (oral esophagus, vagina)	Traumatized regions or random
Dermatitis herpetiformis	Grouped papules, vesicles, urticarial plaques, crusted	None	Predilection sites: elbows, knees, gluteal, sacral, and scapular areas
Linear IgA dermatosis	Annular, grouped papules, vesicles, and bullae	Oral erosions and ulcers, conjunctival erosions and scarring	Anywhere

Disease	Histopathology	Immunopathology/Skin	Serum
PV	Suprabasal acantholysis	IgG intercellular pattern	IgG AB to intercellular substance of epidermis (IIF) ELISA: AB to desmoglein 3 >> desmoglein 1
PF	Acantholysis in granular layer	IgG, intracellular pattern	IgG AB to intercellular substance of epidermis (IIF) ELISA: AB to desmoglein 1 only
PVeg	Acantholysis ± intraepidermal neutrophilic abscesses, epidermal hyperplasia	As in PV	As in PV
Bullous pemphigoid	Subepidermal blister	IgG and C3 linear at BMZ	IgG AB to BMZ (IIF); directed to BPAG1 and BPAG2
EBA	Subepidermal blister	Linear IgG at BMZ	IgG AB to BMZ (IIF) directed to type VII collagen (ELISA, Western blot)
Dermatitis herpetiformis	Papillary microabscesses, subepidermal vesicle	Granular IgA in tips of papillae	Antiendomysial antibodies
Linear IgA dermatosis	Subepidermal blister with neutrophils	Linear IgA at BMZ	Low titers of IgA AB against BMZ