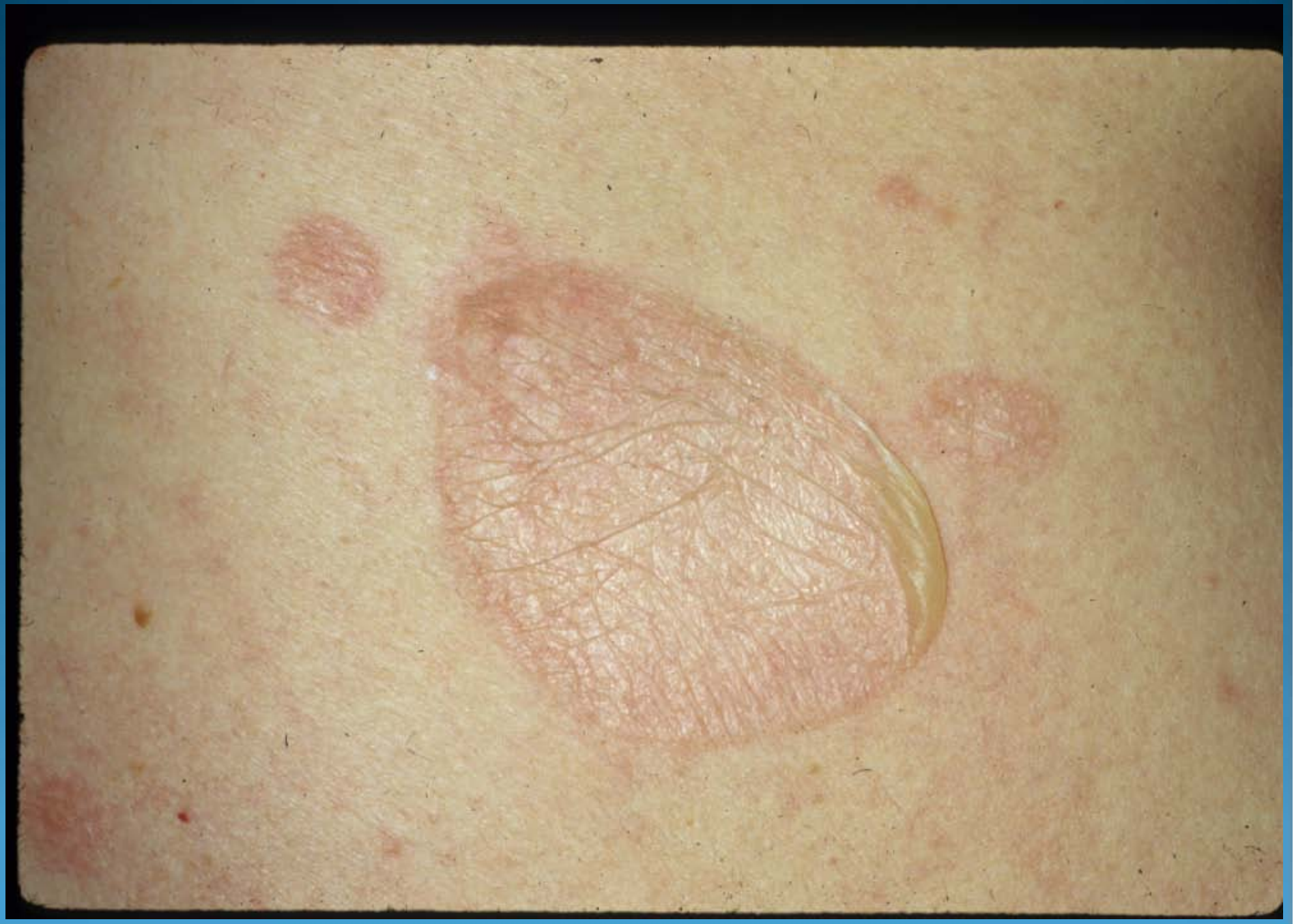
Pemphigus & Pemphigoid from the Microscope to the Bedside

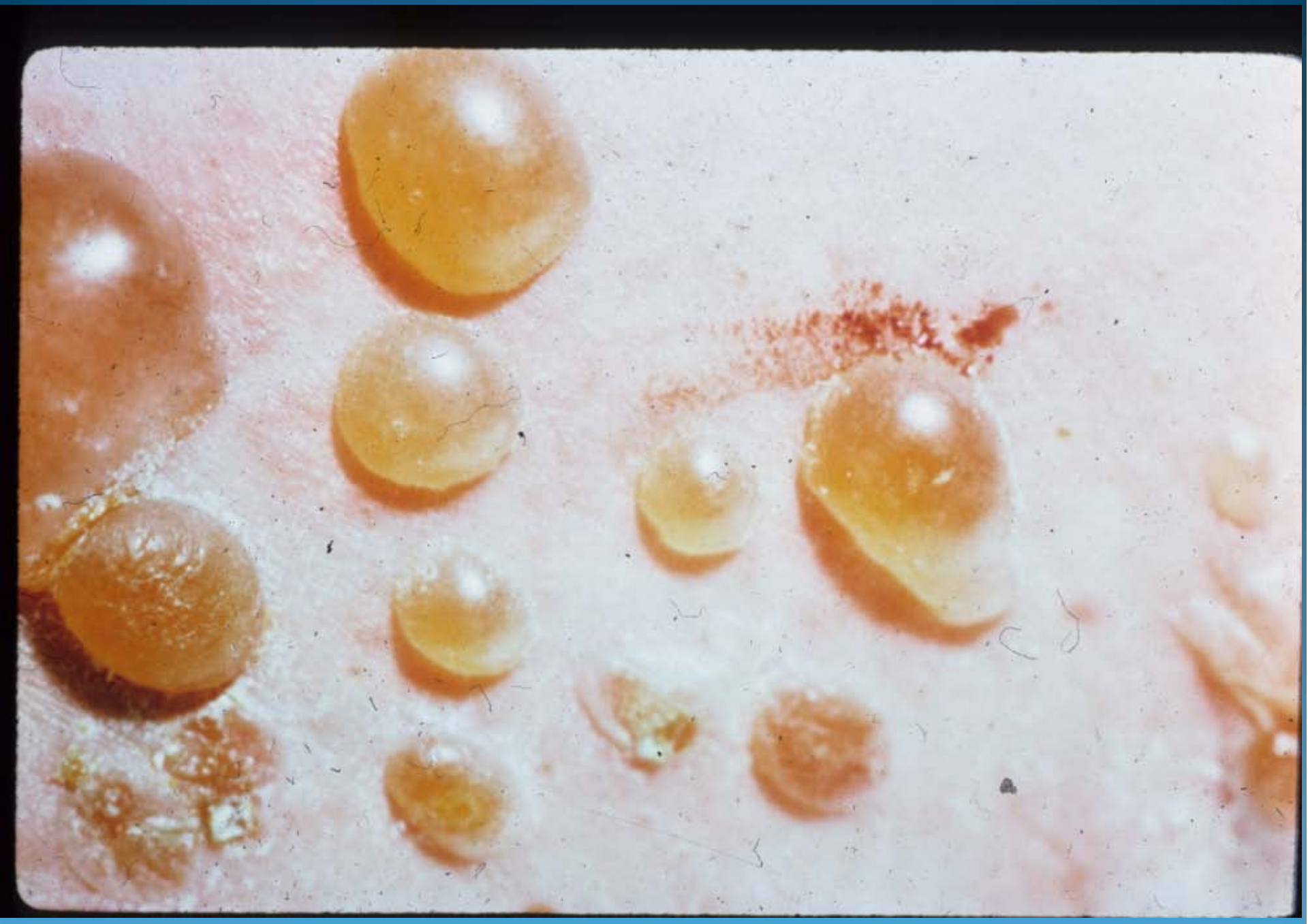
Learning Objectives

- Pemphigus vulgaris
- Paraneoplastic pemphigus
- Bullous pemphigoid
  - Pathophysiology, clinical features, histology
  - Evaluation and management

Pemphigus and Pemphigoid: Overview

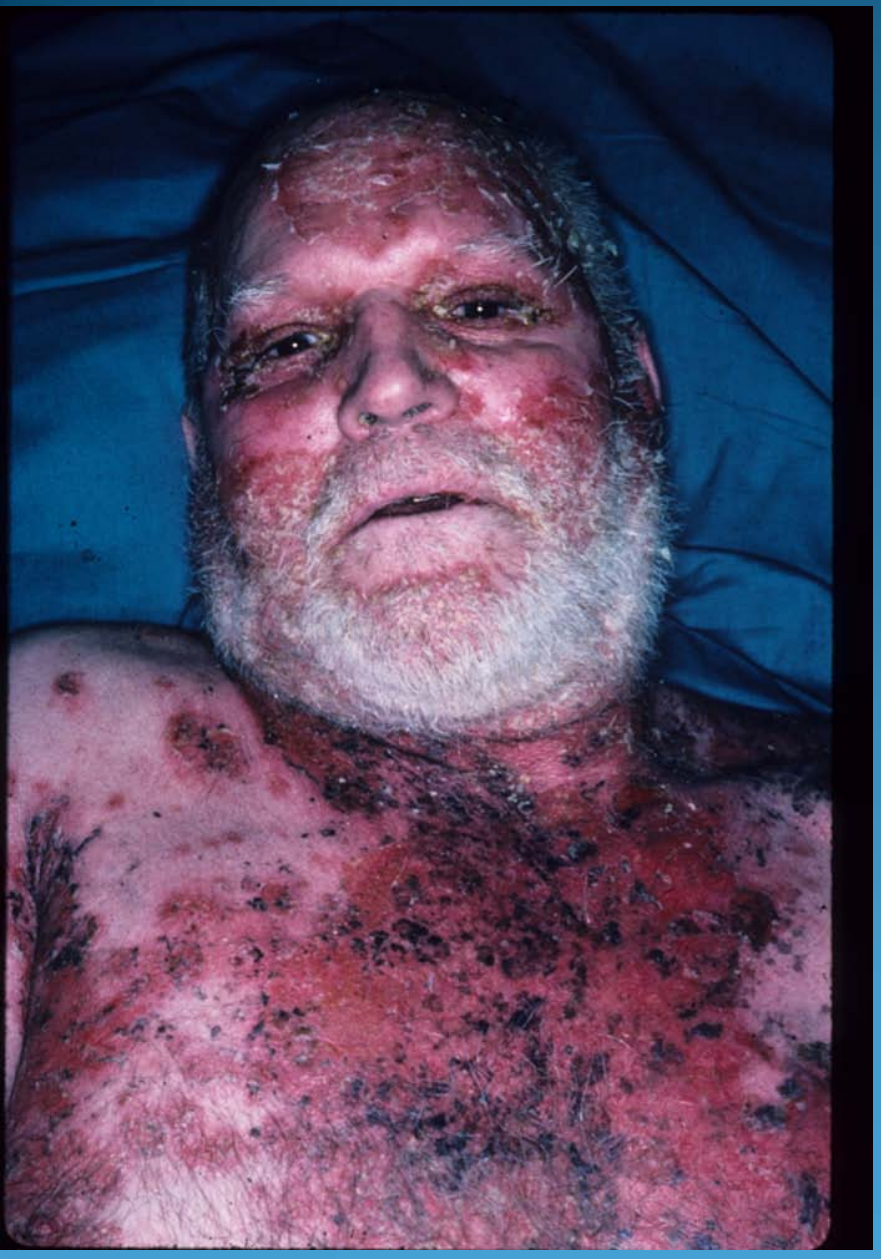
- Distinct set of autoimmune blistering disorders
- Autoantibodies target cell adhesion molecules
- Disadhesion results in chronic blistering
- Level of split determines the major category
  - intraepidermal split: pemphigus group
  - subepidermal split: pemphigoid group



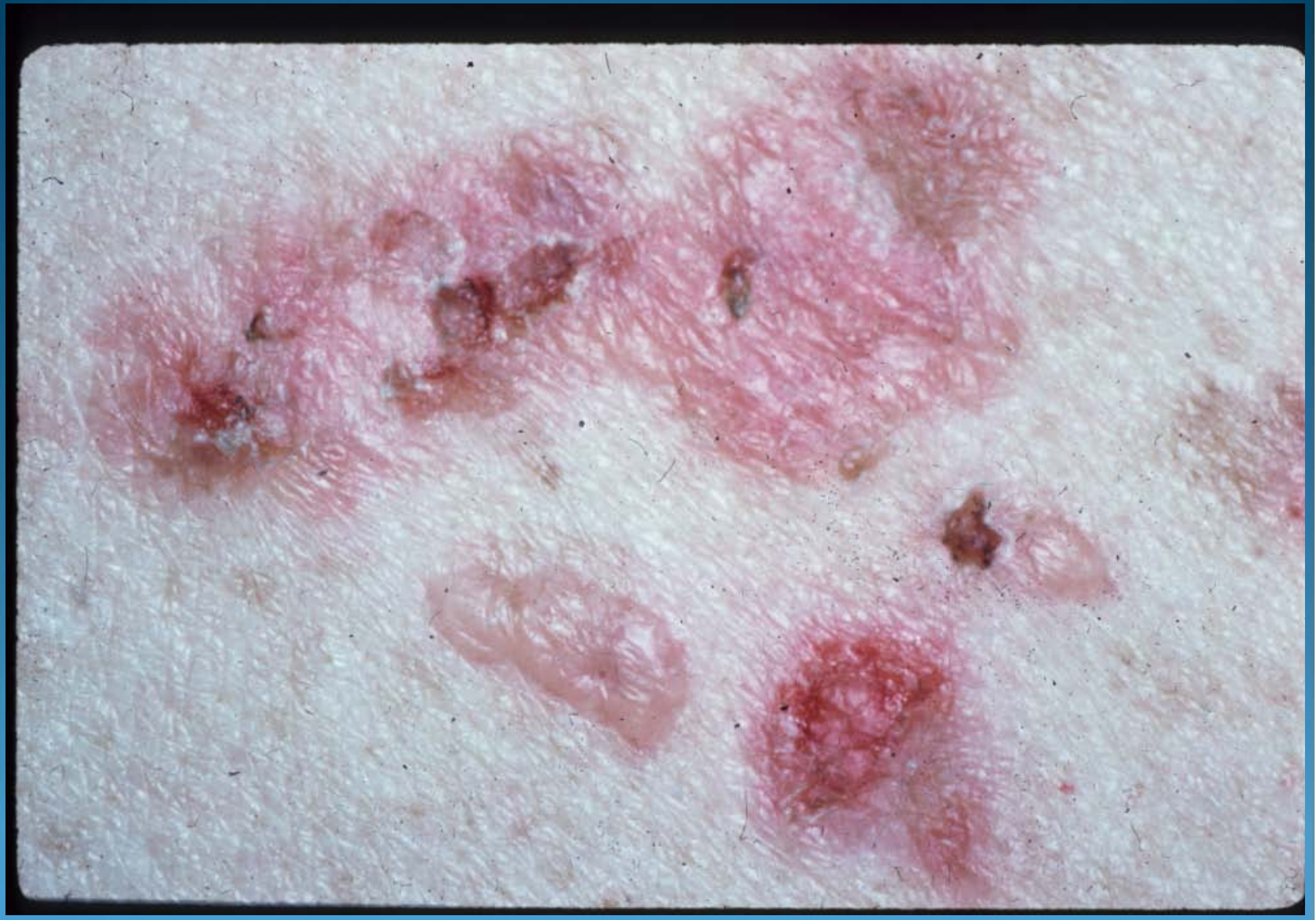


Classification

- Pemphigus vulgaris
  - Pemphigus vegetans
- Pemphigus foliaceus
  - Pemphigus erythematosus (Senear-Usher)
  - Endemic Pemphigus foliaceus (Fogo Selvagem)
- Paraneoplastic pemphigus
- IgA pemphigus
- Drug-induced pemphigus

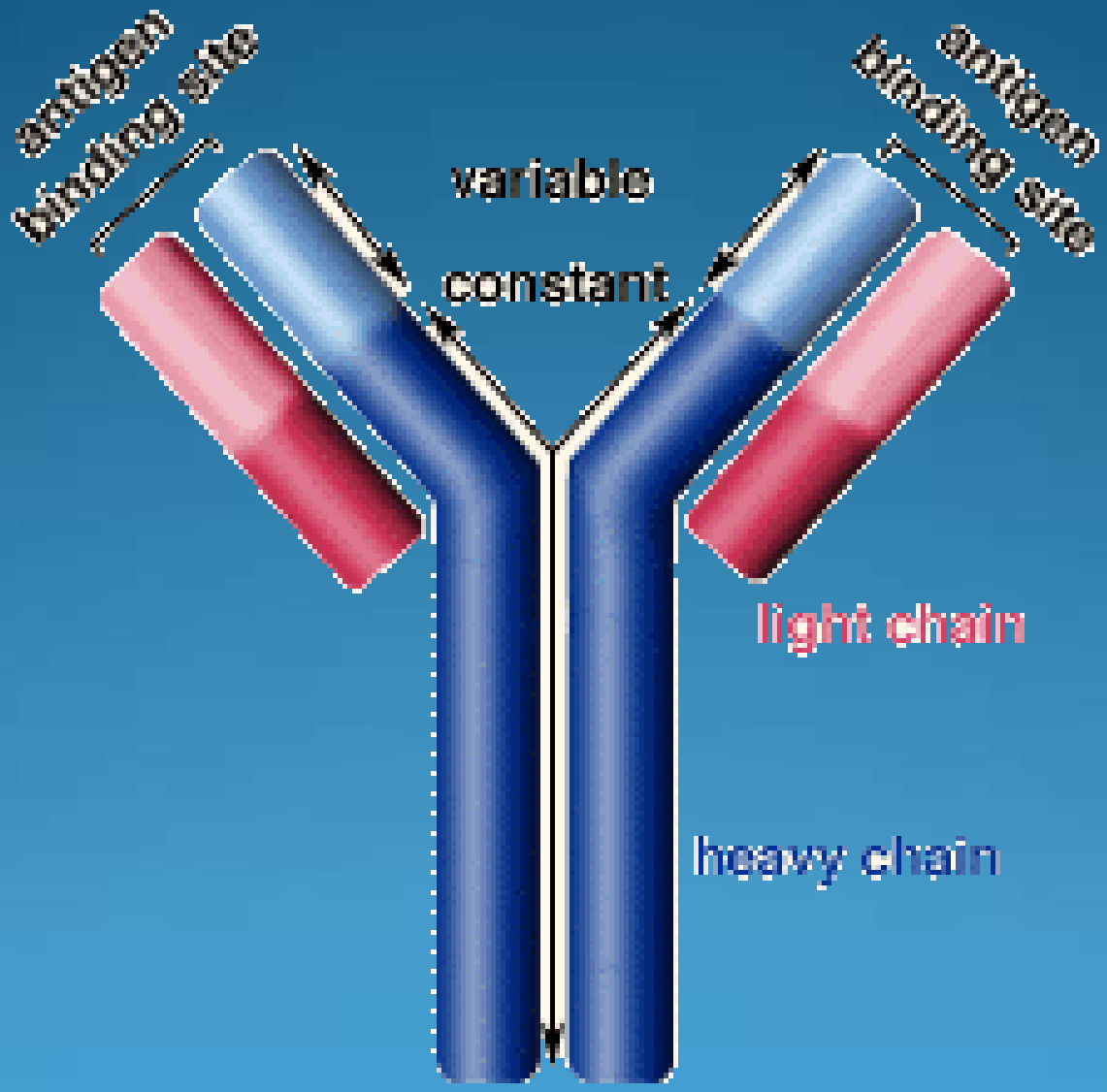


Pemphigus vulgaris



Epidemiology

- Most common form of pemphigus
- Both sexes affected equally
- Mean age of onset is 50-60
- HLA class II genes confer susceptibility
  - ~0.75-5 new cases per million per year
  - ~16-32 in Ashkenazi Jewish population


antigen binding site
variable
constant
antigen binding site
light chain
heavy chain

IgG autoantibodies target desmosomal adhesion molecules

(desmogleins)

↓

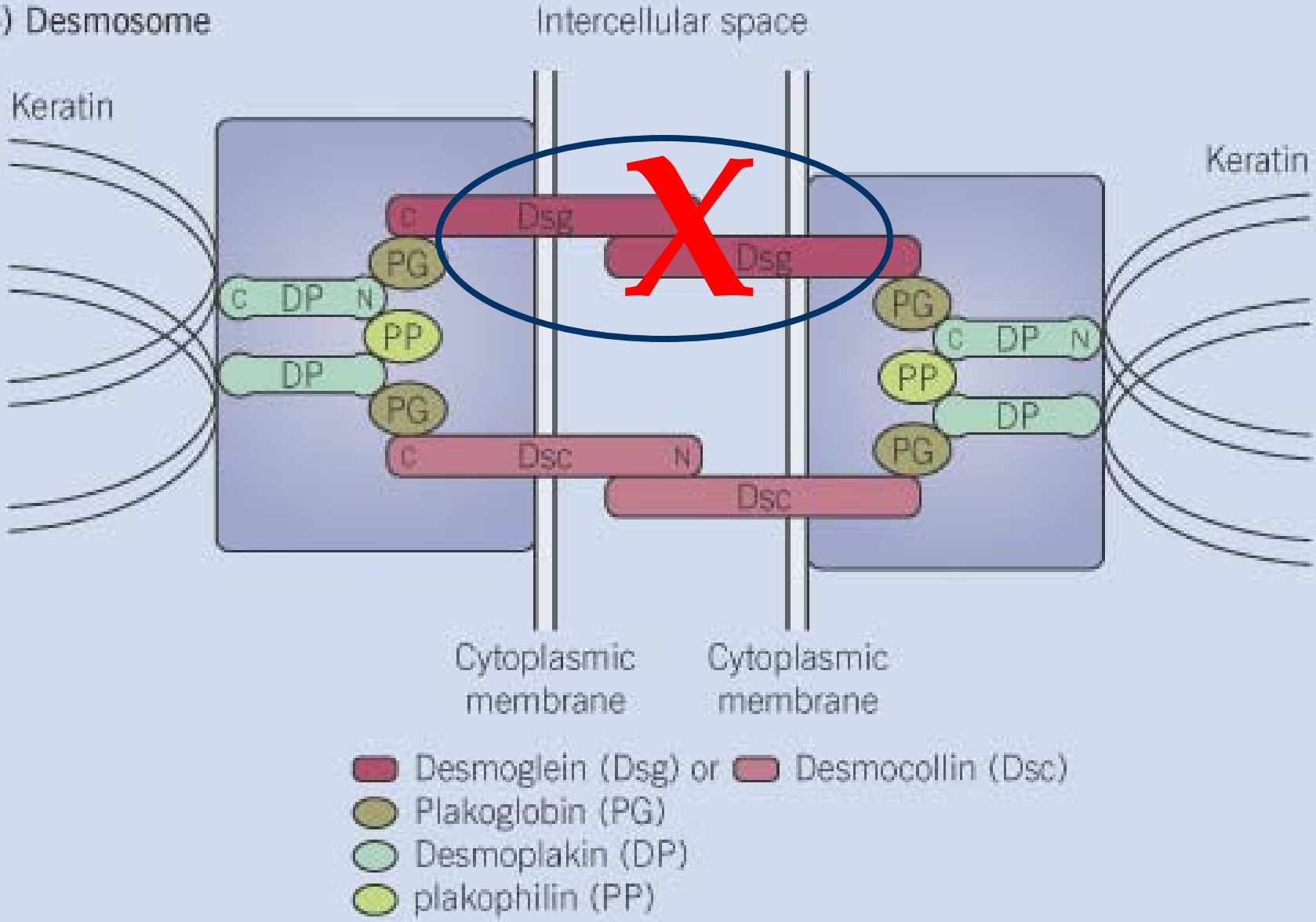
Loss of cell to cell adhesion

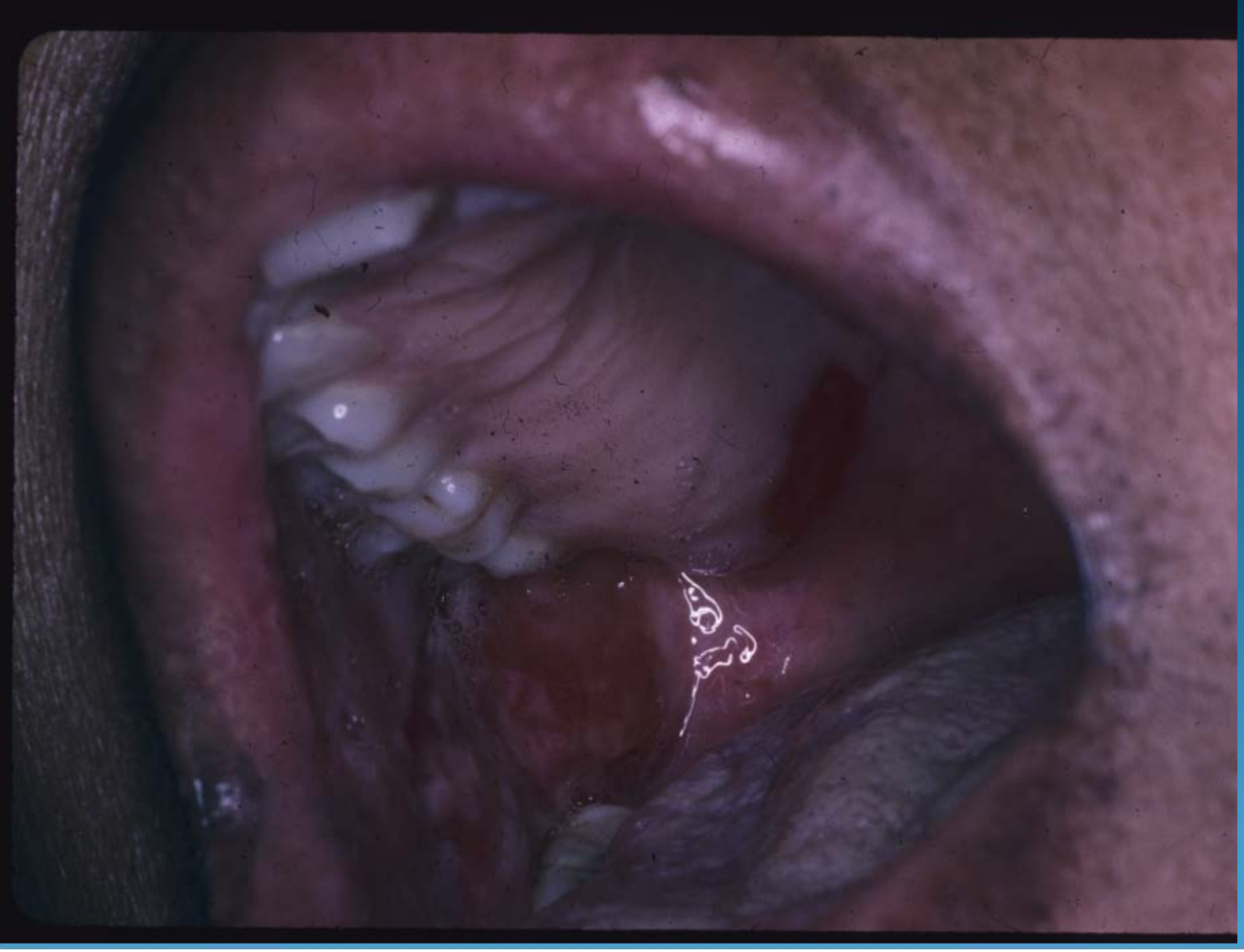
↓

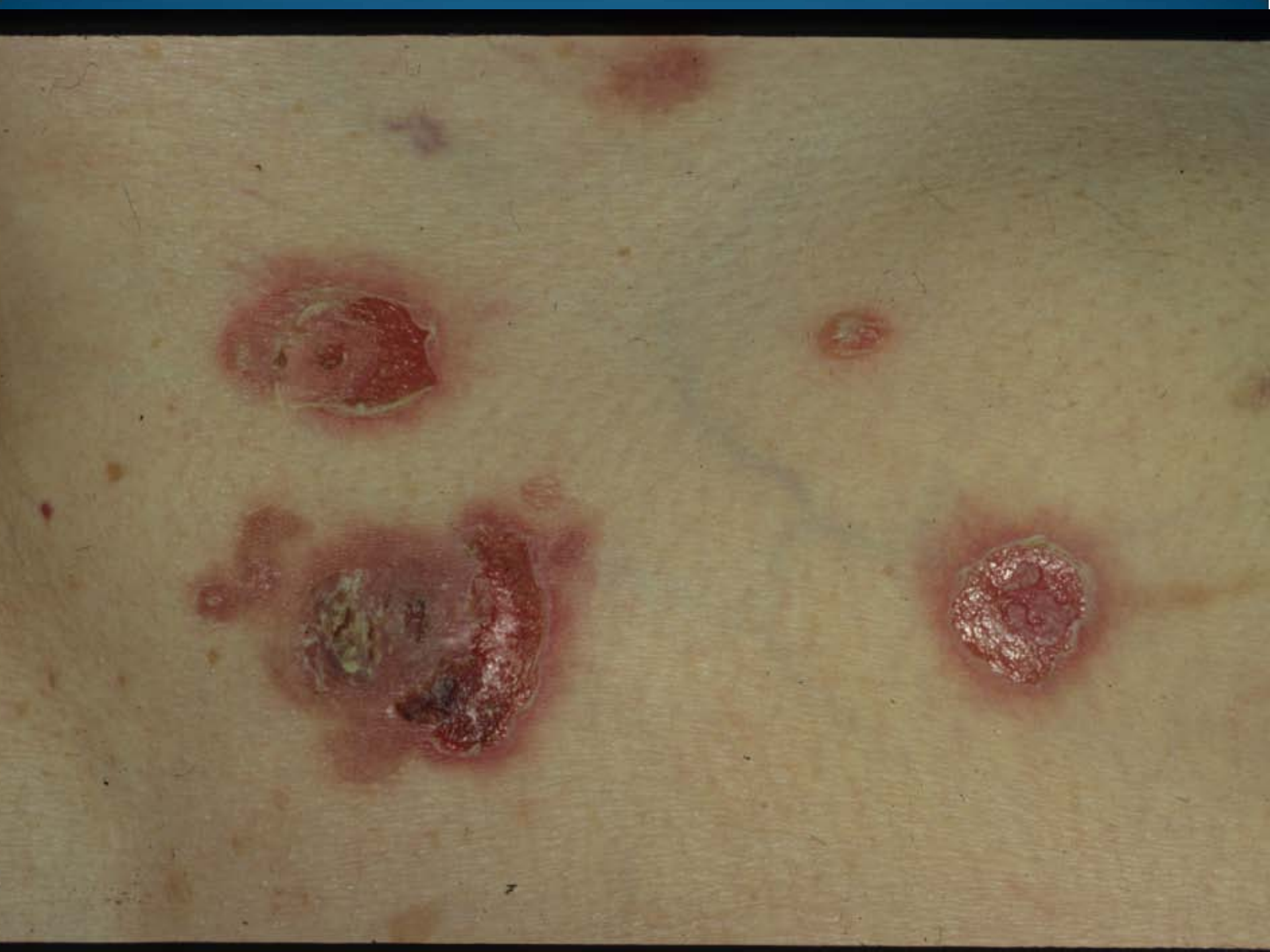
Acantholysis

↓

Blistering

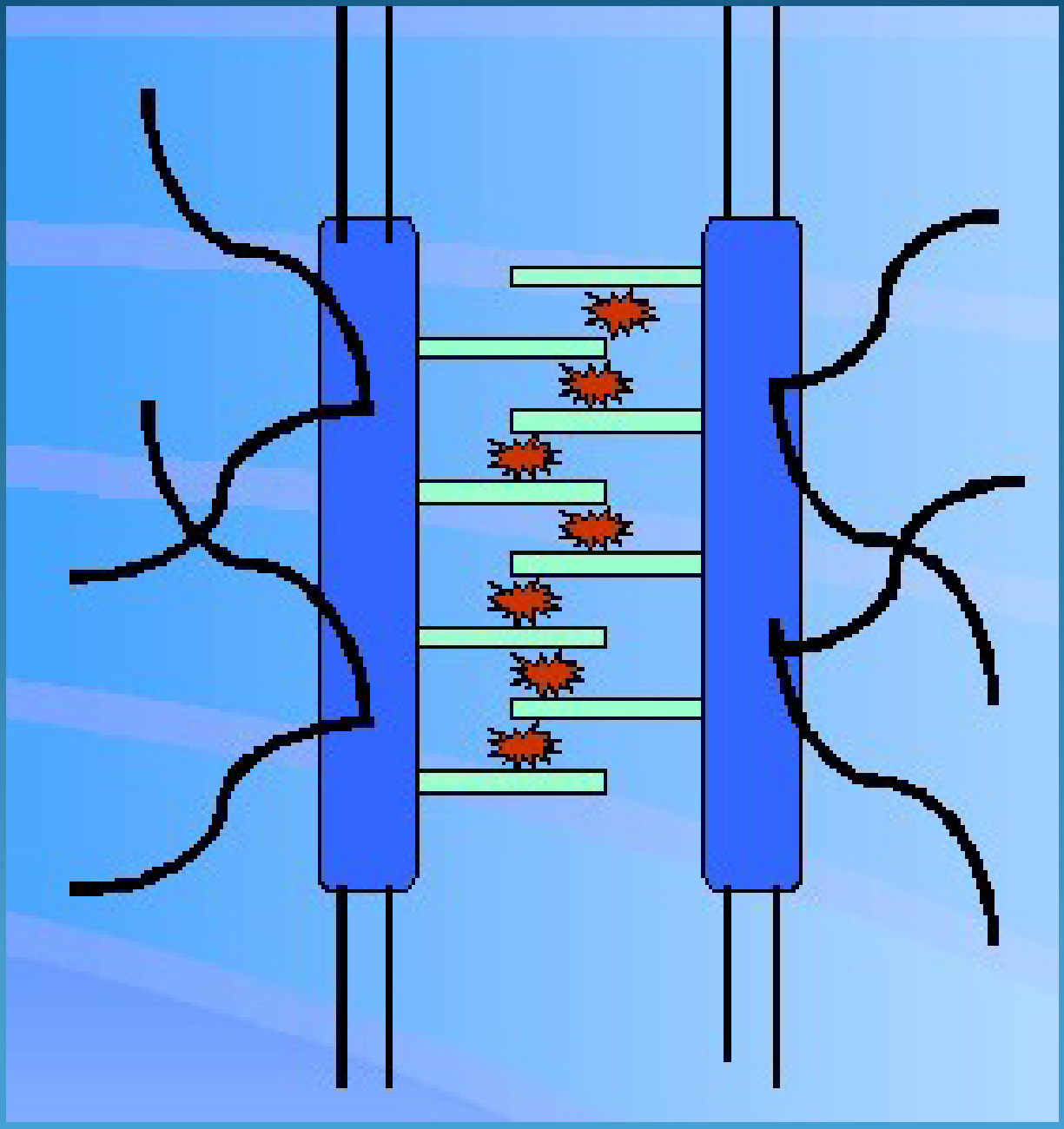

(b) Desmosome
Intercellular space
Keratin
Keratin
C
Dsg
N
Dsg
PG
C DP N
PP
DP
PG
C
Dsc
N
Dsc
PG
C DP N
PP
DP
PG
Cytoplasmic membrane
Cytoplasmic membrane
Desmoglein (Dsg) or
Desmocollin (Dsc)
Plakoglobin (PG)
Desmoplakin (DP)
plakophilin (PP)





Desmogleins

- Cadherin superfamily
  - Calcium-dependent adhesion proteins
- 3 isoforms: desmoglein 1-3
  - **1 (160 kd): superficial layers of SSE**
  - 2: all desmosome- possessing tissues
  - **3 (130 kd): suprabasilar layers of SSE**



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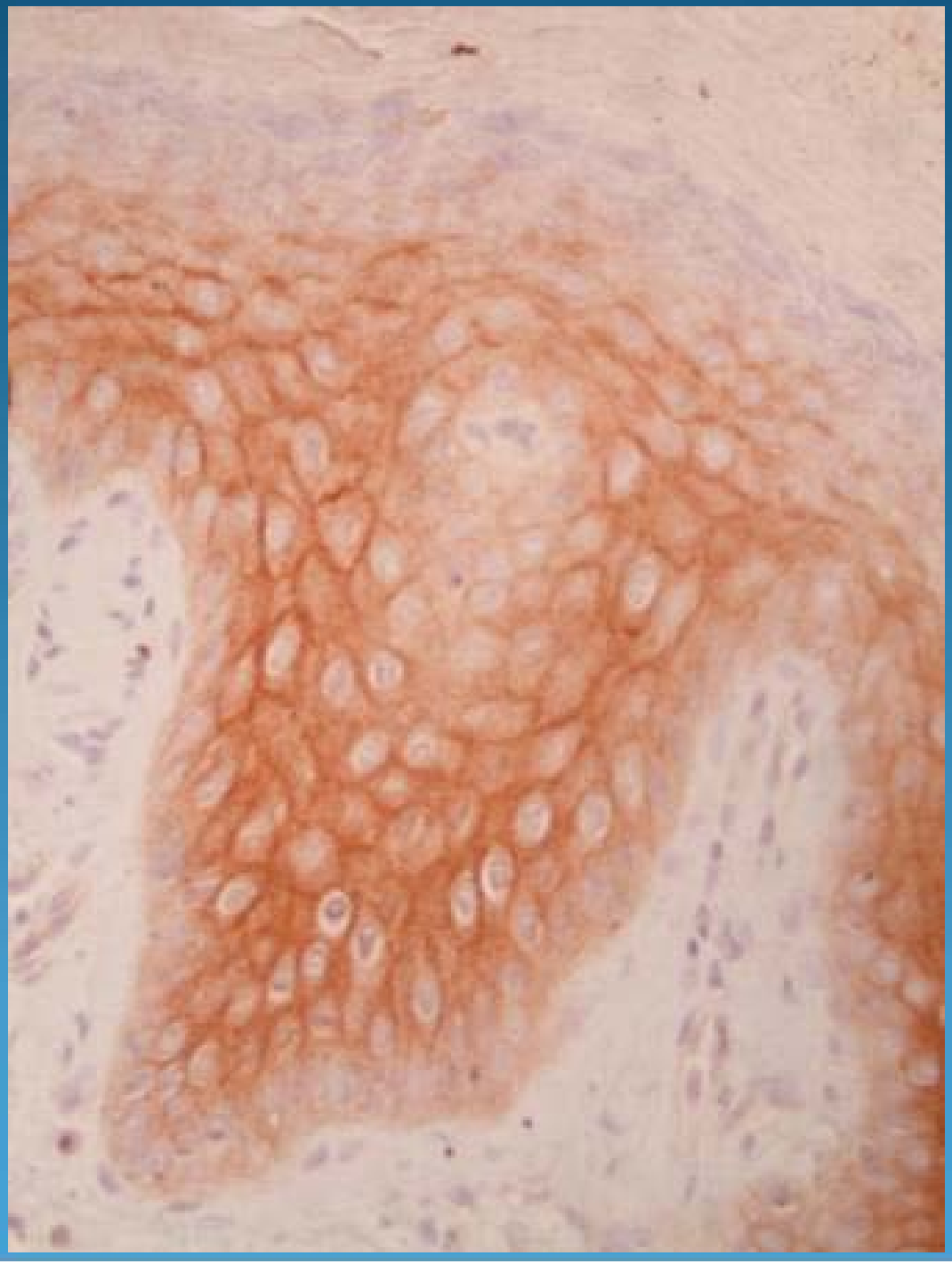
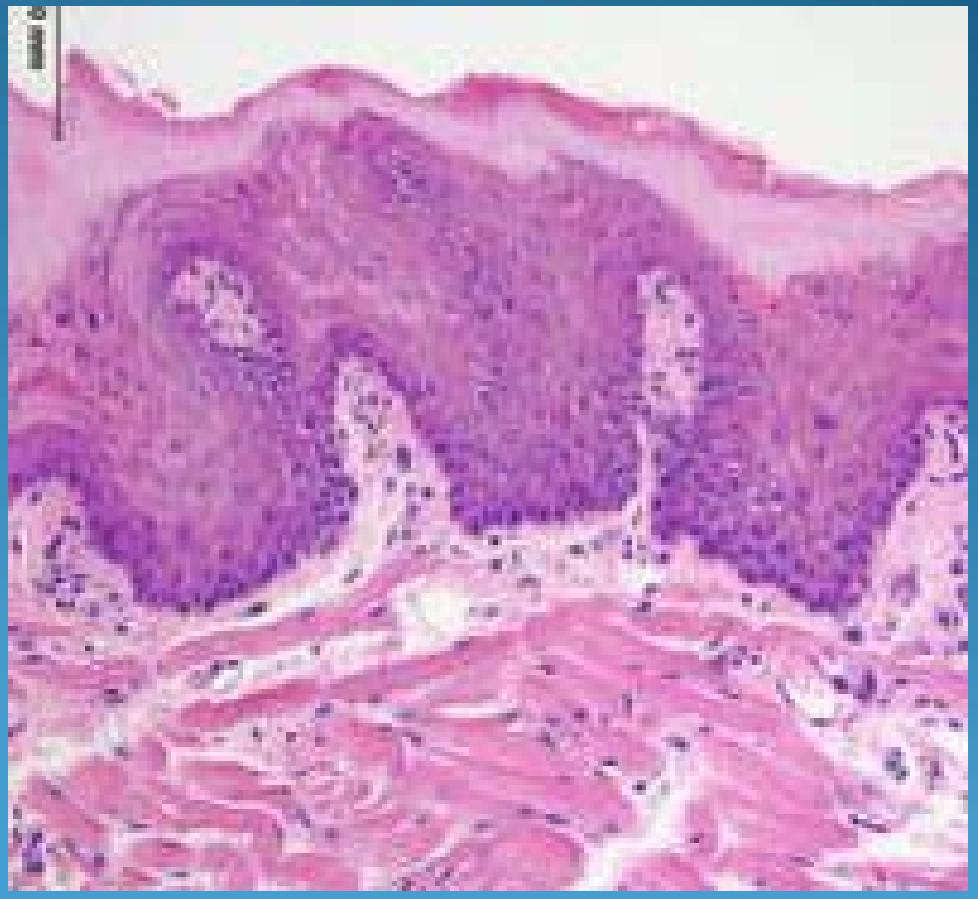


Desmoglein Compensation Theory

- Desmoglein 1 and 3 expression in skin and mucosa differ and are compensatory
- The specific desmoglein(s) targeted determines the localization of blisters
- *The clinical features of pemphigus are determined by the autoantibody profile*

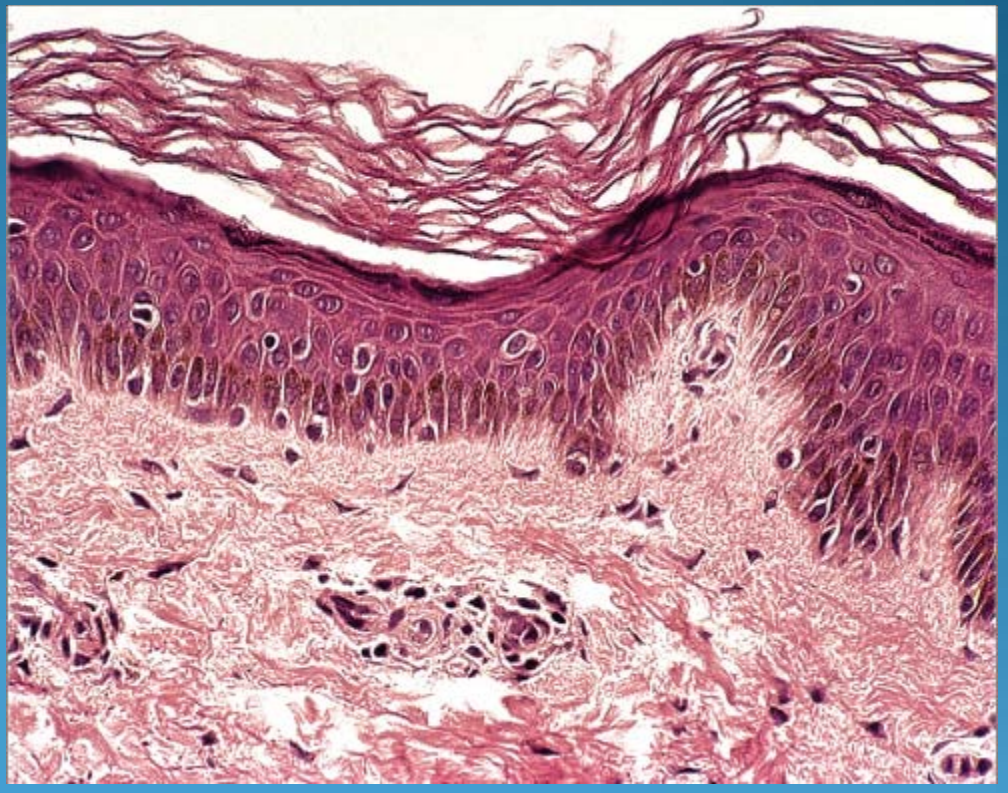
Desmoglein Expression Patterns: Mucosa

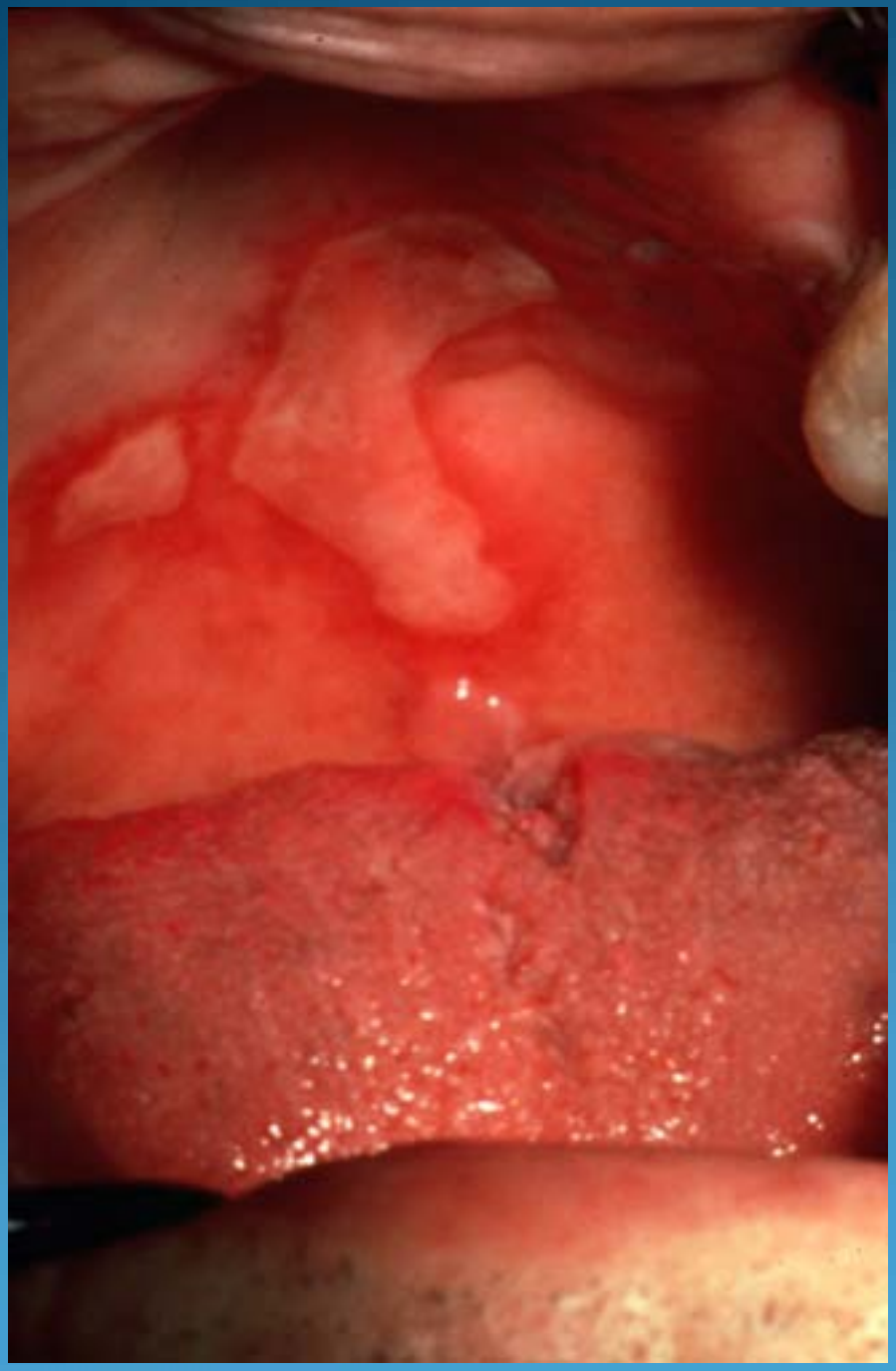
- **Desmoglein 1**
  - low quantity
- **Desmoglein 3**
  - high quantity



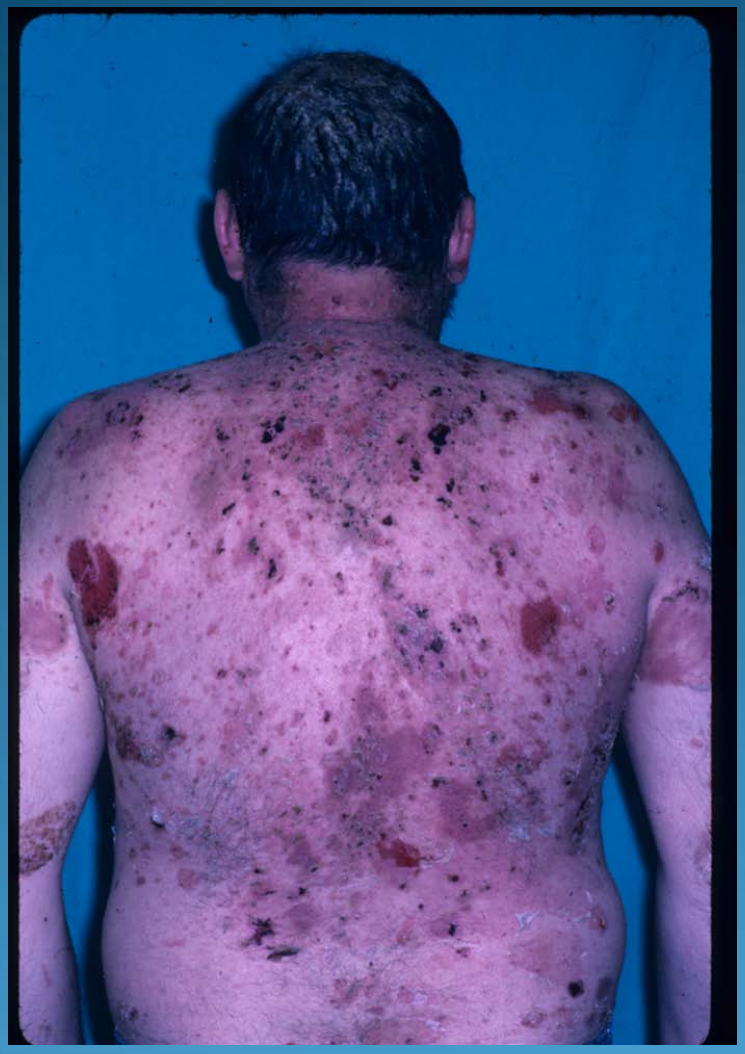
Desmoglein Expression Patterns: Skin

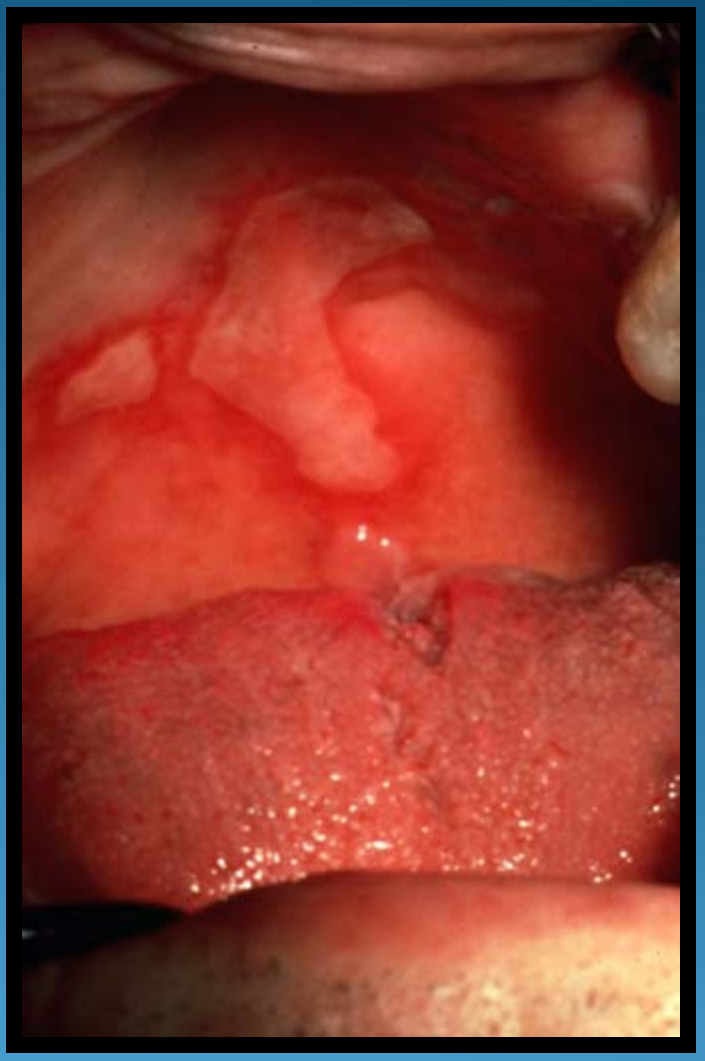
- **Desmoglein 1**
  - superficial layers
- **Desmoglein 3**
  - basal layers





Mucosal Dominant: Desmoglein 3



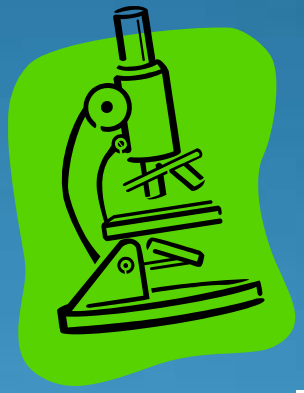


Mucocutaneous: Desmogleins 1 and 3

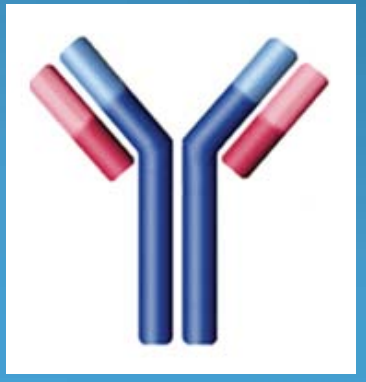
Diagnostic Criteria

- Clinical findings

- Histopathology

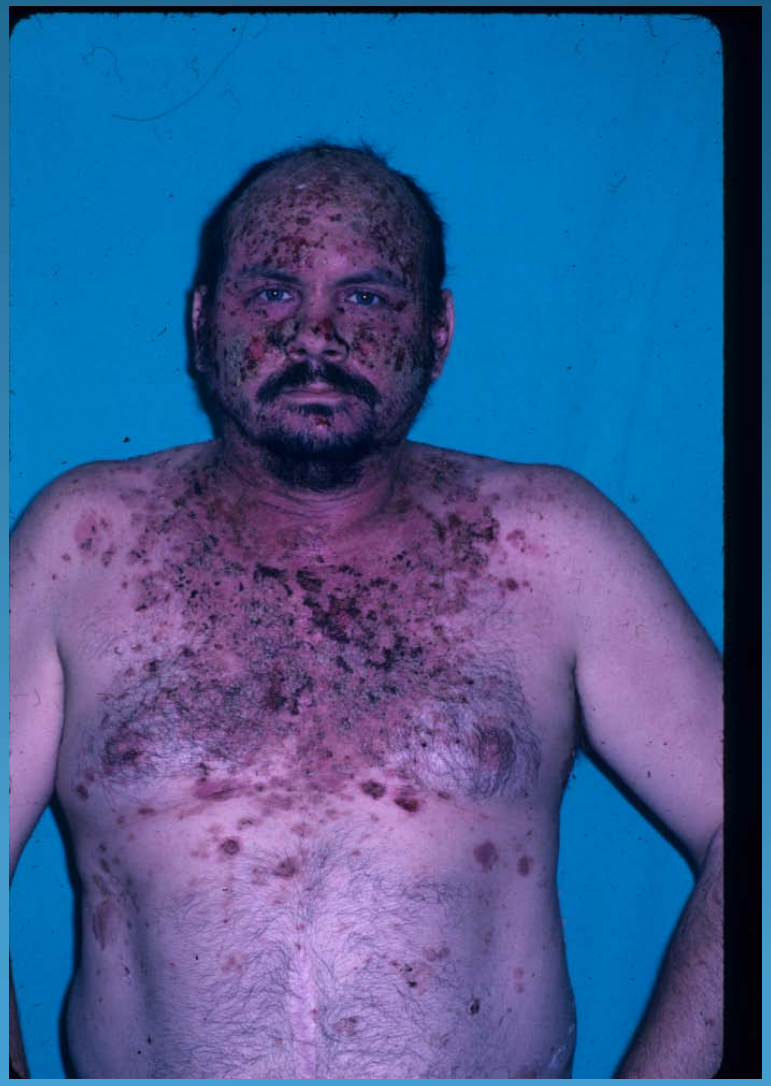


- Autoantibodies

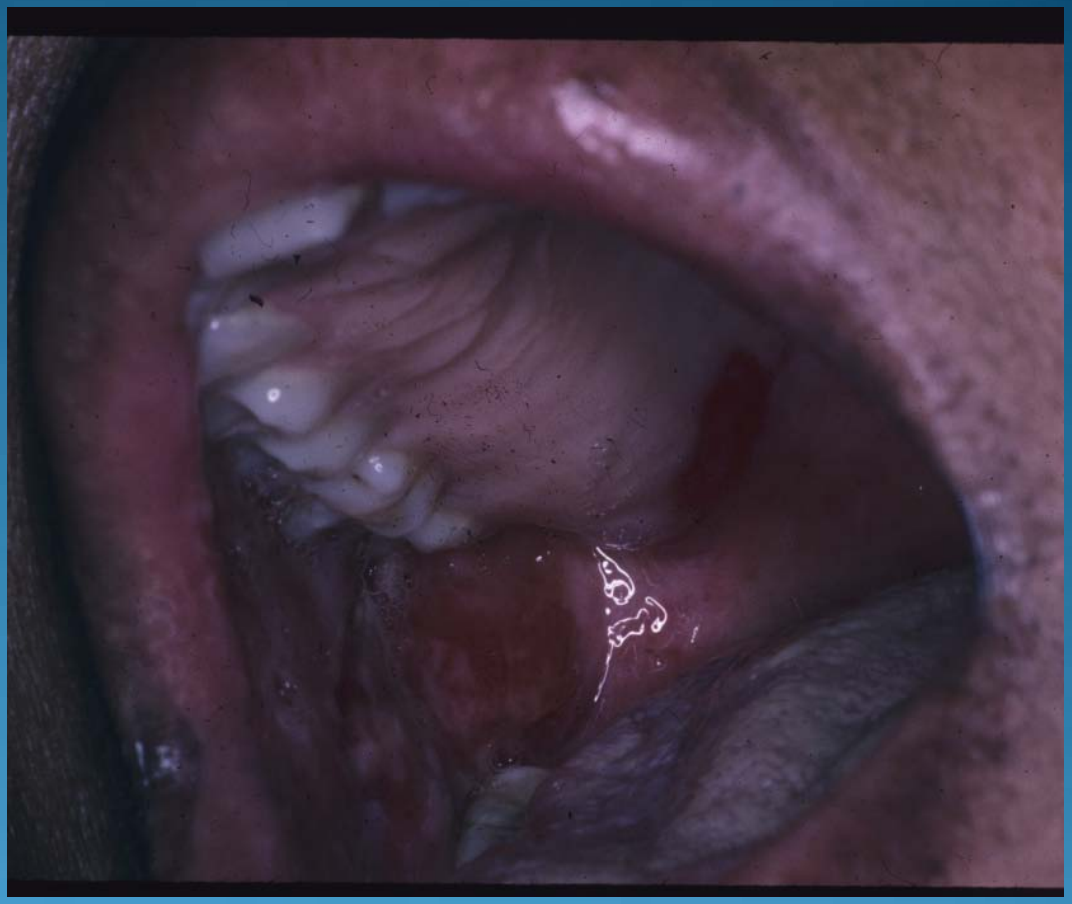


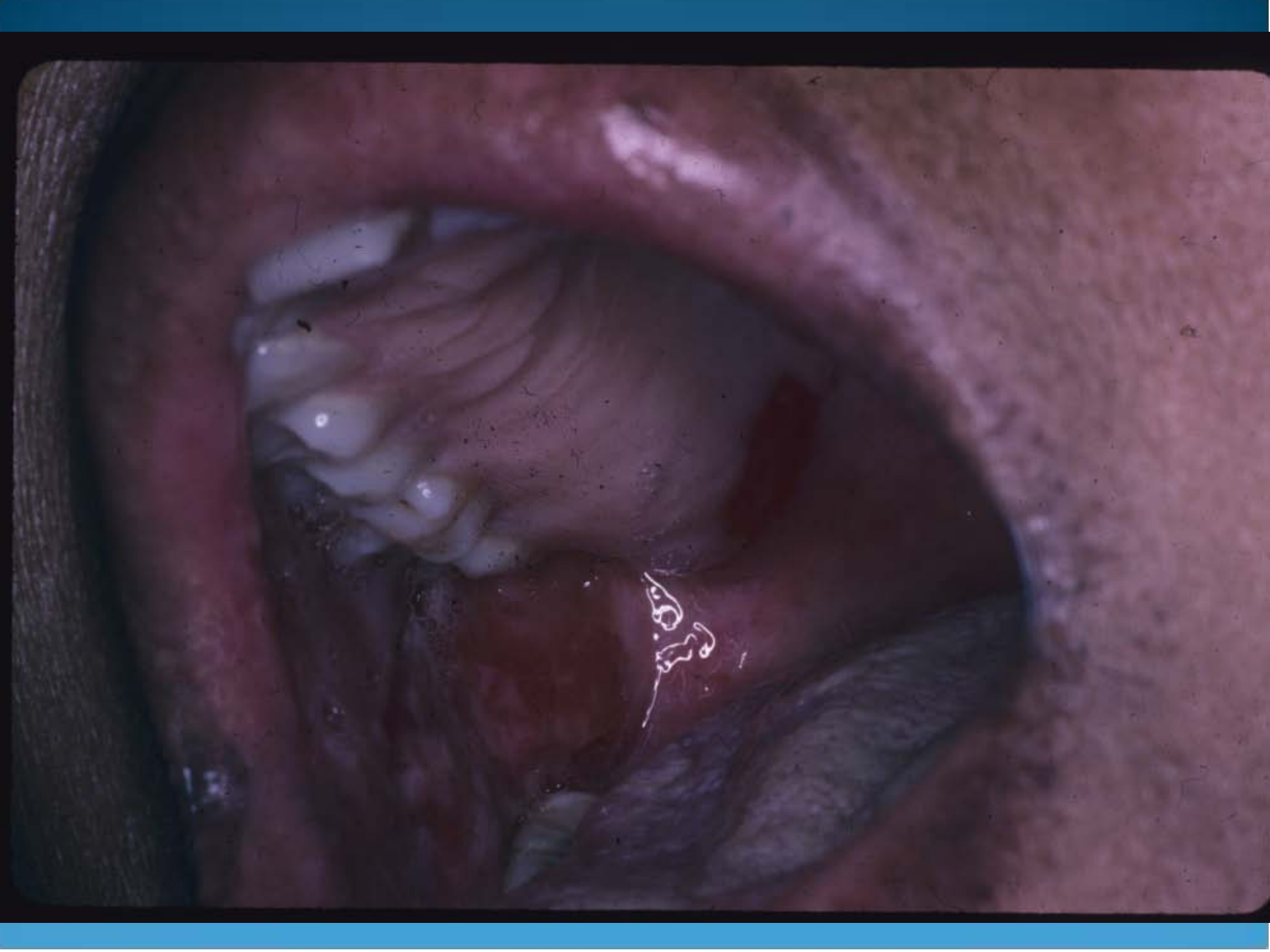
Clinical Features

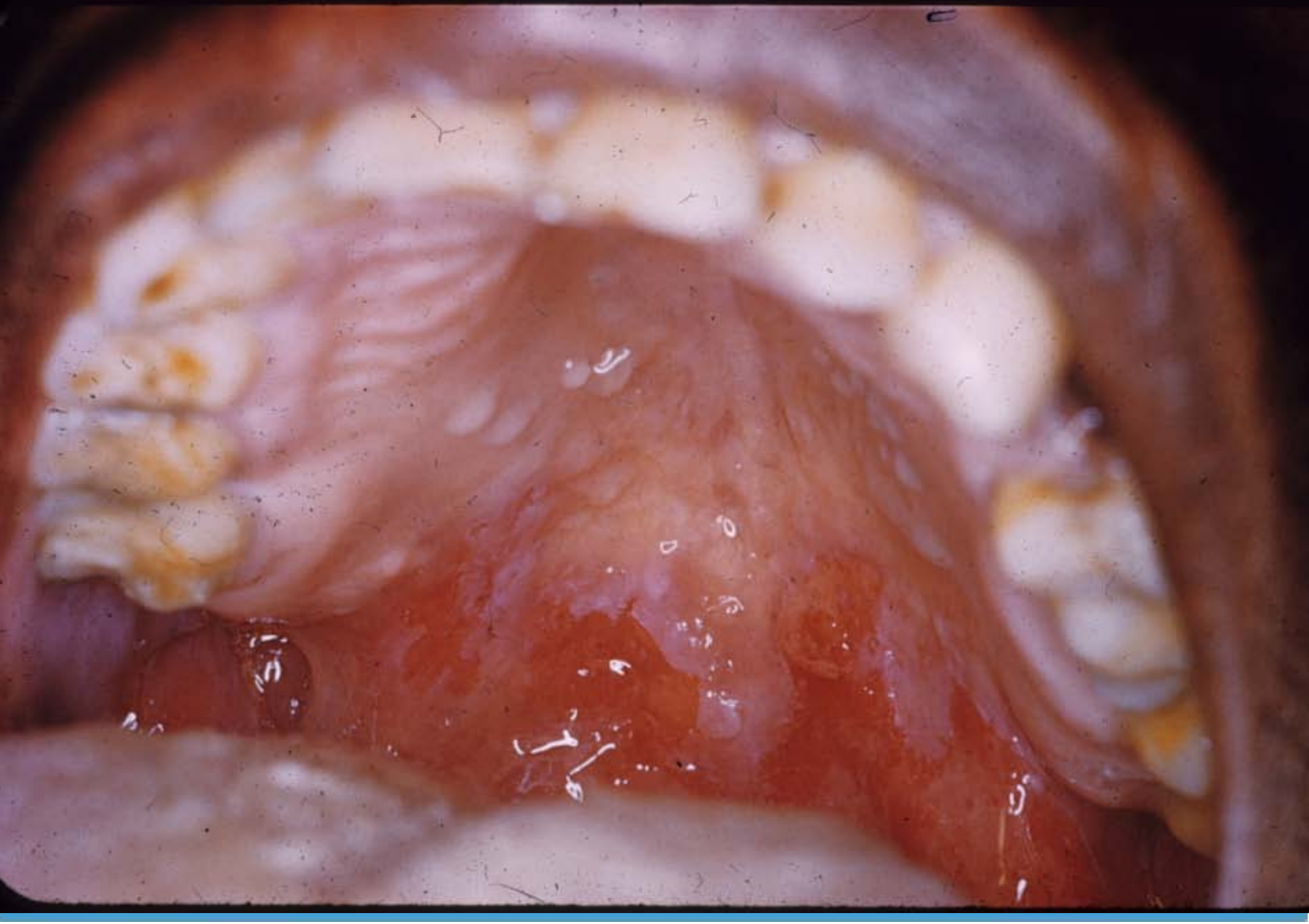
- Insidious onset
- Oral erosions
- Skin blisters/erosions
- Remissions/relapses
- Mucosal Dominant
  - Dsg 3
- Mucocutaneous
  - Dsg 3 and 1

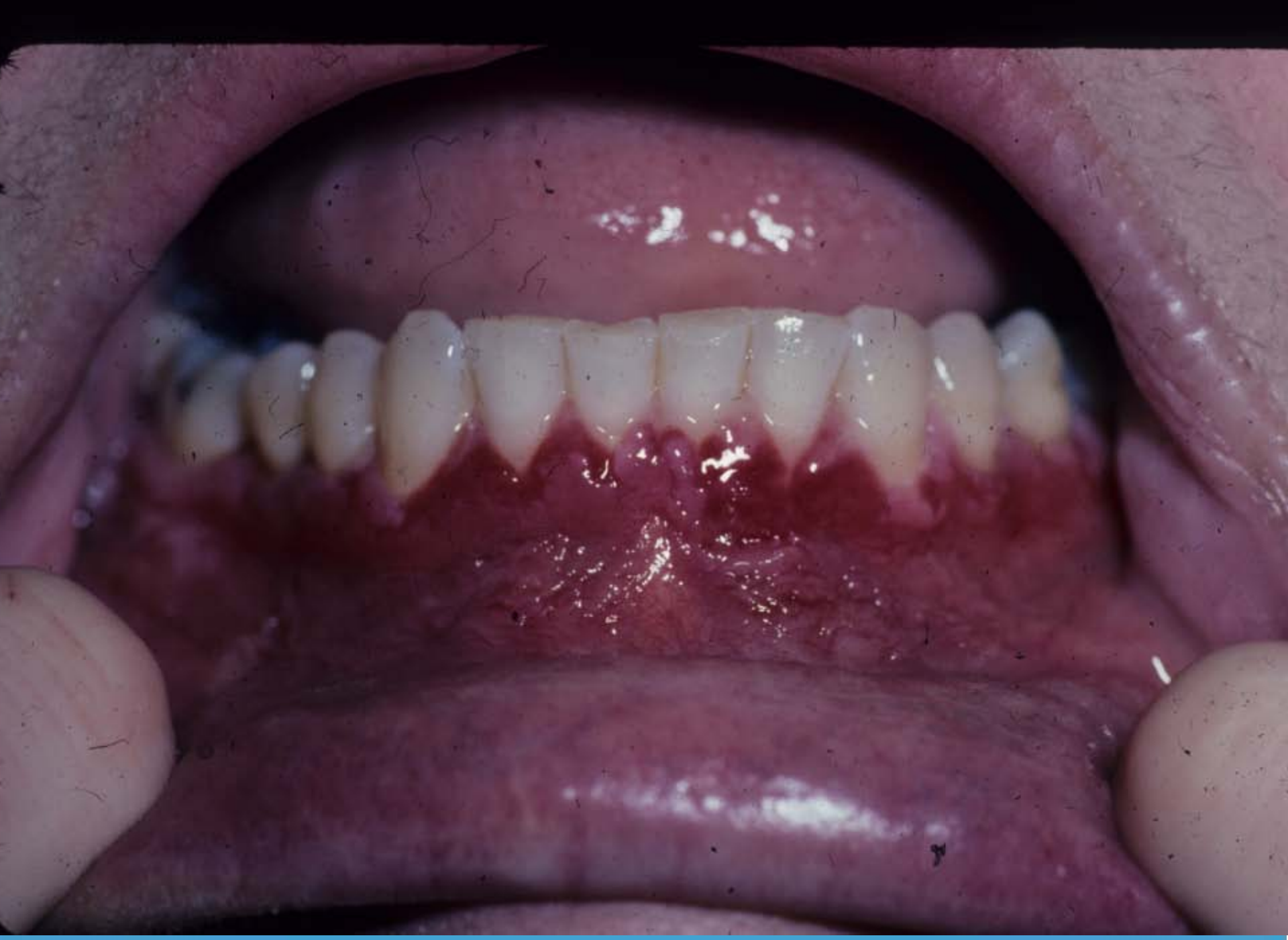


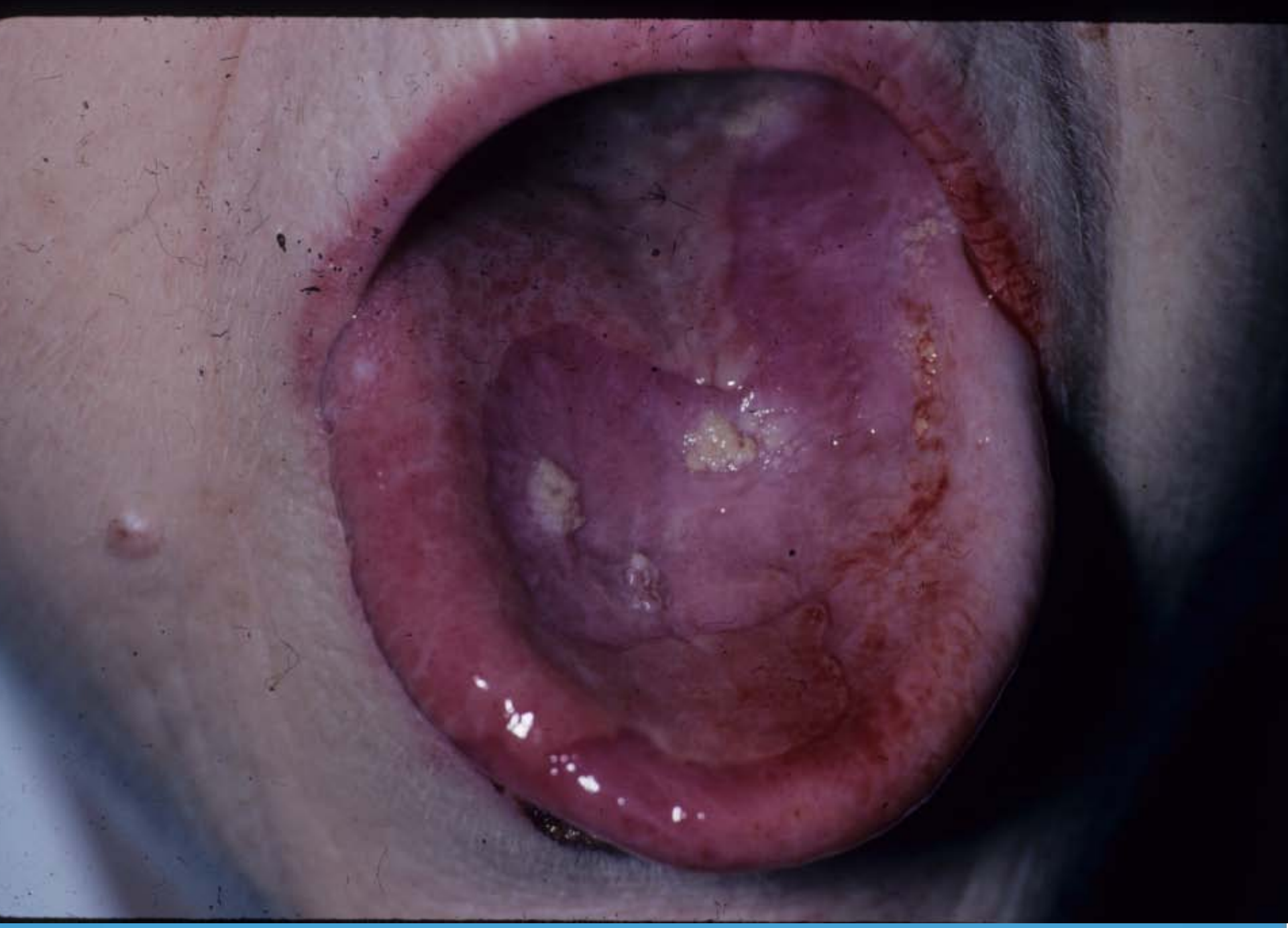
- Painful oral erosions
- Presenting sign
- Irregular
- Ill-defined borders
- Blisters are rare
- Buccal, palatine and gingival mucosa 1°

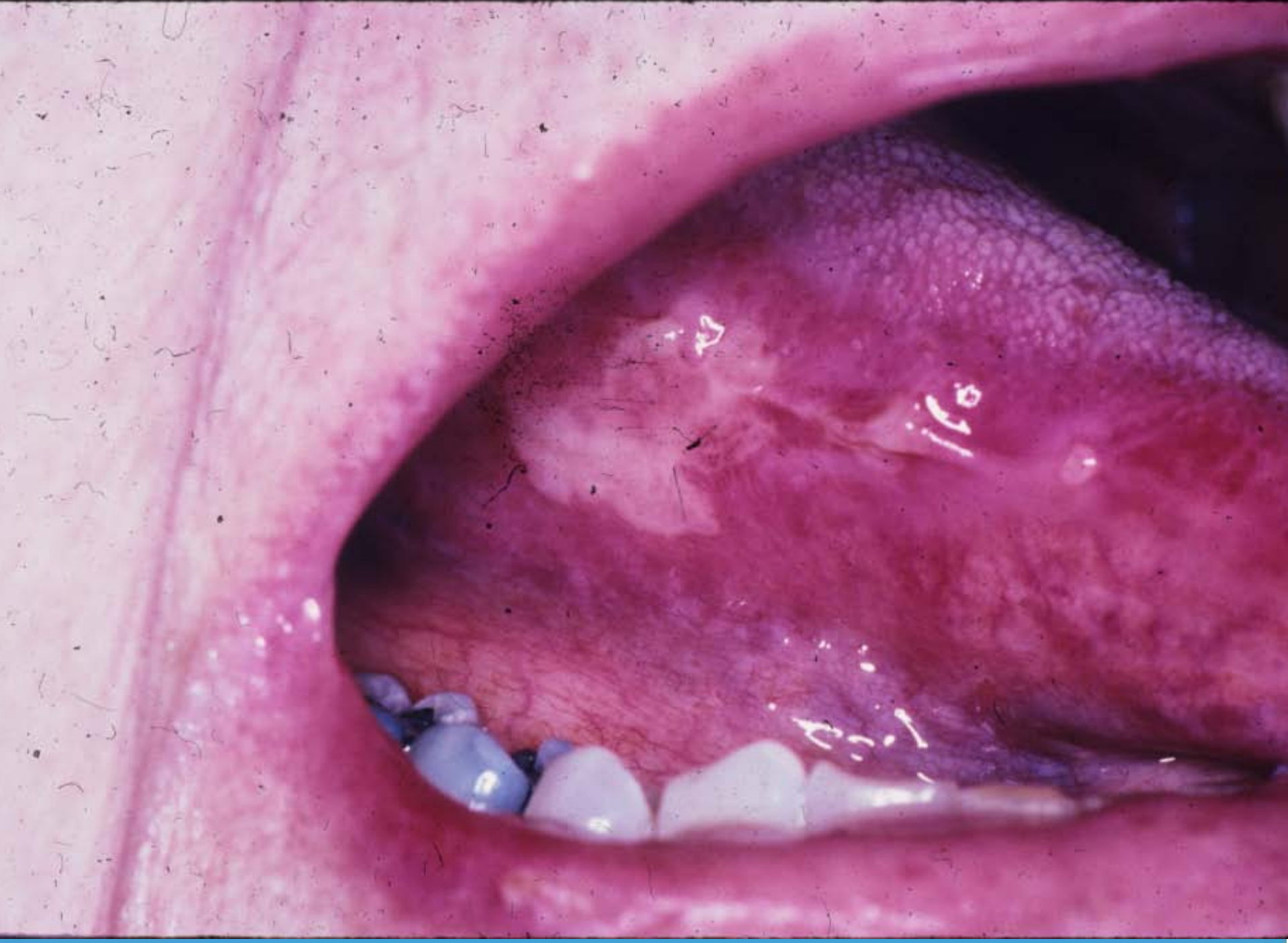


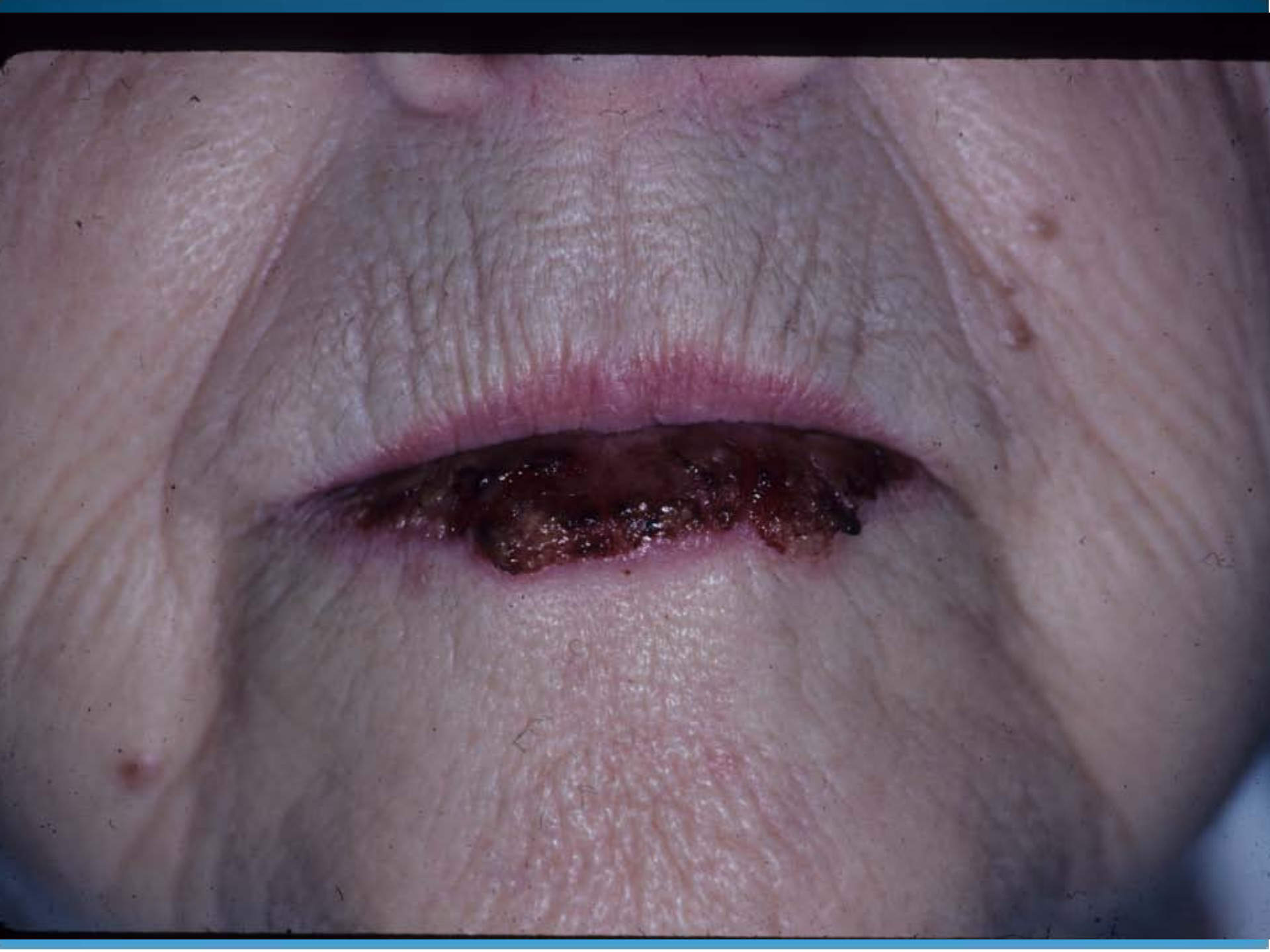


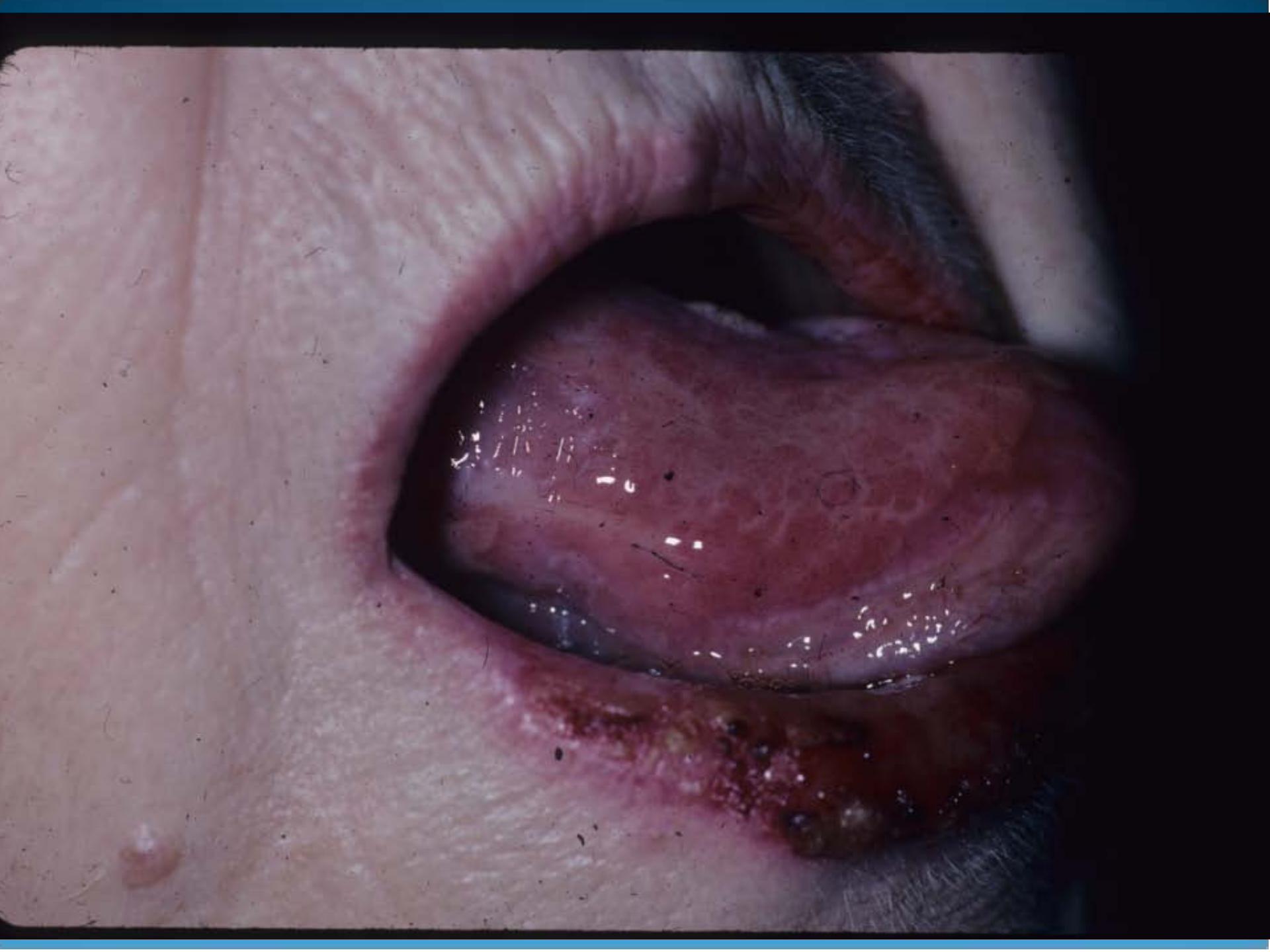




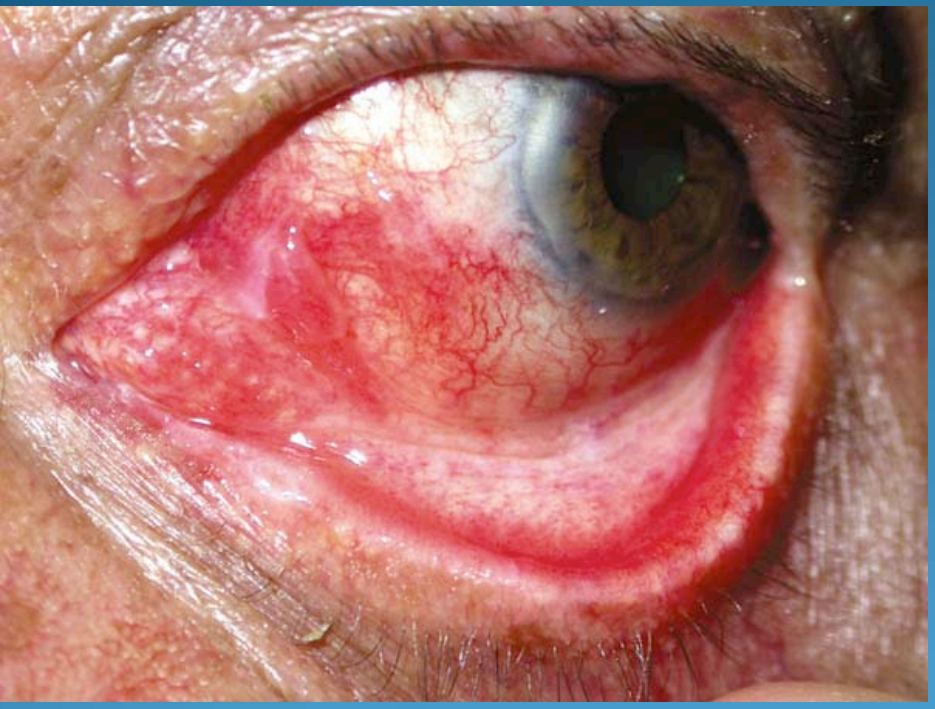


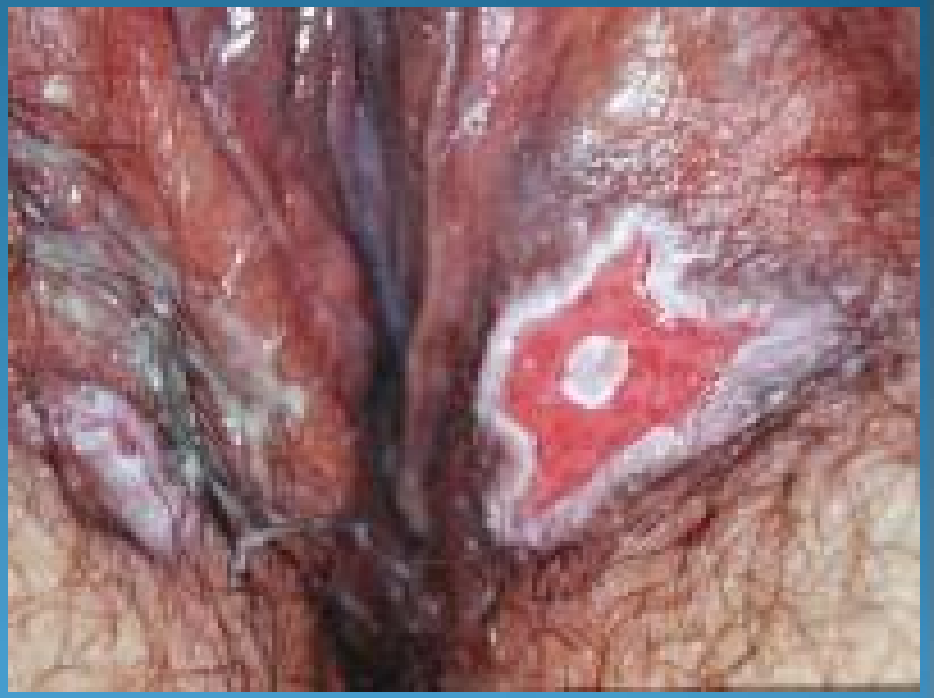




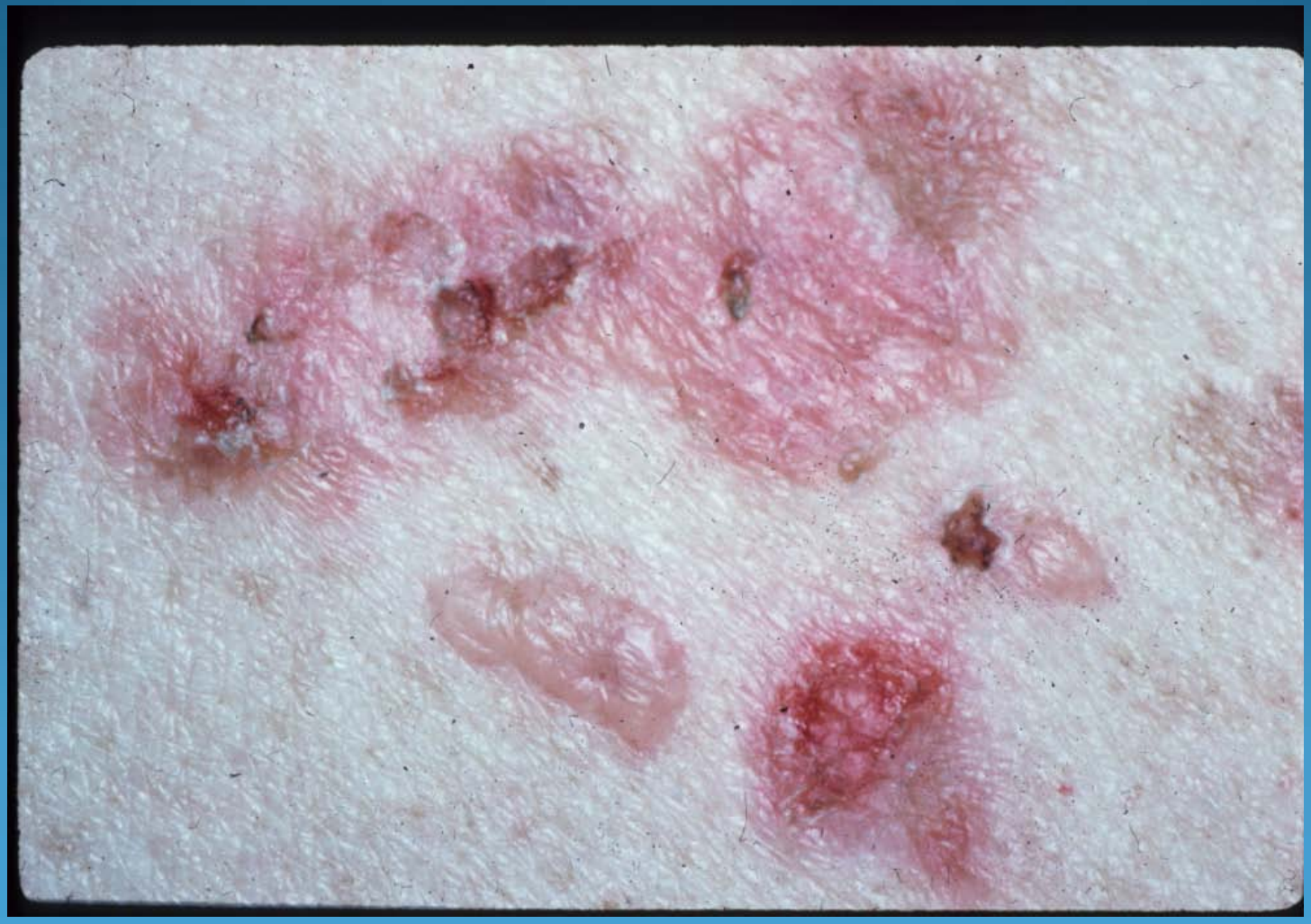


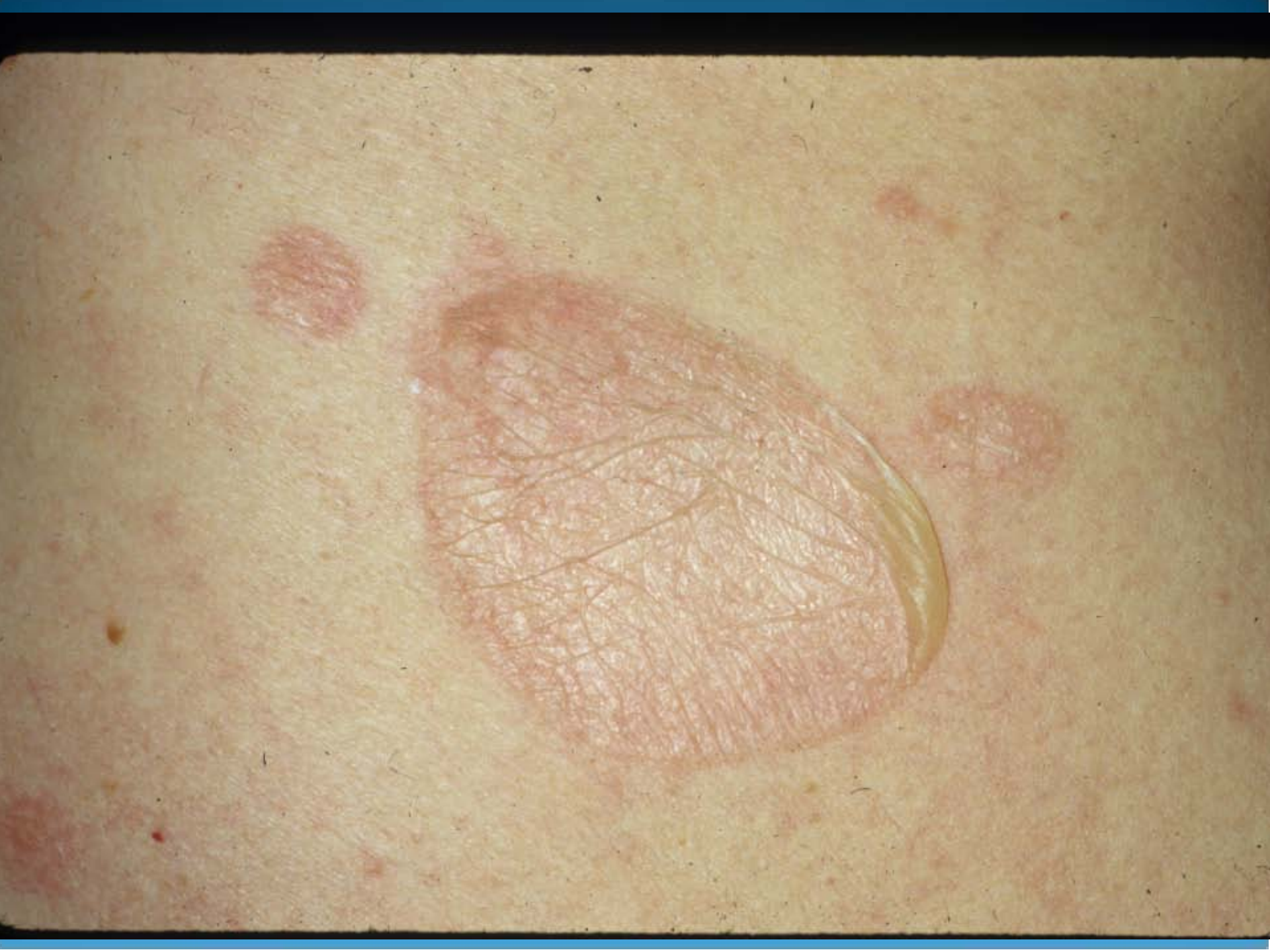
Any mucosa covered with SSE is vulnerable

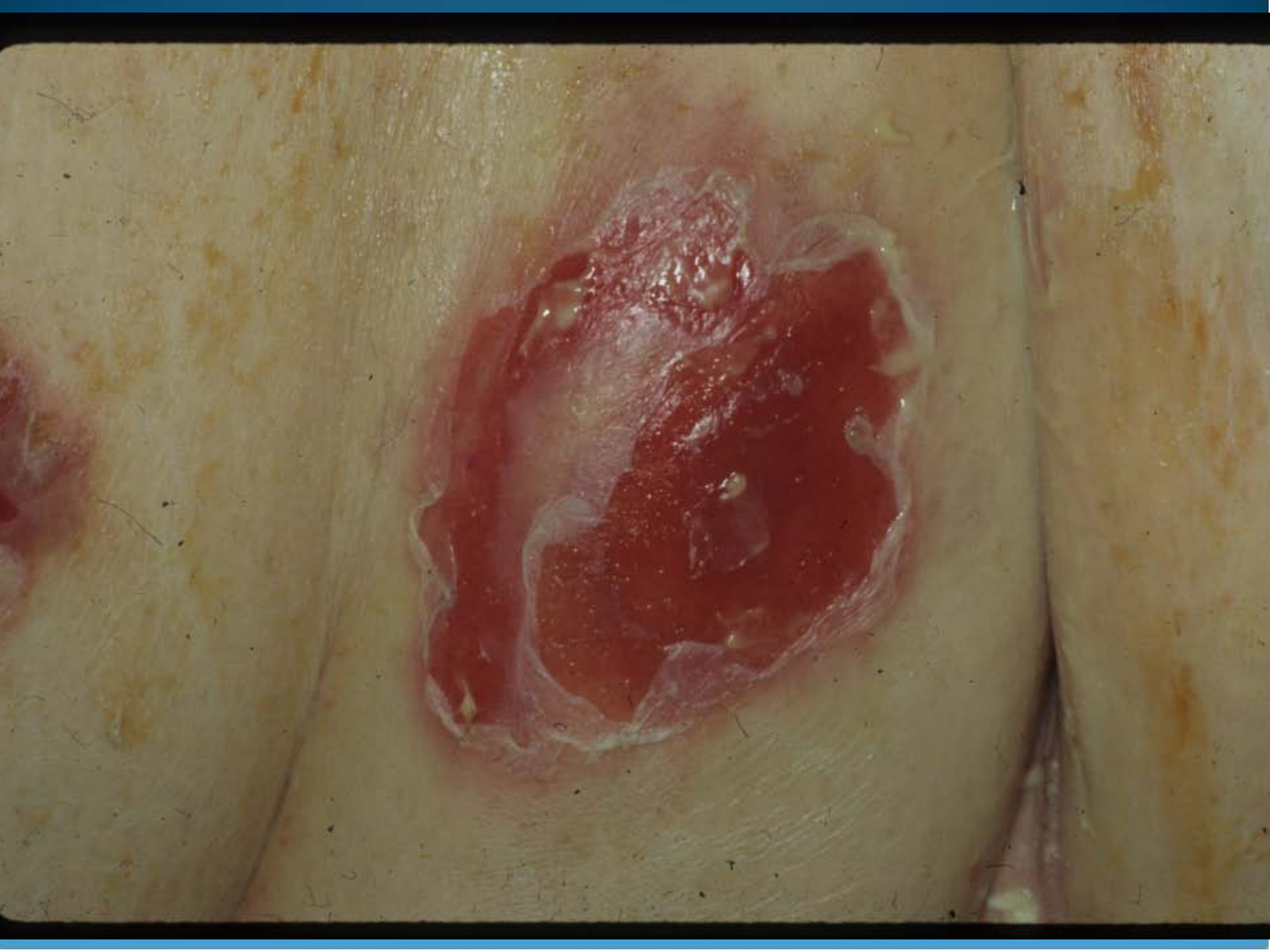




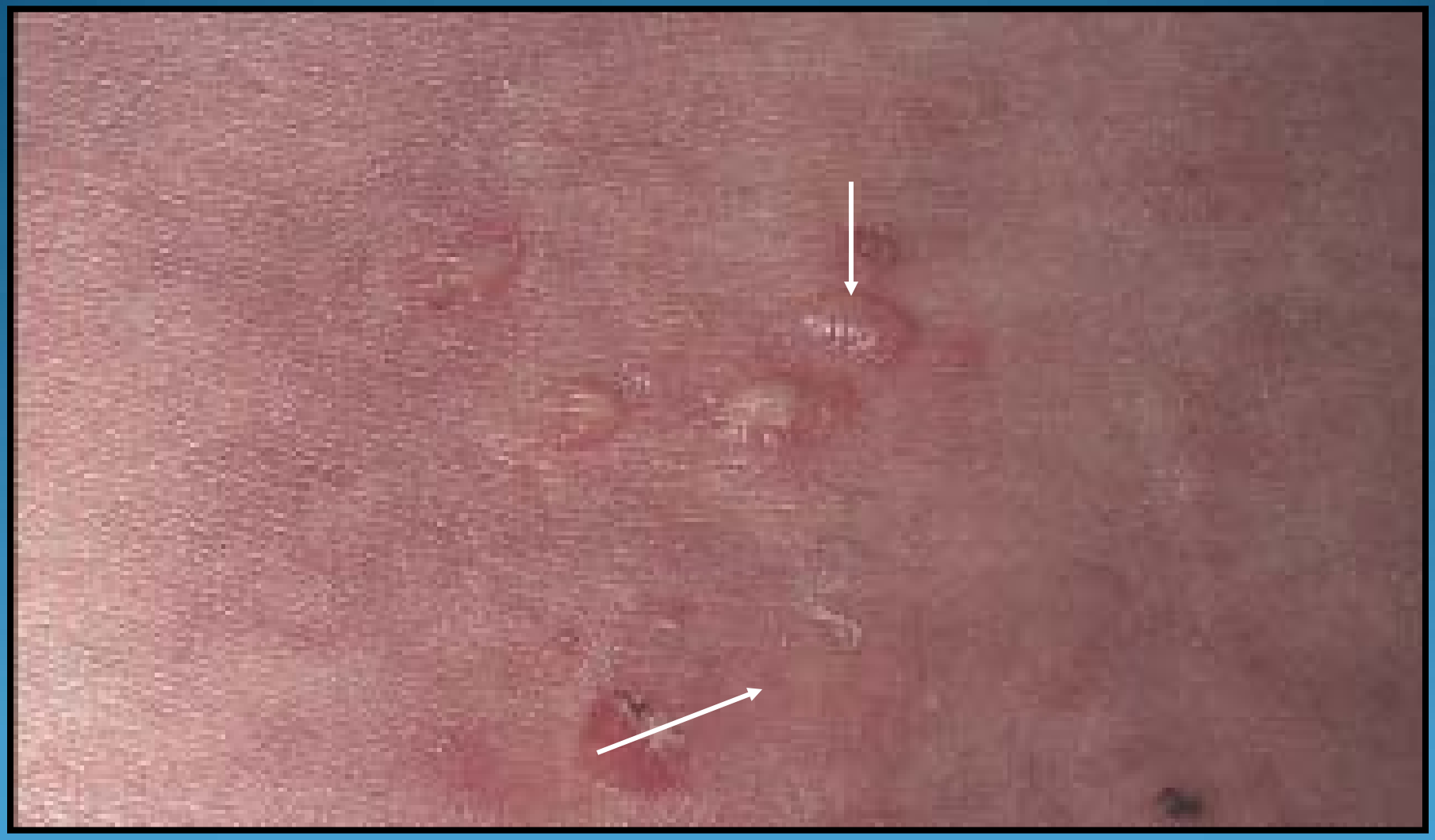
Flaccid vesicles/bullae → erosions



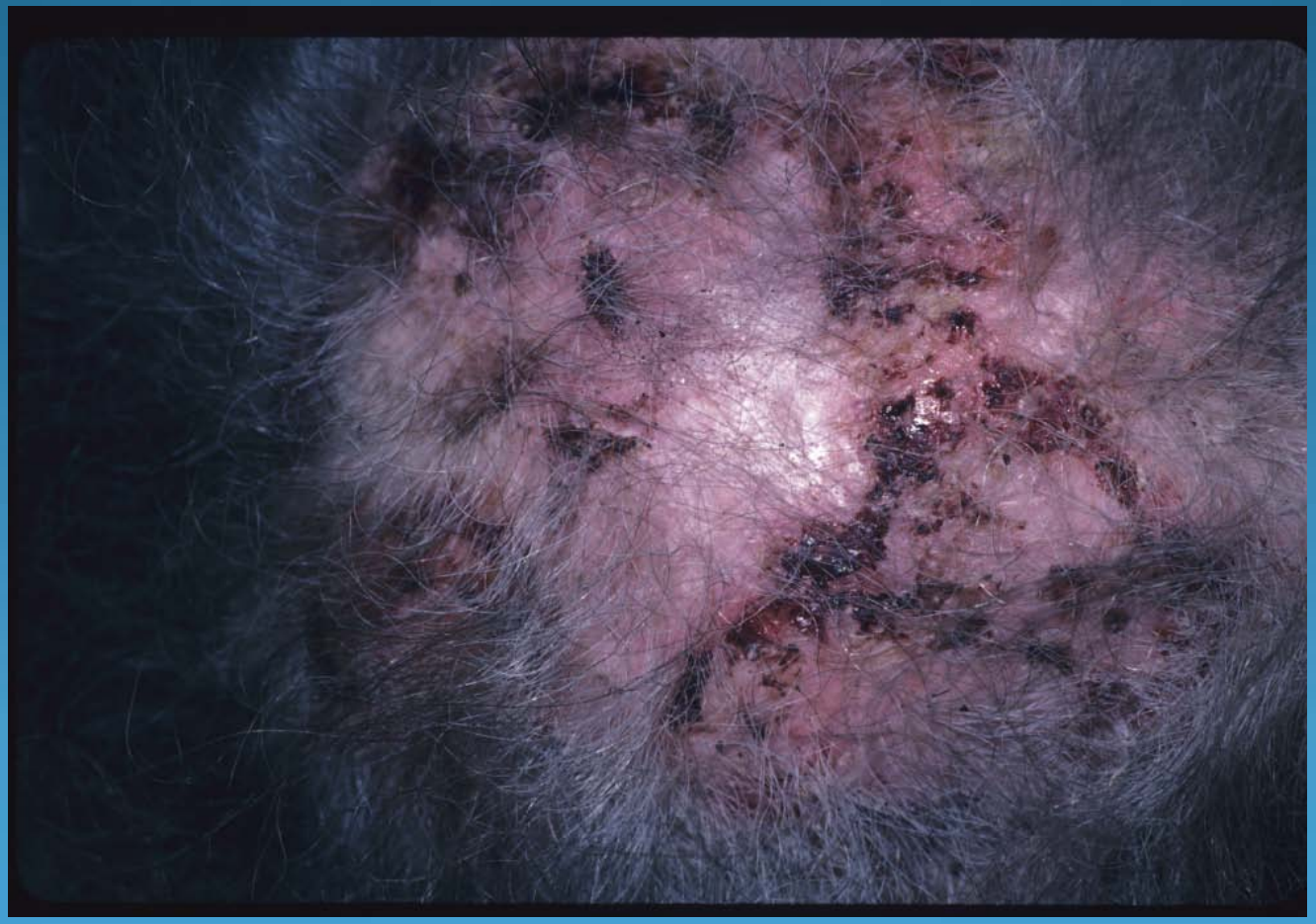


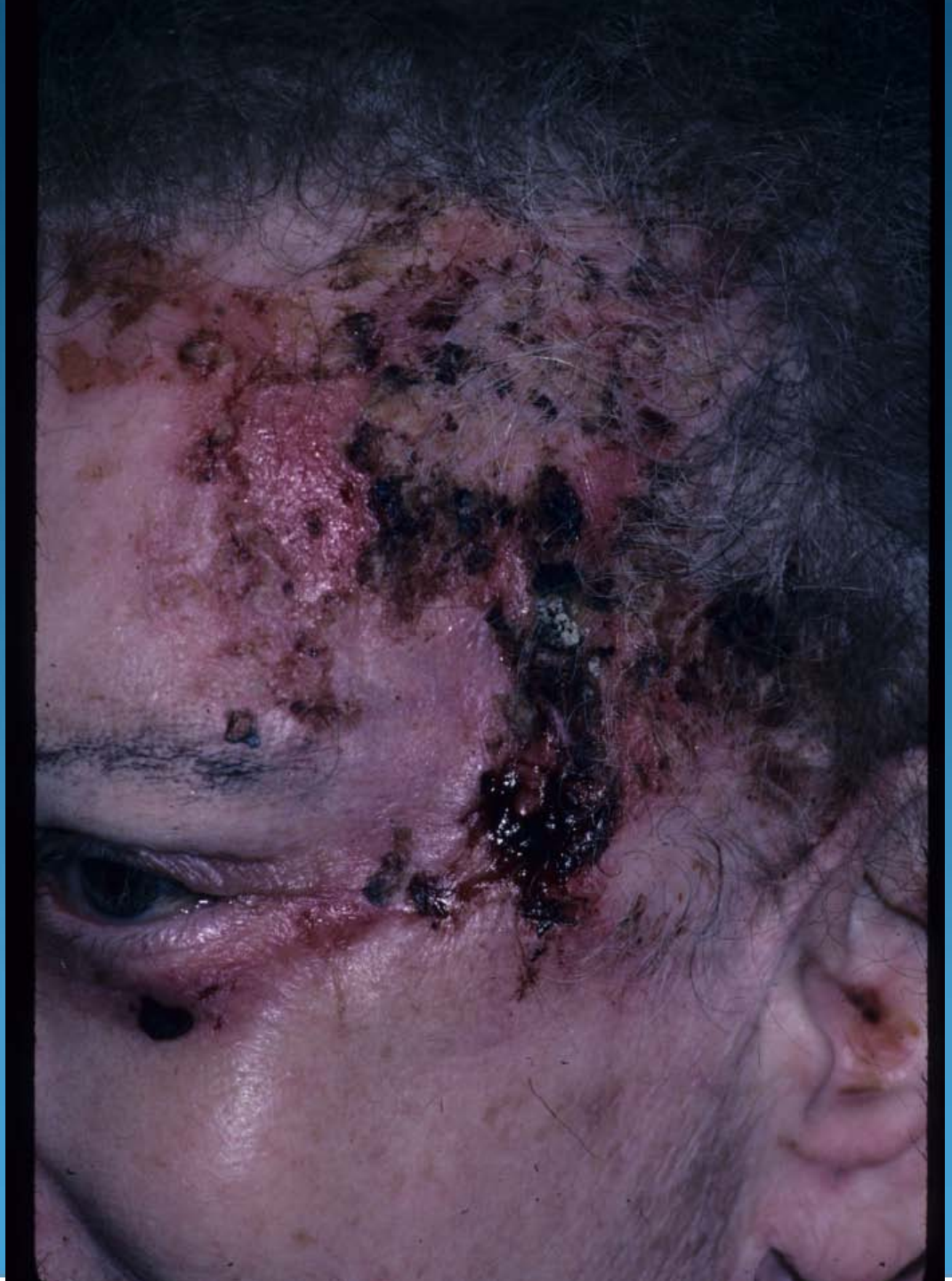


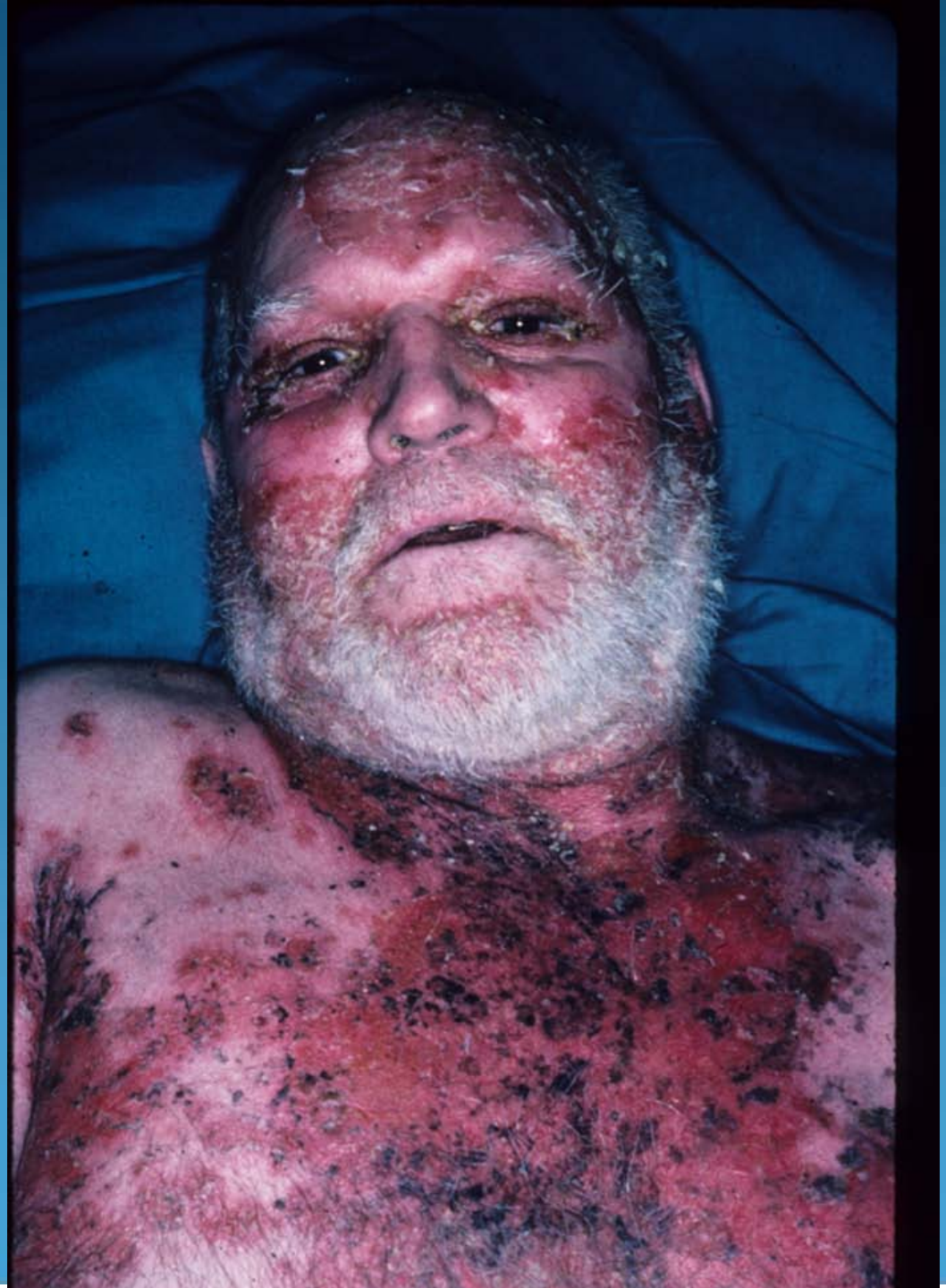
Nikolsky and Asboe-Hansen Signs

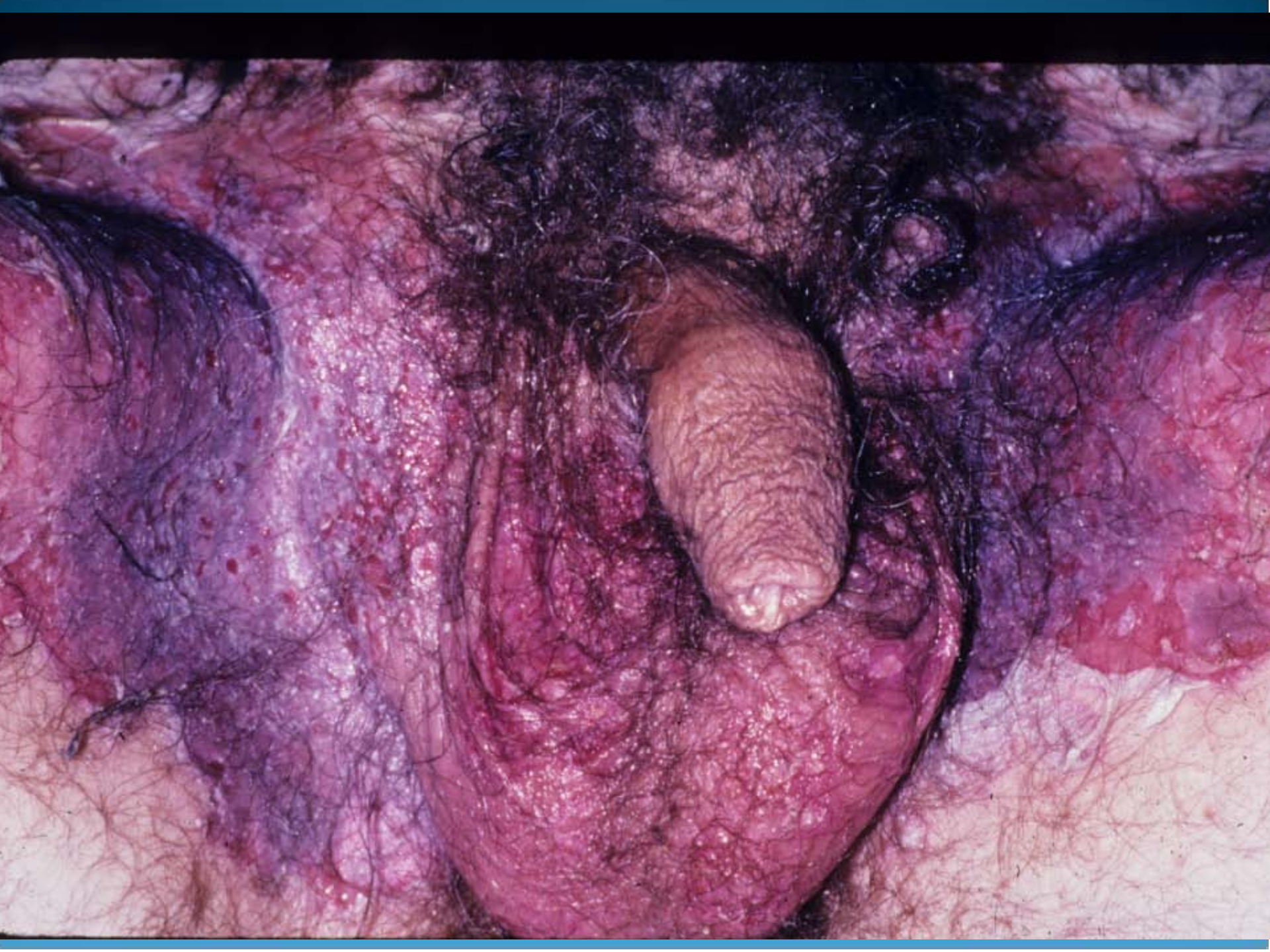


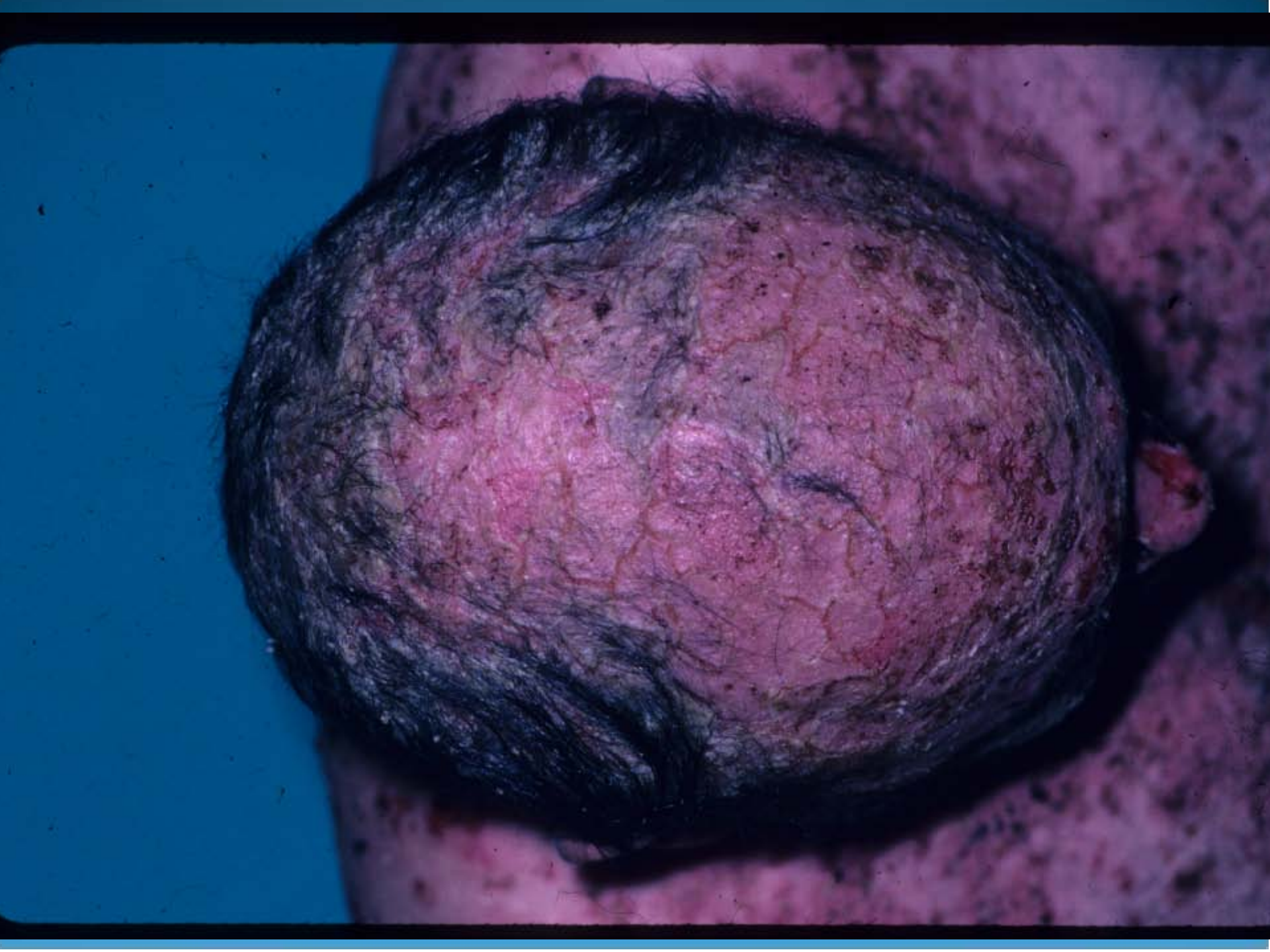
Head/neck → trunk/flexures → generalizes

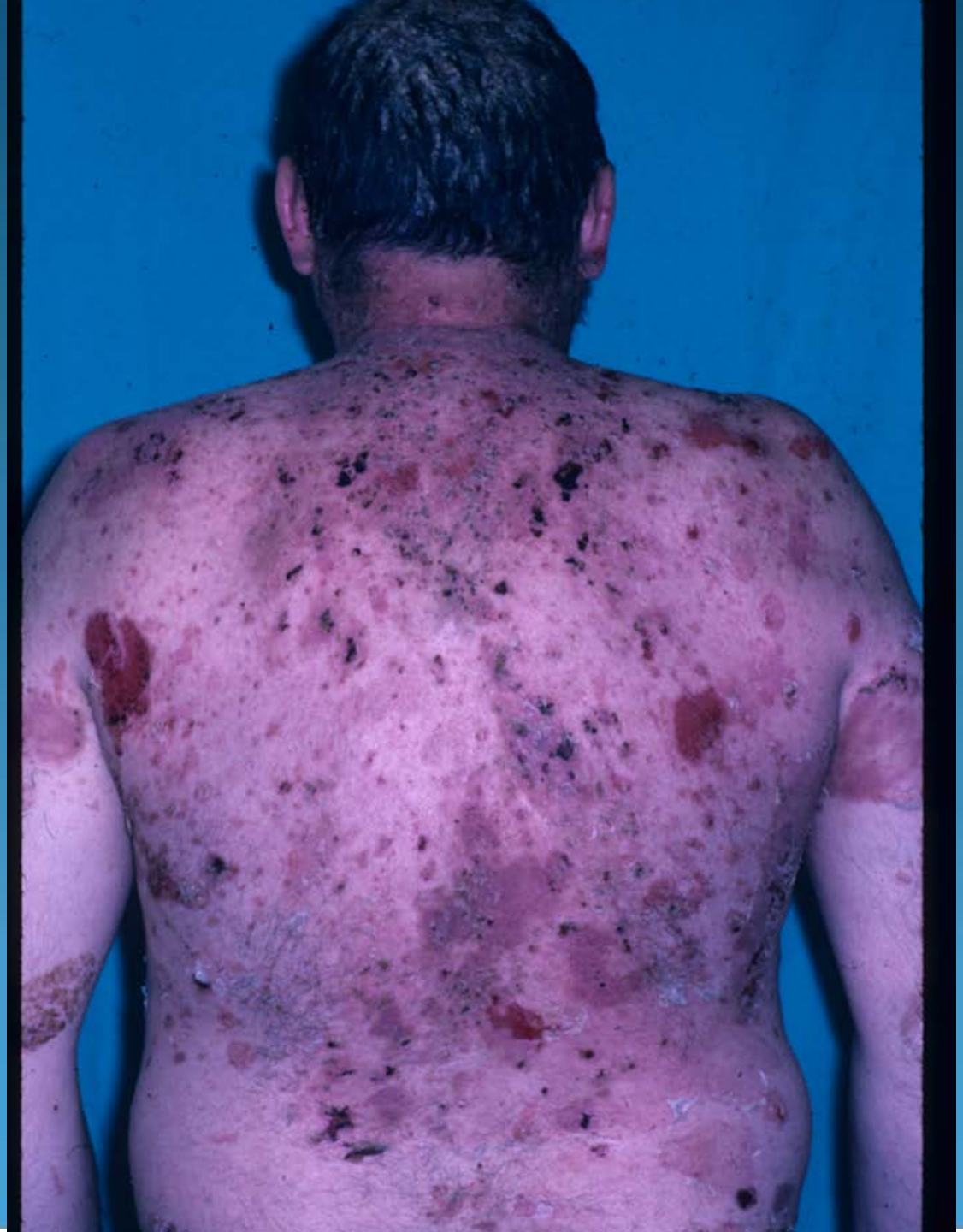






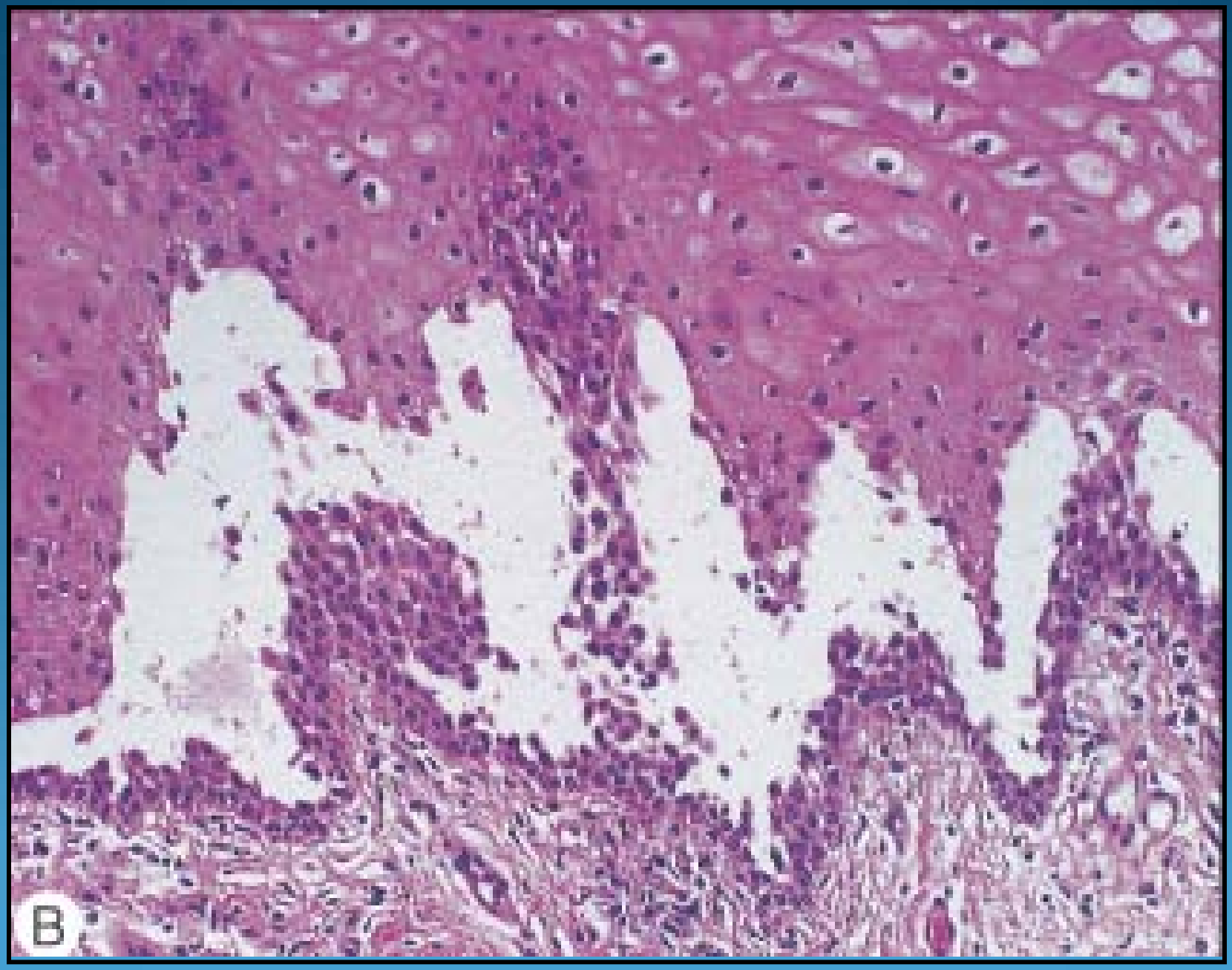






Biopsy Material

- H&E: early, intact vesicle
- DIF: normal, perilesional skin
- IIF: serum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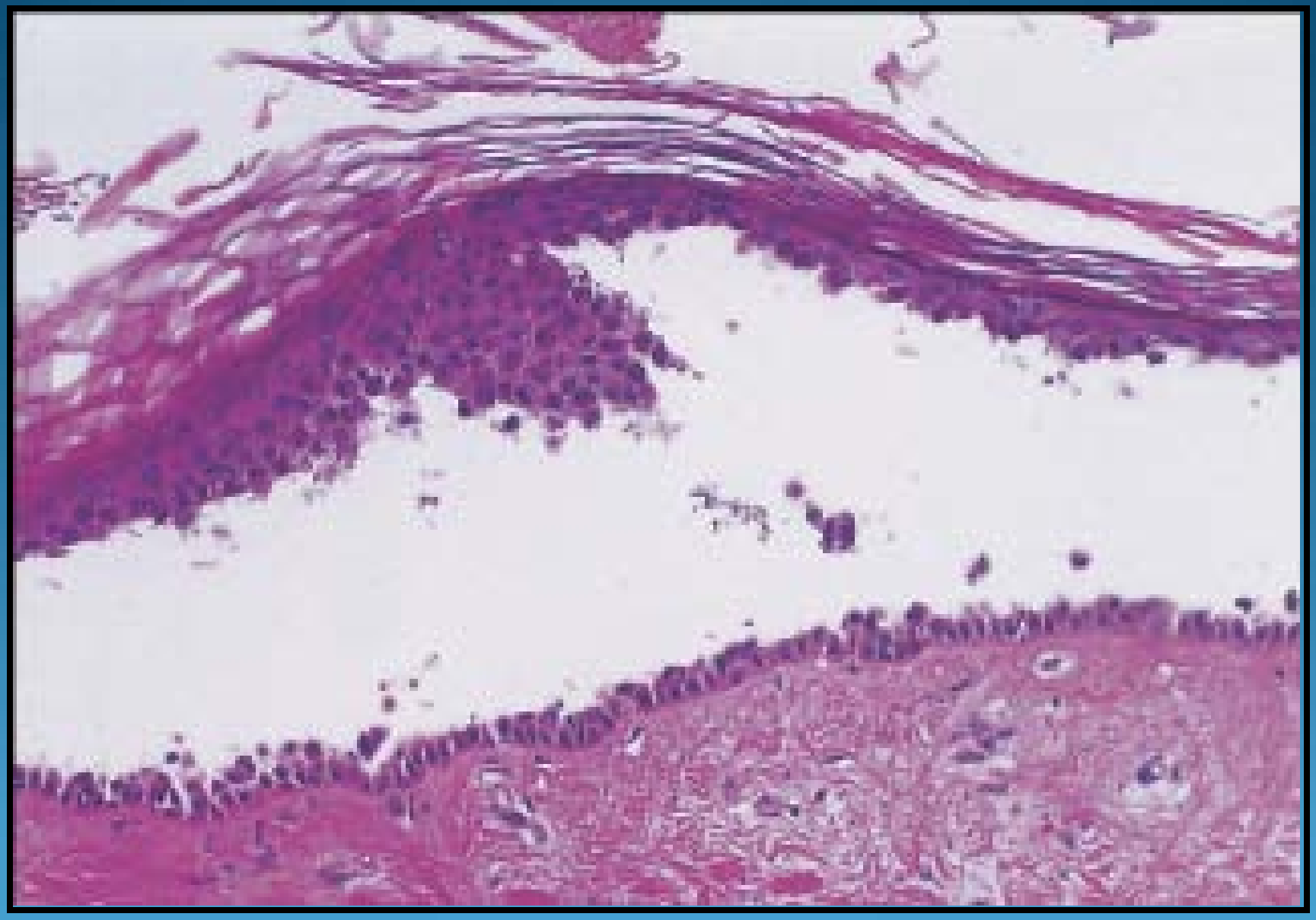
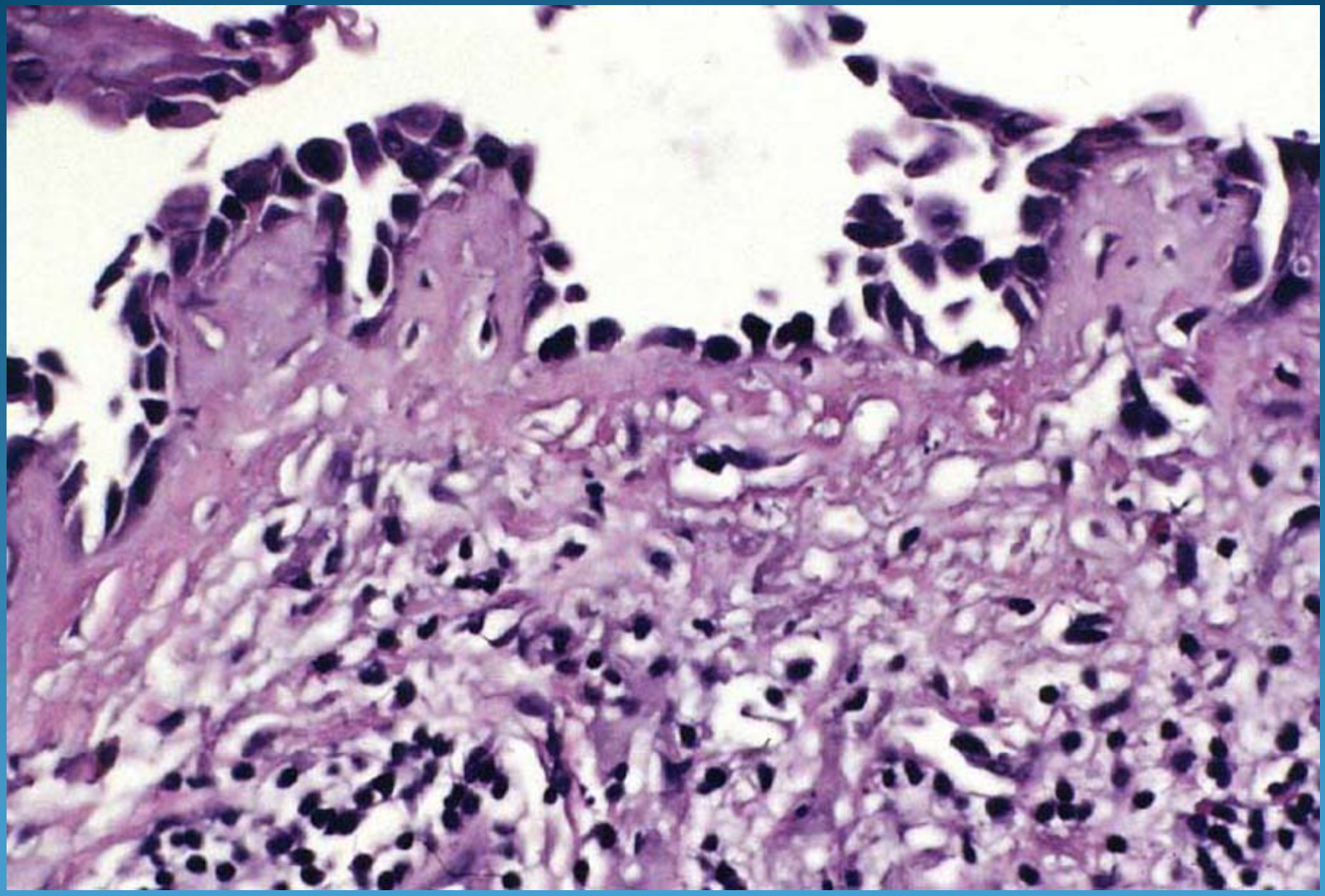
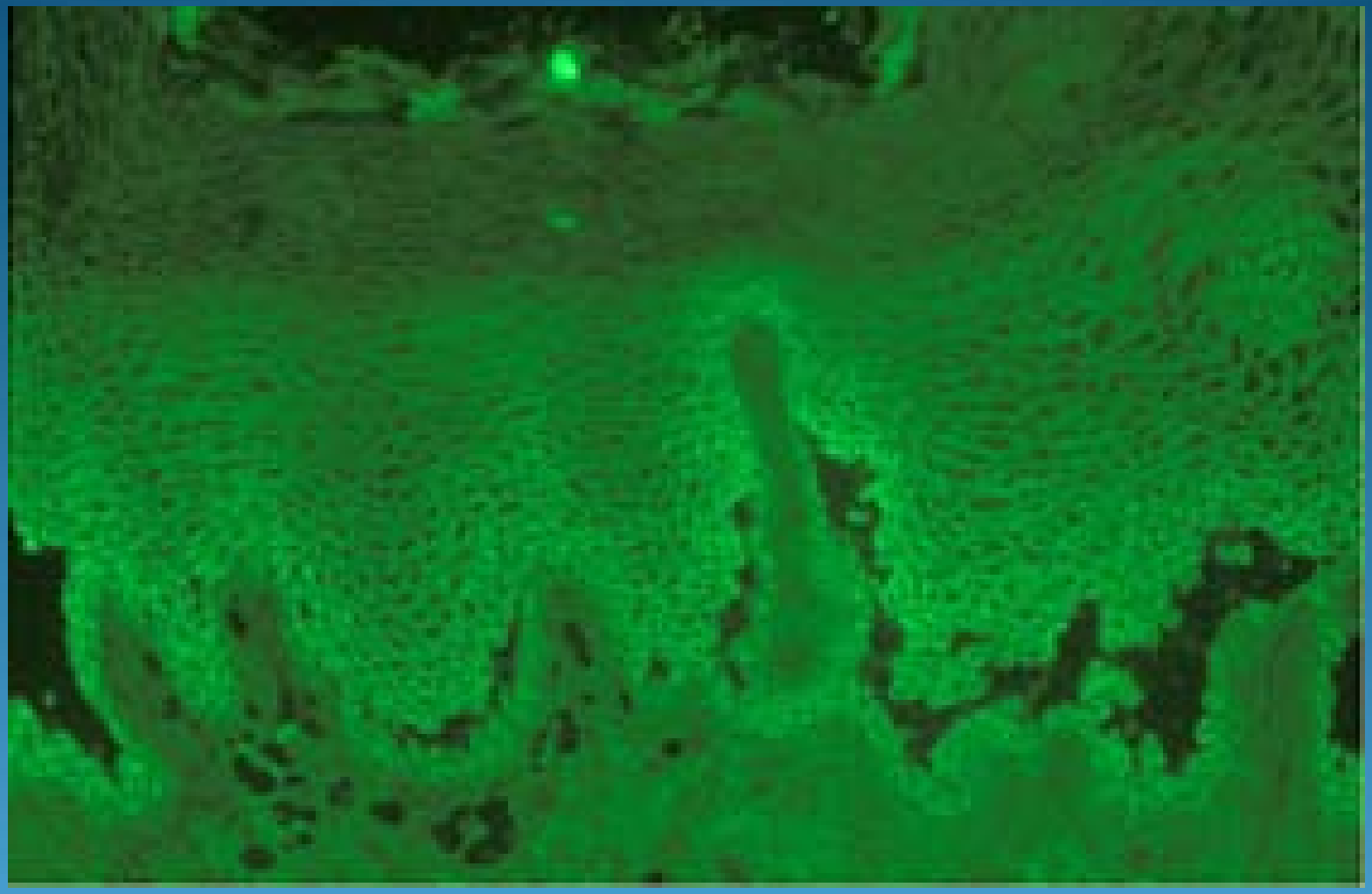




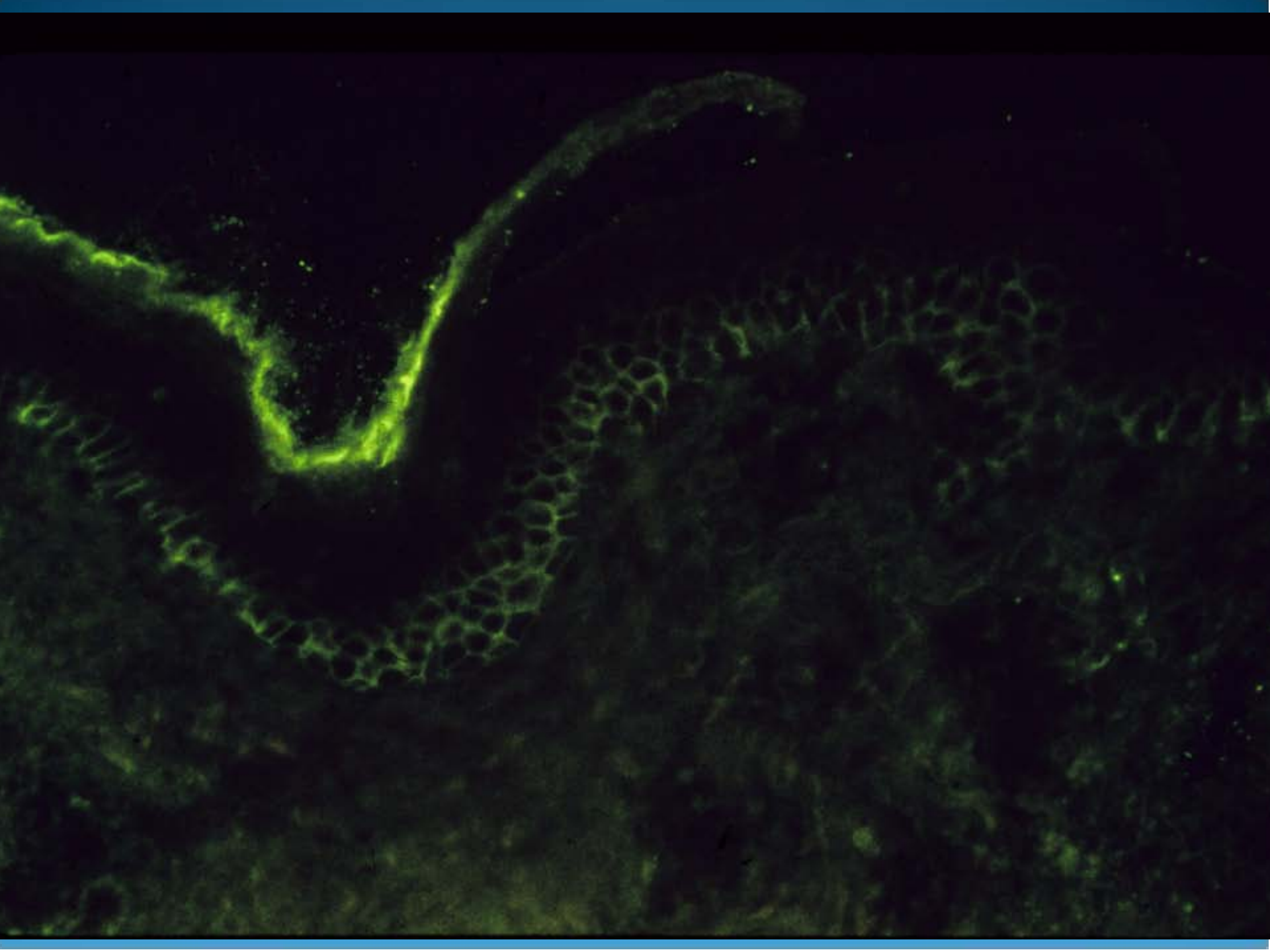
Direct Immunofluorescence

- Detects *in vivo* bound IgG on patients' skin or mucosa
- High sensitivity
- Intercellular, suprabasilar IgG4
- Variable C3 deposition
- No deposition at BMZ



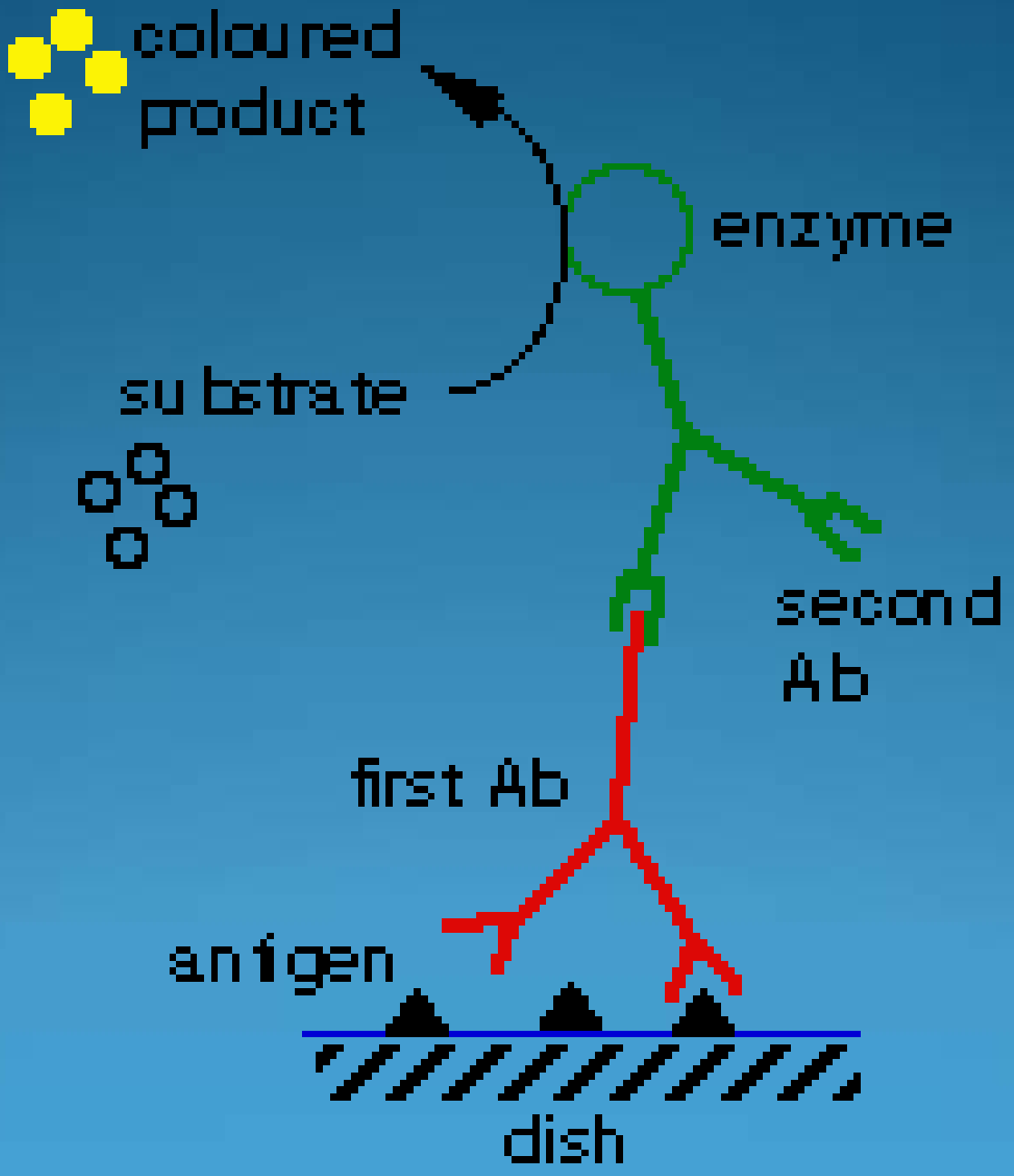
Indirect Immunofluorescence

- Examines patients' sera for circulating Ab
- Autoantibodies specifically bind to SSE
  - Monkey esophagus substrate
- 80-90% with active disease have circ Ab
- Correlates well with disease activity



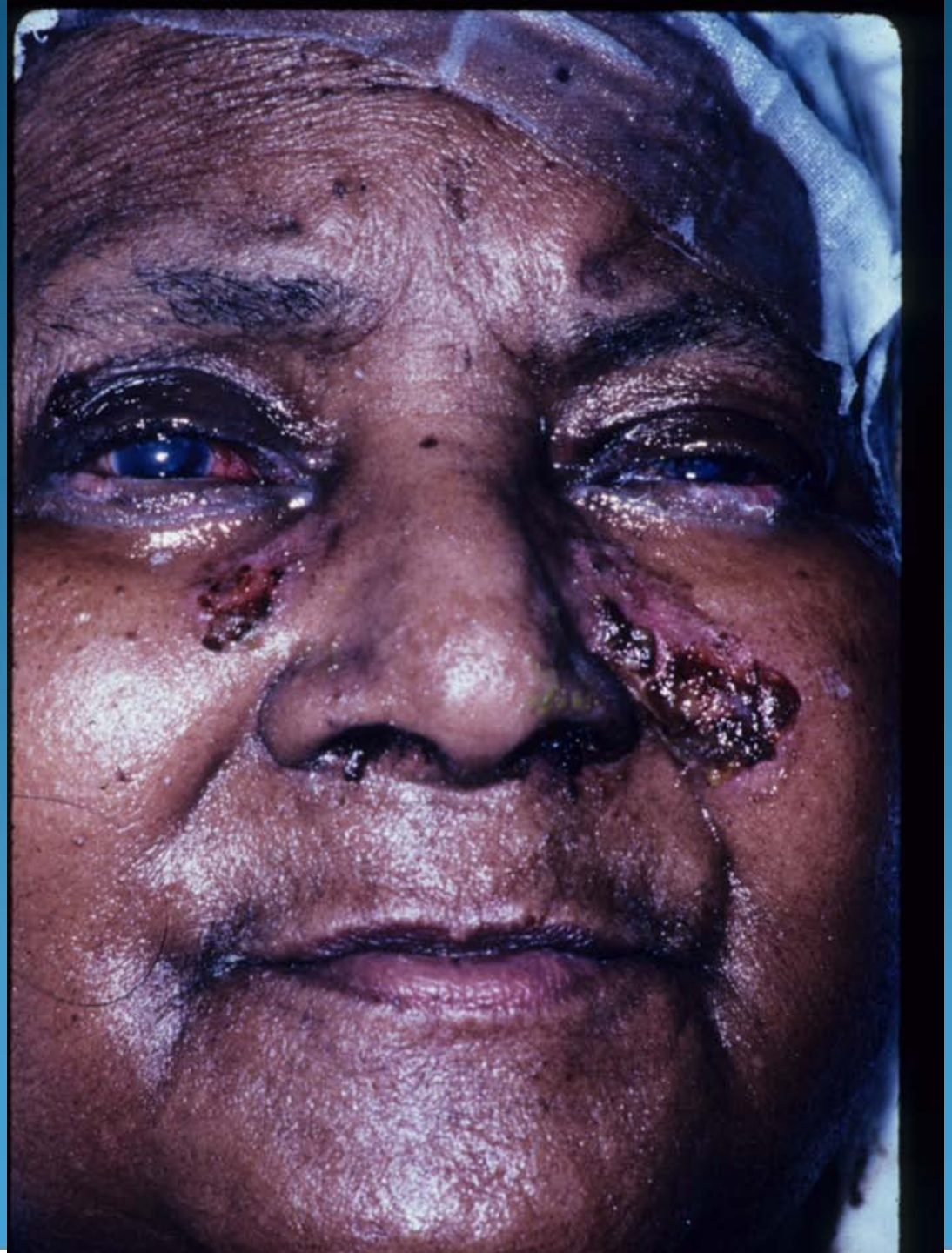
ELISA

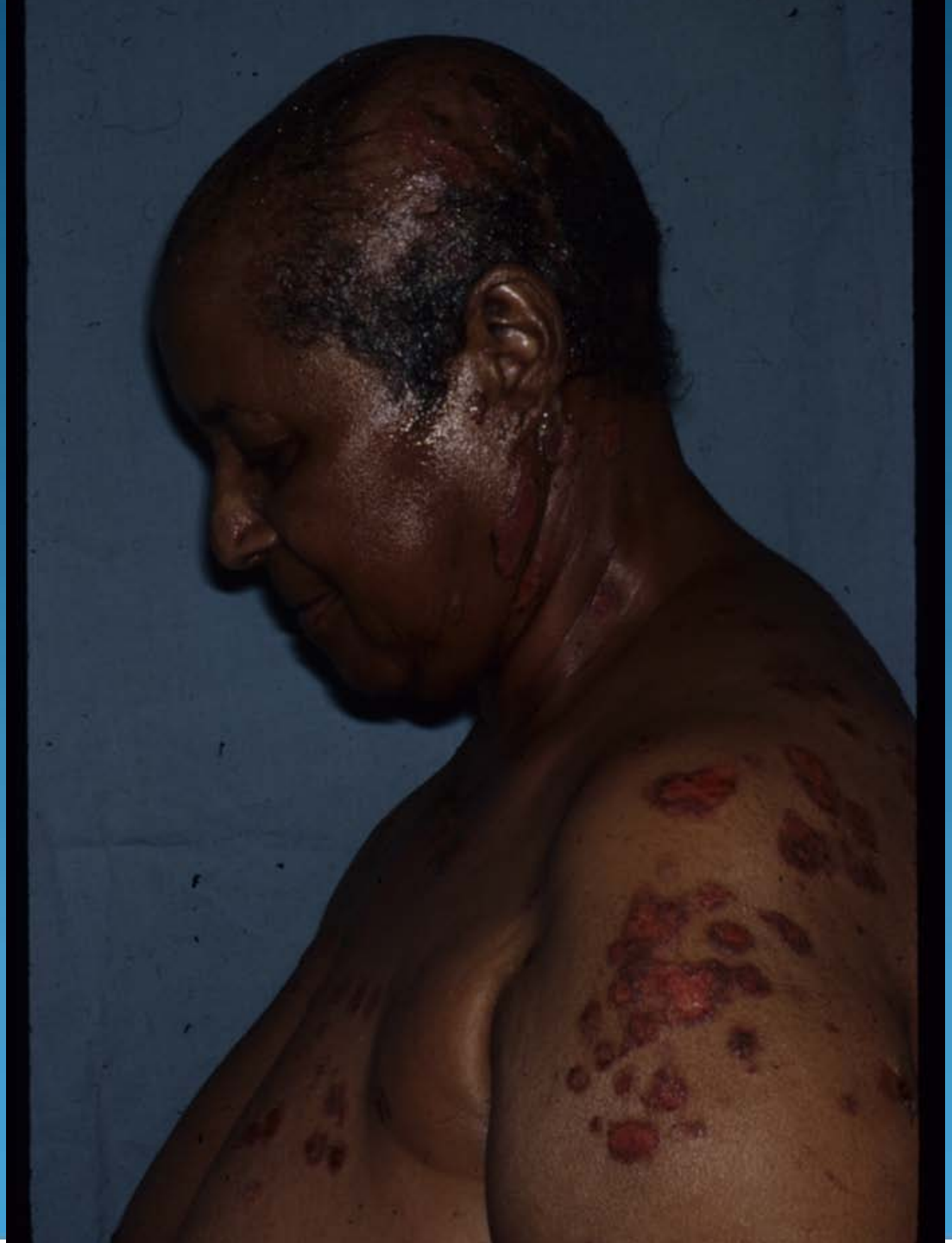
- Detects antibodies to desmogleins in serum
- Serum added to desmoglein-coated plates
- Enables serological distinction between subtypes
- Scores parallel clinical fluctuations
- Sensitive and specific
- *If Ab levels are high, results are not quantitative*


coloured
product
enzyme
substrate
second
Ab
first Ab
antigen
dish

Pemphigus Vulgaris

Natural History





- Relentless and progressive
- < 50%: sustained med-free remission
- Loss of epidermal barrier function
  - Metabolic imbalance; superinfection
- Mortality, pre-prednisone
  - 50% at 2 years, ~100% at 5 (sepsis)
- Mortality today is < 5%
  - Often due to complications of therapy

Treatment Objectives

Reduce autoantibody synthesis

Achieve long-term remission

Minimize side effects of therapy

Management Approach

1. Confirm the diagnosis
2. Assess for comorbid conditions
   - PUD, TB, DM, HTN, lipids, osteoporosis
3. Baseline evaluation
   - CBC, CMP, HBV/HCV, HIV, CXR/PPD
   - Bone densitometry
   - Serum antibodies by IIF or ELISA
   - Pneumonia and influenza vaccine

Management Approach

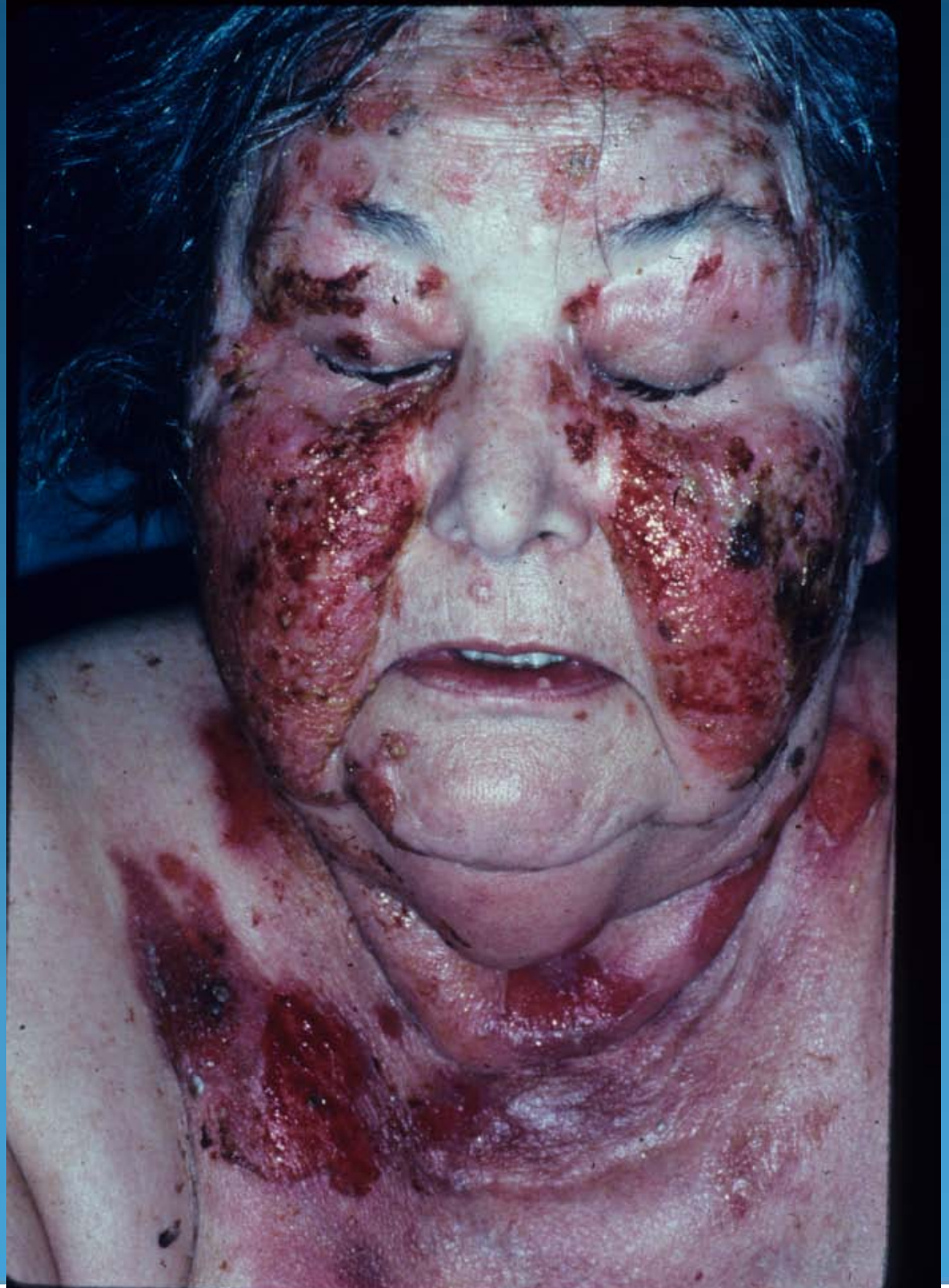
4. Systemic treatment
5. Wound care
6. Supportive care
7. Close clinical/laboratory monitoring

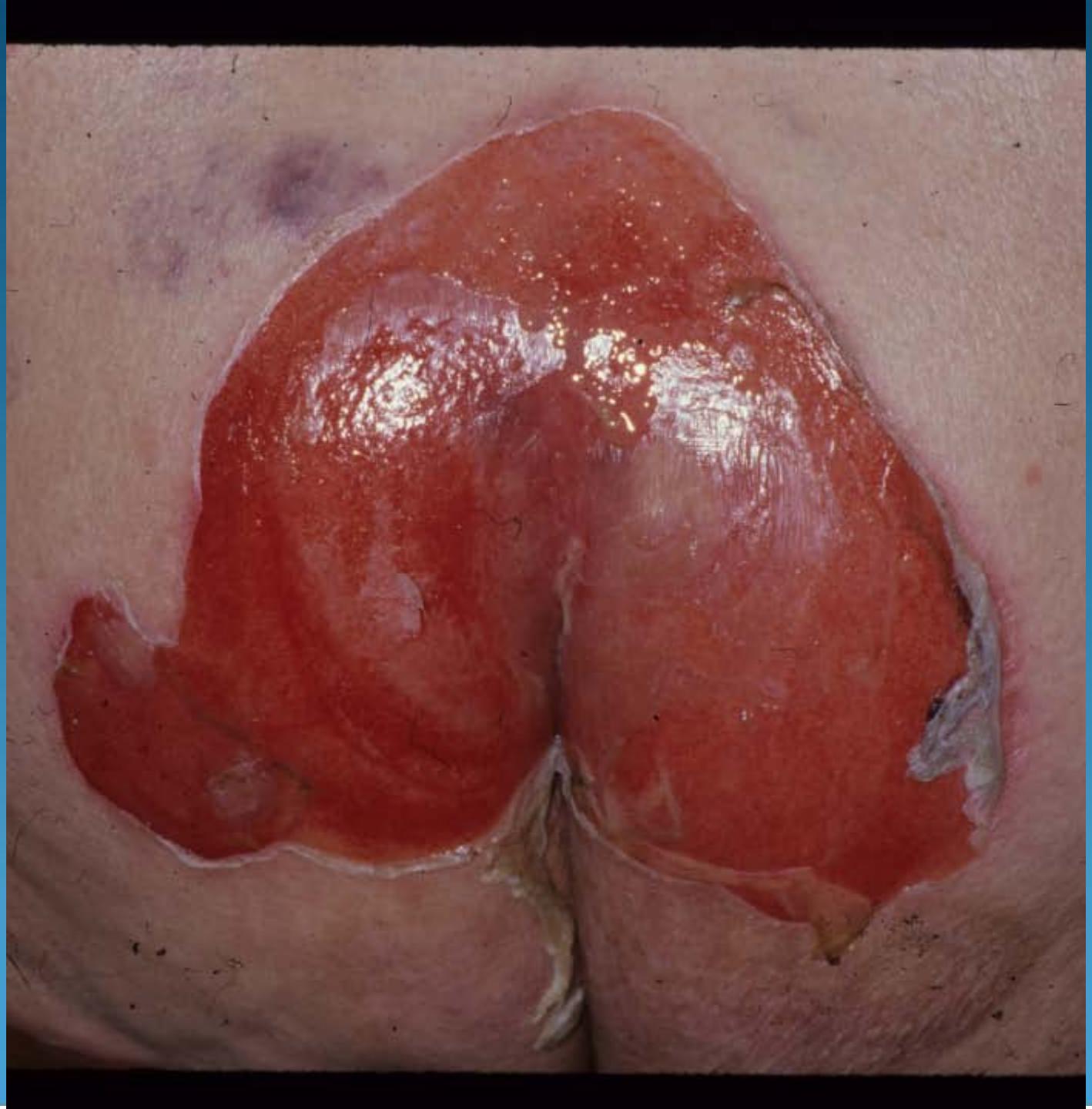
Management Principles

Early systemic treatment is key

- Less chance of *epitope spreading*
- Greater chance of better control and prolonged remission

Limited disease will generalize





Management Principles

<u>Goal</u>: Reduce autoantibody production

- Limited number of agents
- Specific antibody suppression is impossible
- Basis of therapy is *nonspecific immunosuppression*

Treatment Efficacy

1. Clinical parameters
   - ✓ New lesions
   - ✓ Healing of existing lesions
   - ✓ Nikolsky sign
2. Laboratory monitoring
   - ✓ Antibody levels via IIF
   - ✓ Less reliable than clinical exam
   - ✓ Goal: absence of circulating and bound Ab

Treatment Considerations

- The disease
  - Severity, duration, sites of involvement
- The patient
  - Age, comorbidities, drug tolerance, quality of life
- The drugs
  - Mechanism, onset of action, safety, cost, practicality

1. Get control
   - ✓ Correct drug at the correct dose
2. Keep control
   - ✓ Steady dosing during healing
3. Maintain control
   - ✓ Lowest dose necessary

Combination Therapy

systemic corticosteroids

+

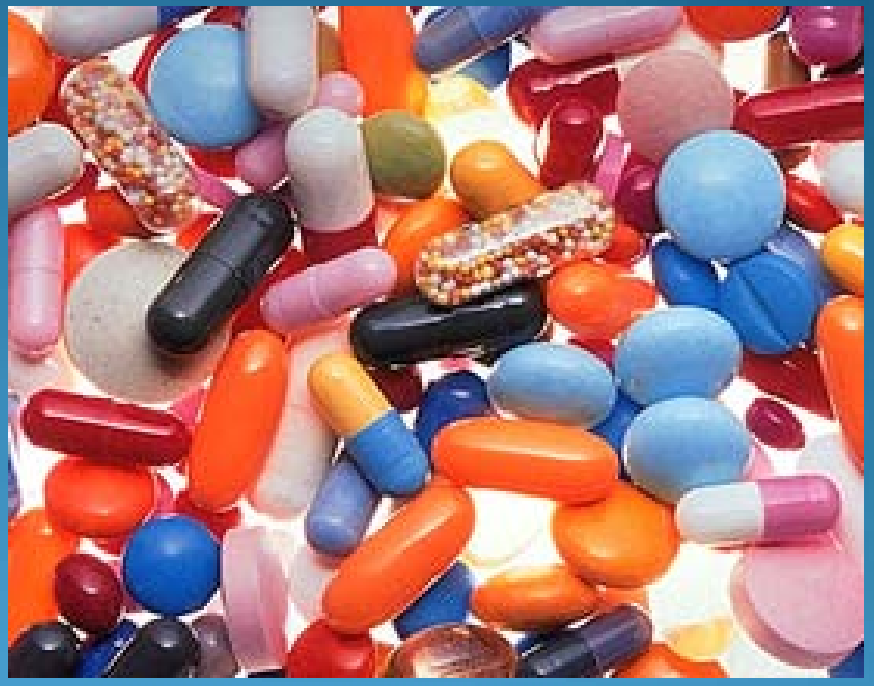
systemic immunosuppressives

↓

maximizes efficacy

&

minimizes side effects



Therapeutic Choices

Rapid Onset

- Systemic steroids
- IVIG
- Plasmapheresis

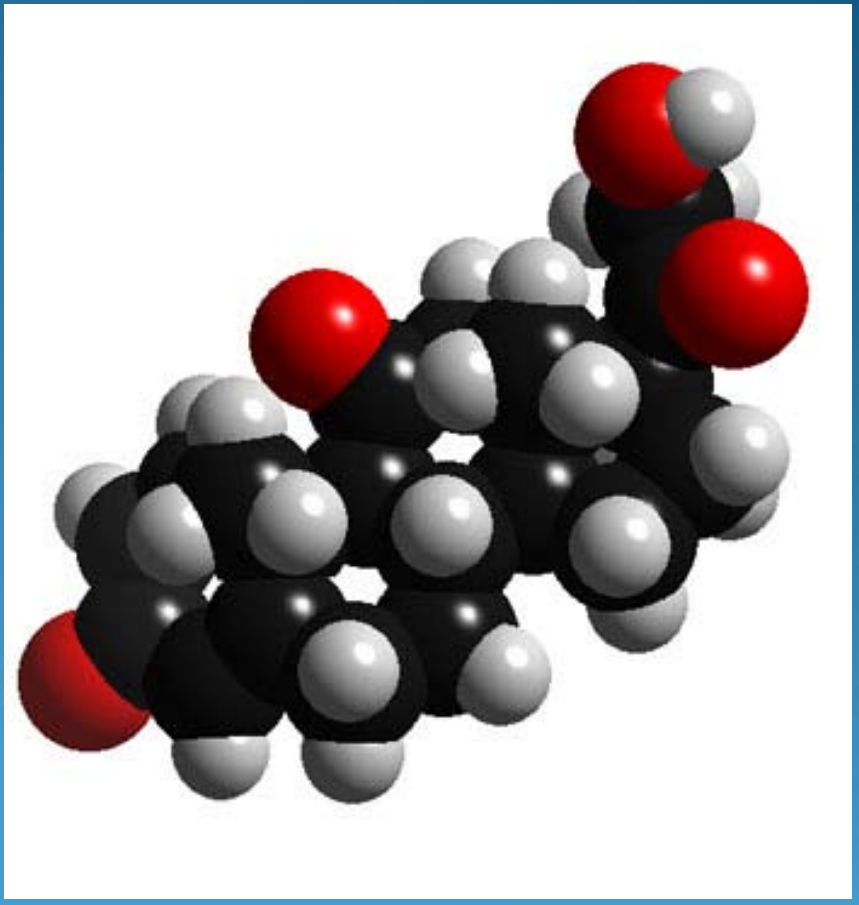
Delayed Onset

- Immunosuppressives
  - Azathioprine
  - Mycophenolate
  - Cyclophosphamide
  - Methotrexate
  - Others…

Get Control

Prednisone 1 mg/kg/d

- 1st line initial therapy
- Alone or in combo
- Dosing frequency varies
- Goal: halt disease progression/remission



Adjuvant Therapies

- If disease is progressing despite prednisone **or** as initial adjuvant therapy with prednisone
  - Mycophenolate mofetil (40 mg/kg/d; 2-3g/d)
  - Azathioprine (2-4 mg/kg/d)
  - Cyclophosphamide (2-3 mg/kg/d)

If improving / remitting

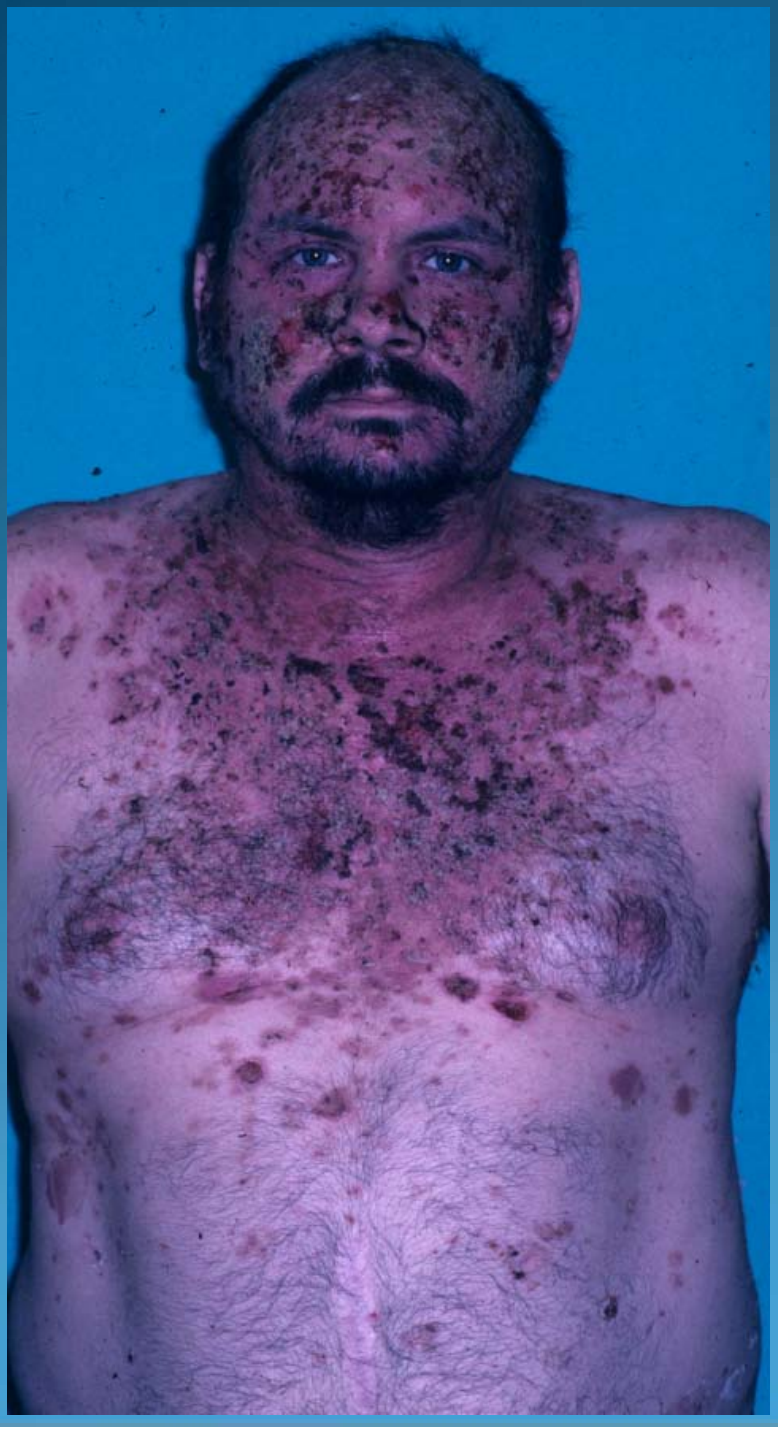
- Maintain regimen until most lesions have healed
- Continue nonsteroidal agent
- Taper steroids

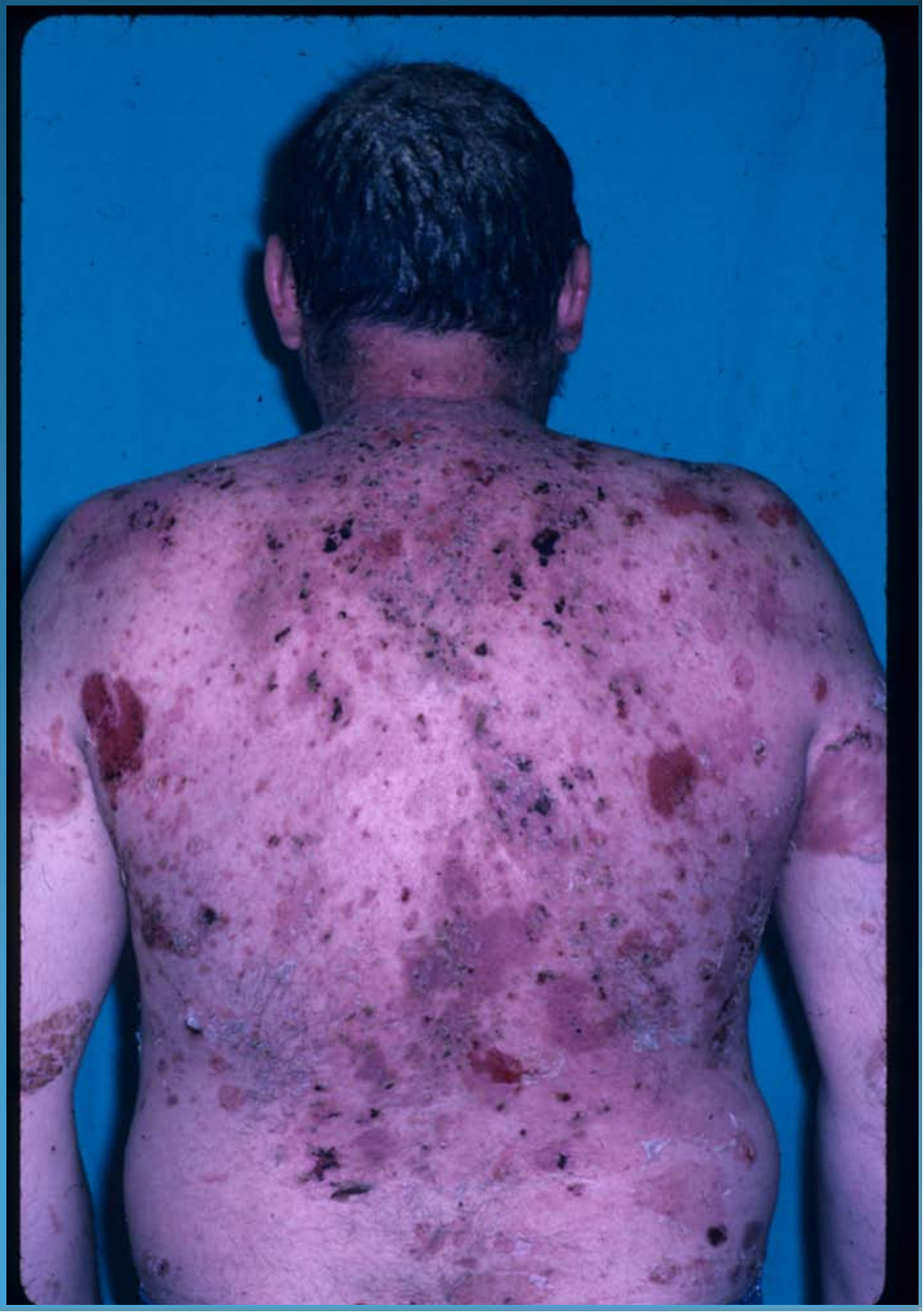
If not improving / deteriorating

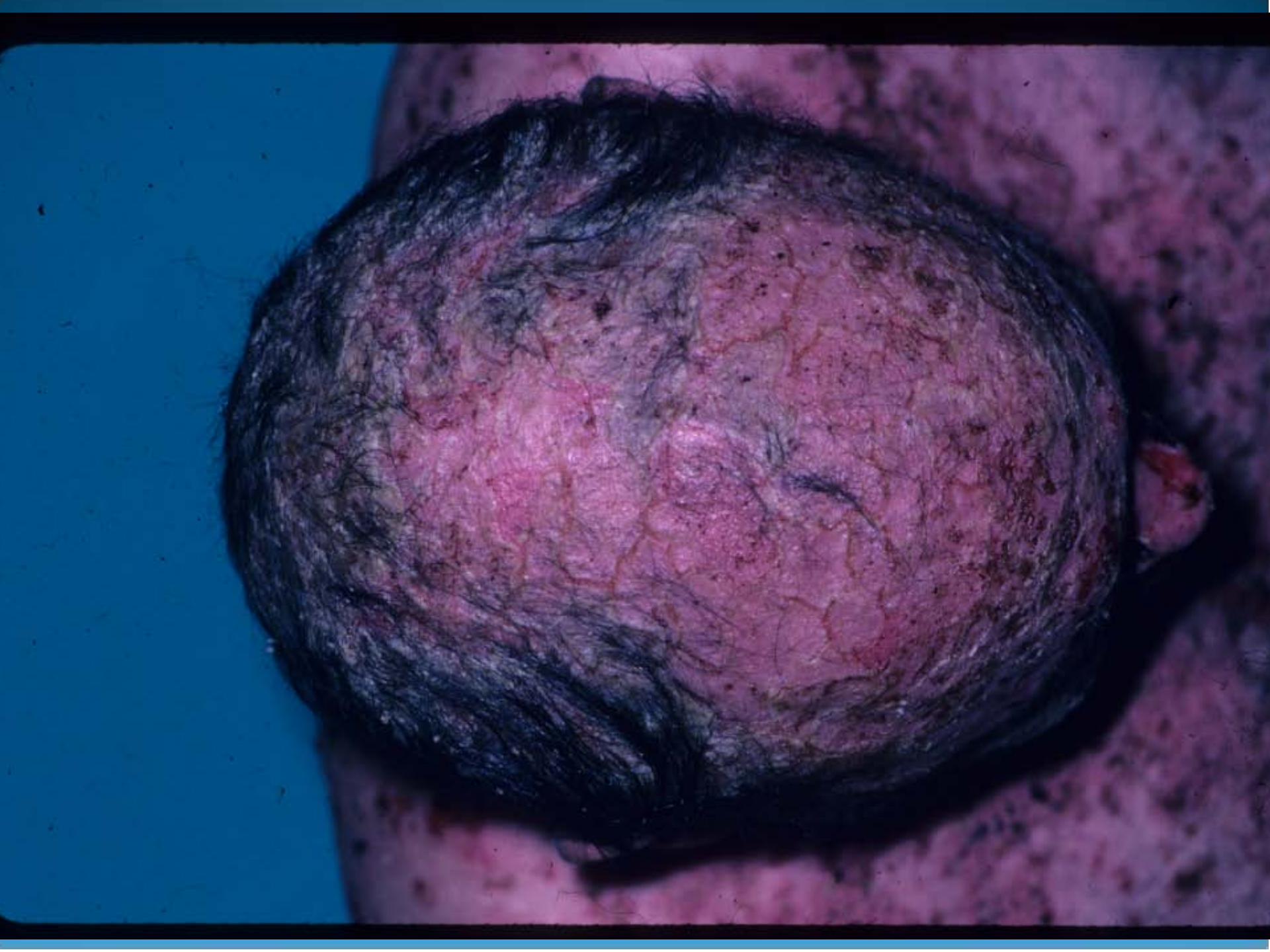
- Assure compliance, look for infection
- Continue prednisone at max dose
- Transition or dose-adjust immunosuppressive
- Consider plasmapheresis, IVIG

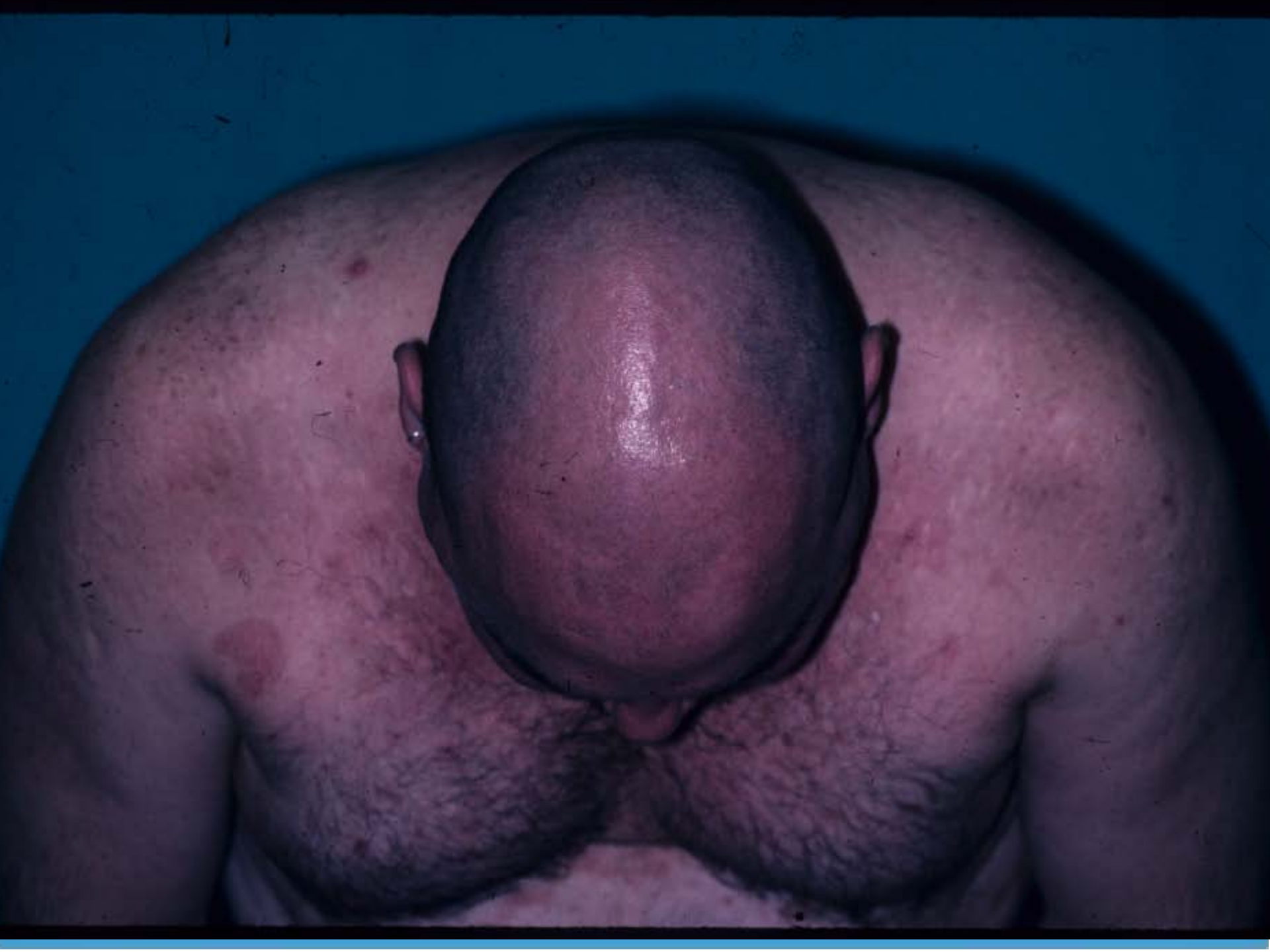
Keep Control

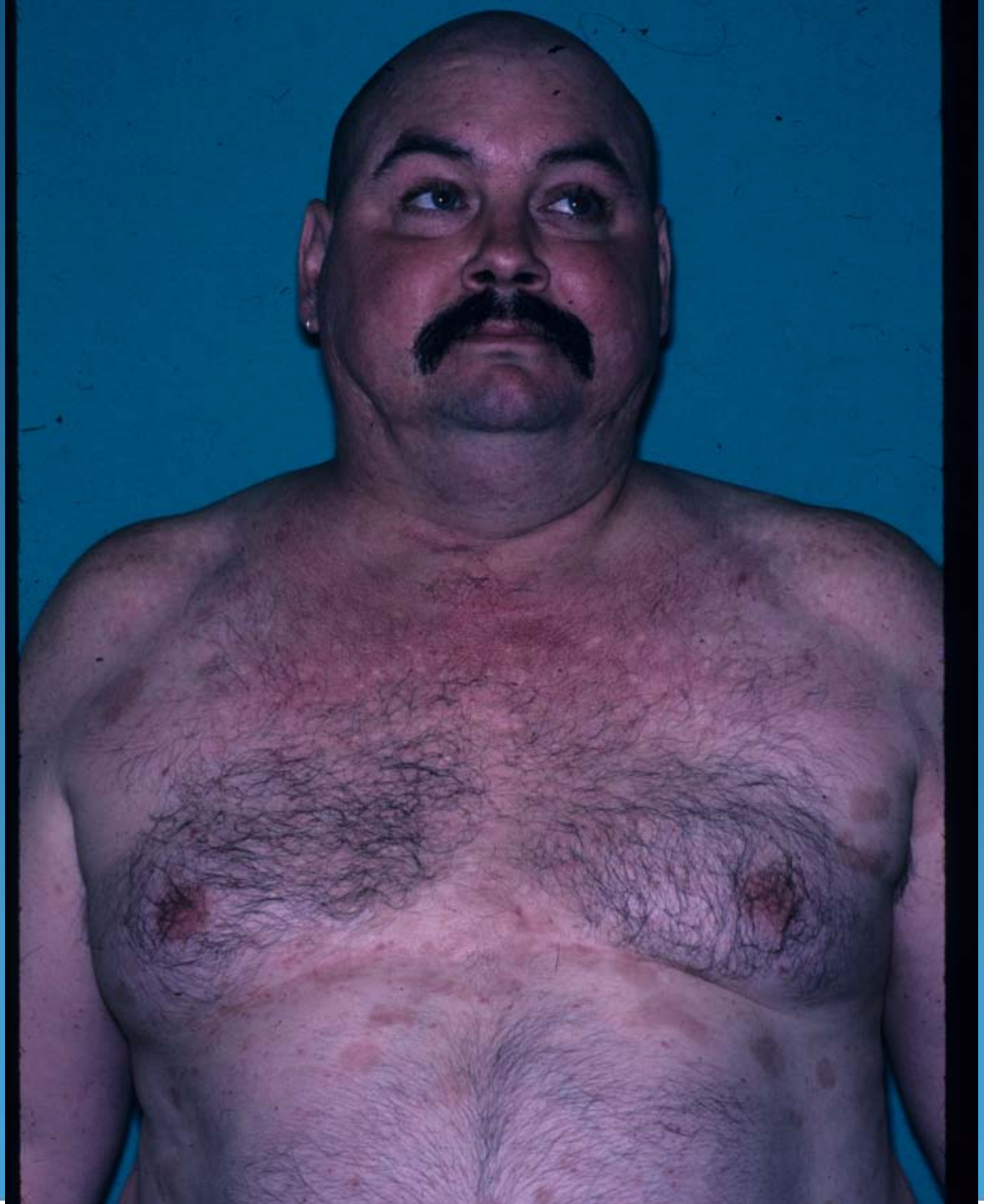
- Maintain the meds/dosages needed to control disease until lesions have healed
- Slow healing signals inadequate treatment or complicating factors











Maintain Control

- Goal: off all drugs
- Taper meds to lowest suppressive dose
- Taper one medication at a time
- Clinical and serologic factors guide taper

Prednisone

- Achieves *early* control in most cases
- Long term control at this dose is rare
- Majority will require additional agents
- BID: better control; more SE (HPA axis)
- qOD: less side effects (except osteoporosis)

Prednisone Tapering (if use exceeds 2-3 weeks)

- Change dose no more than once weekly
- Decrease by 10 mg/d until dose is 40 mg/d
- From 40-20 mg, taper by 5 mg/week
- From 20-10 mg, taper by 2.5 mg/week

Prednisone Tapering

- Alternate day dosing
  - can start at 40mg
  - + and - by 10 on alternate days until qod
    - 50/30 x 1 week
    - 60/20 x 1 week
    - 70/10 x 1 week
    - 80 qod, then taper per prior schedule

Prednisone Tapering

- Below 10 mg, taper by 1mg/week until 3-5 mg/day
- Check 8 am serum cortisol
  - >10ug/dl: continue taper to off
  - <10ug/dl: continue current dose, check monthly
- Stress dose steroids required for one year

Prednisone Prophylaxis Regimens

- Osteoporosis
  - Calcium 1500 mg/d and vit D 800 IU/d
  - Bisphosphonates (alendronate)
  - HRT per PCP
  - Bone densitometry every 6-12 months
  - Alternate day dosing does not decrease risk

Prednisone Prophylaxis Regimens

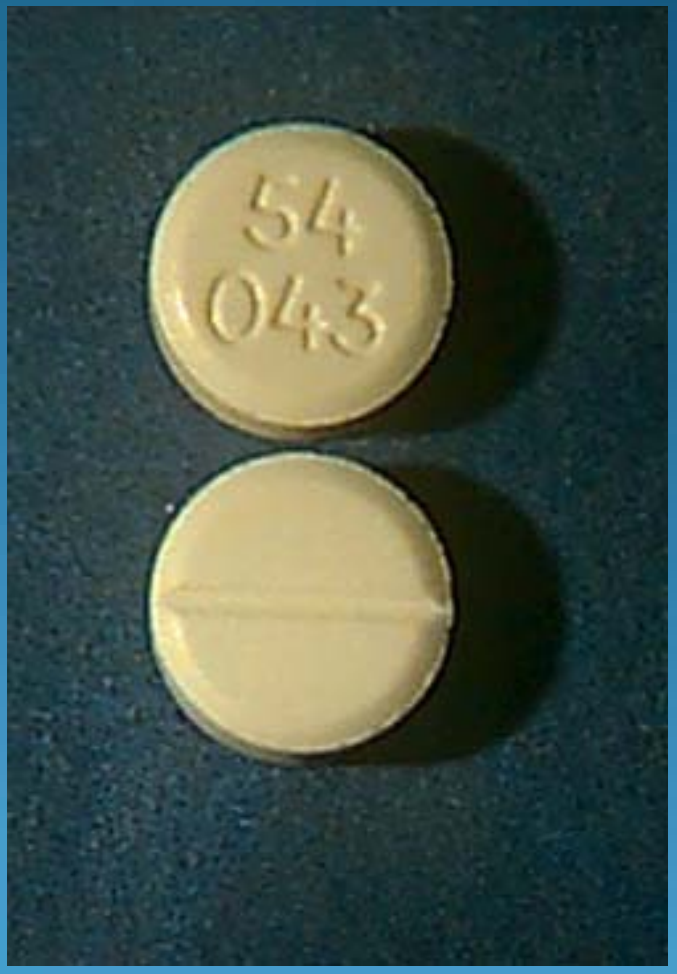
- Pneumocystis carinii pneumonia
  - TMP-SMX if 15mg/d pred used > 2 months
  - Alternate day dosing decreases risk
- Screen regularly for:
  - Diabetes, hypertension, peptic ulcers
  - Glaucoma, cataracts
  - Alternate day dosing does not protect against cataracts

Mycophenolate mofetil

- Purine synthesis inhibitor: B and T cells
- Dosing: 35-45 mg/kg/d (2-3 g/d ÷ BID)
- Onset of action: 2-3 months
- Reports of efficacy as *monotherapy*
- Favorable safety profile: GI distress
- Neutropenia, infection, lymphoma

Azathioprine

- Purine synthesis inhibitor
- Complex metabolism
- Dosing: 2-4 mg/kg/day
- Effective as *adjuvant* therapy
- Safety profile is “middle of the road”
  - versus cytoxan and MMF

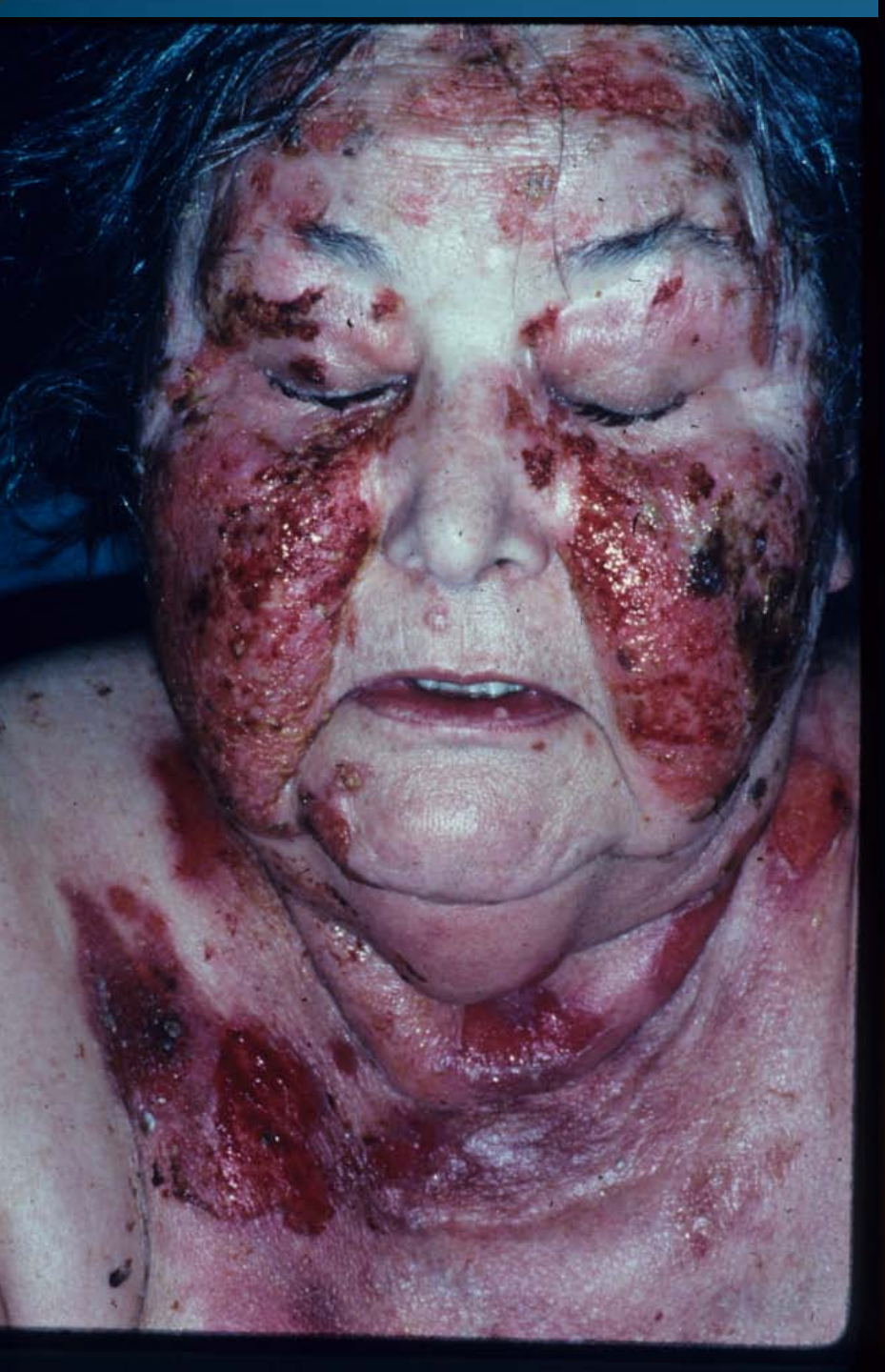


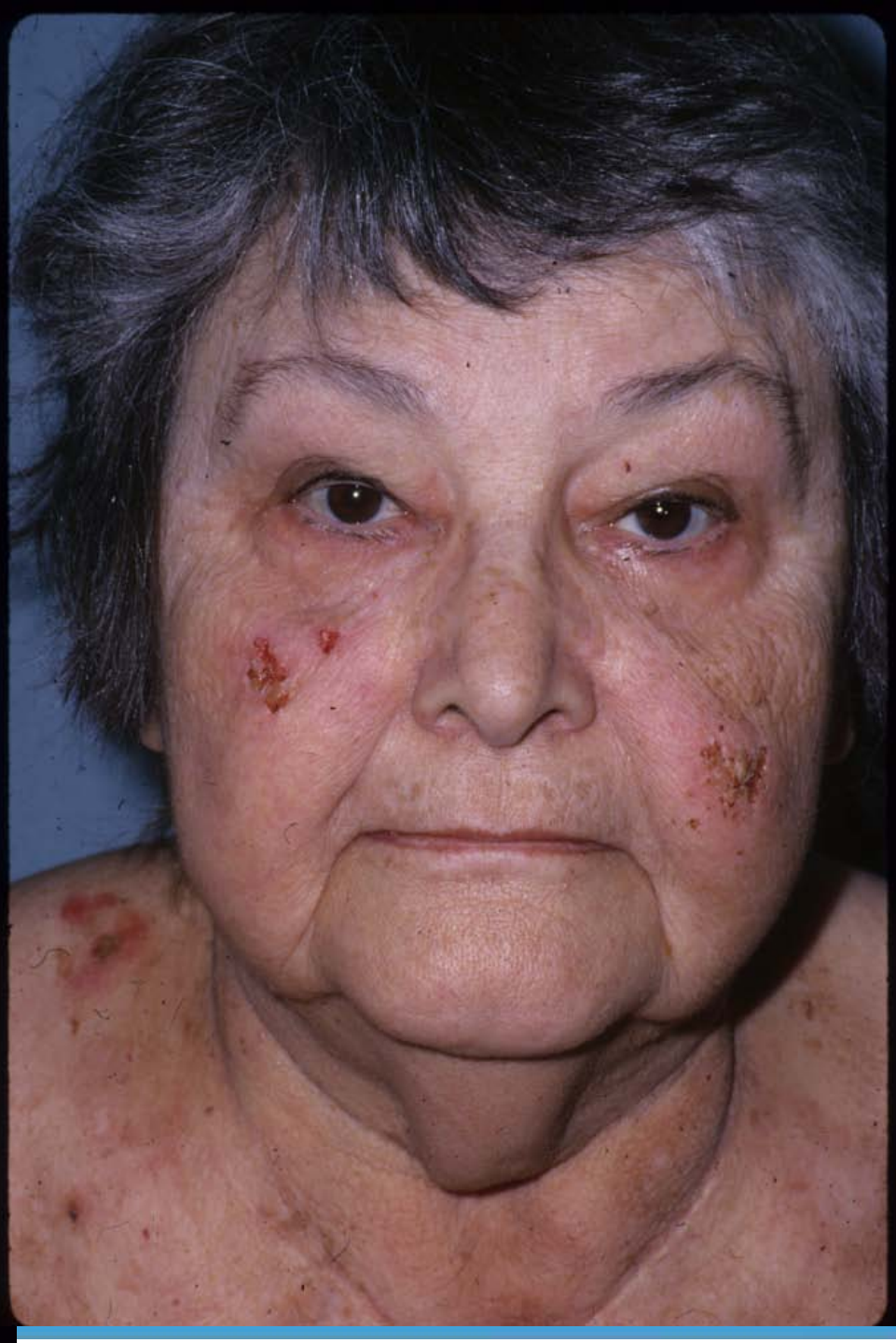
Azathioprine

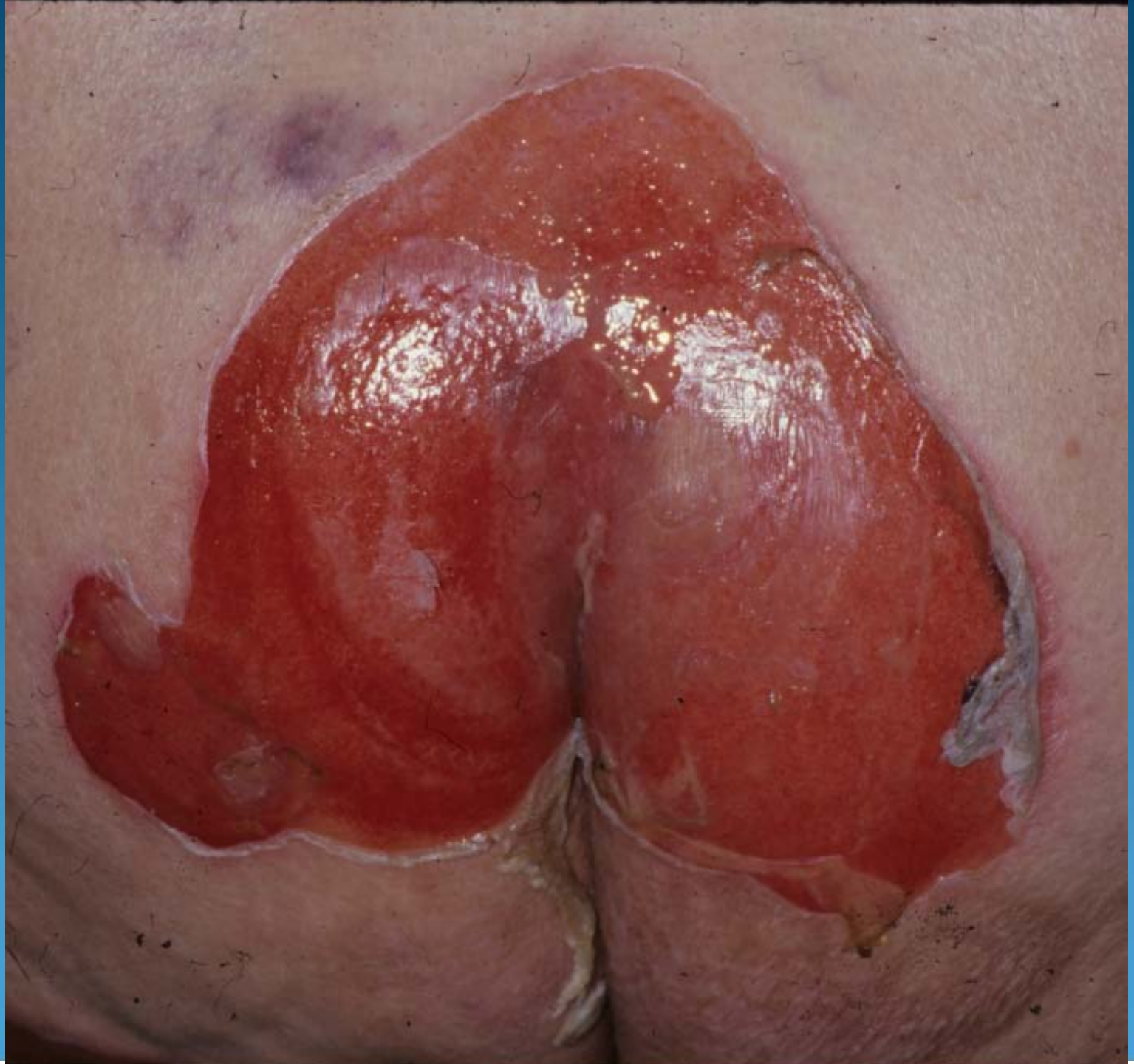
- Bone marrow suppression → leukopenia
- Hepatotoxicity; GI intolerance
- Hypersensitivity syndrome; drug fever
- Advantages for younger patients:
  - Lower lifetime risk of malignancy and sterility

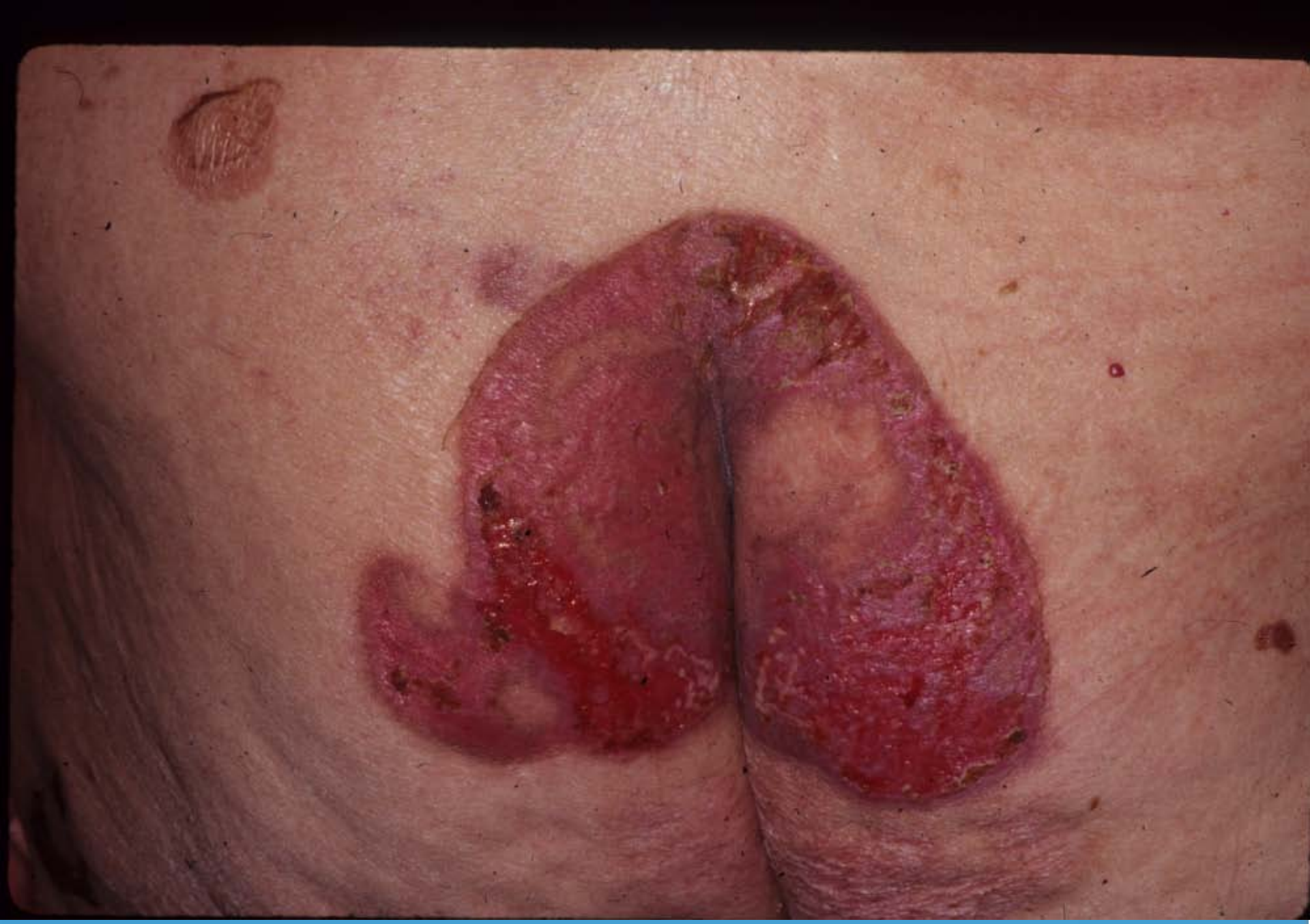
Azathioprine → 6-mercaptopurine

- Hypoxanthine-Guanine Phosphoribosyltransferase
  - Anabolizes 6-MP to active purine analogs
- Thiopurine Methyltransferase
  - Catabolizes 6-MP to inactive, nontoxic metabolites
  - Functional enzyme assay for level of activity
  - Low activity: ↑ risk of pancytopenia
  - High activity: ↓ efficacy
- Xanthine Oxidase
  - Catabolizes 6-MP to inactive, non-toxic metabolites
  - Allopurinol inhibits









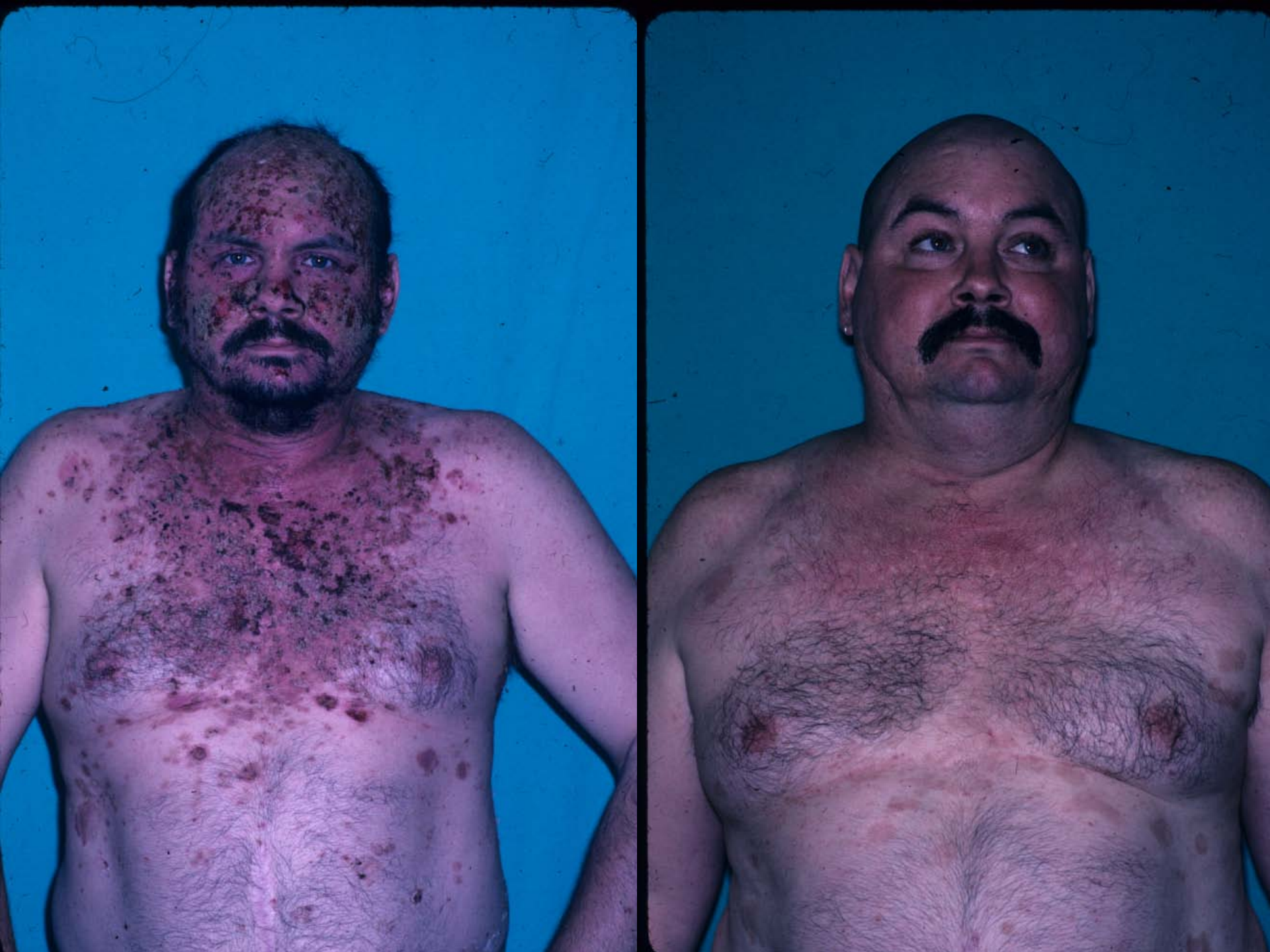
Cyclophosphamide

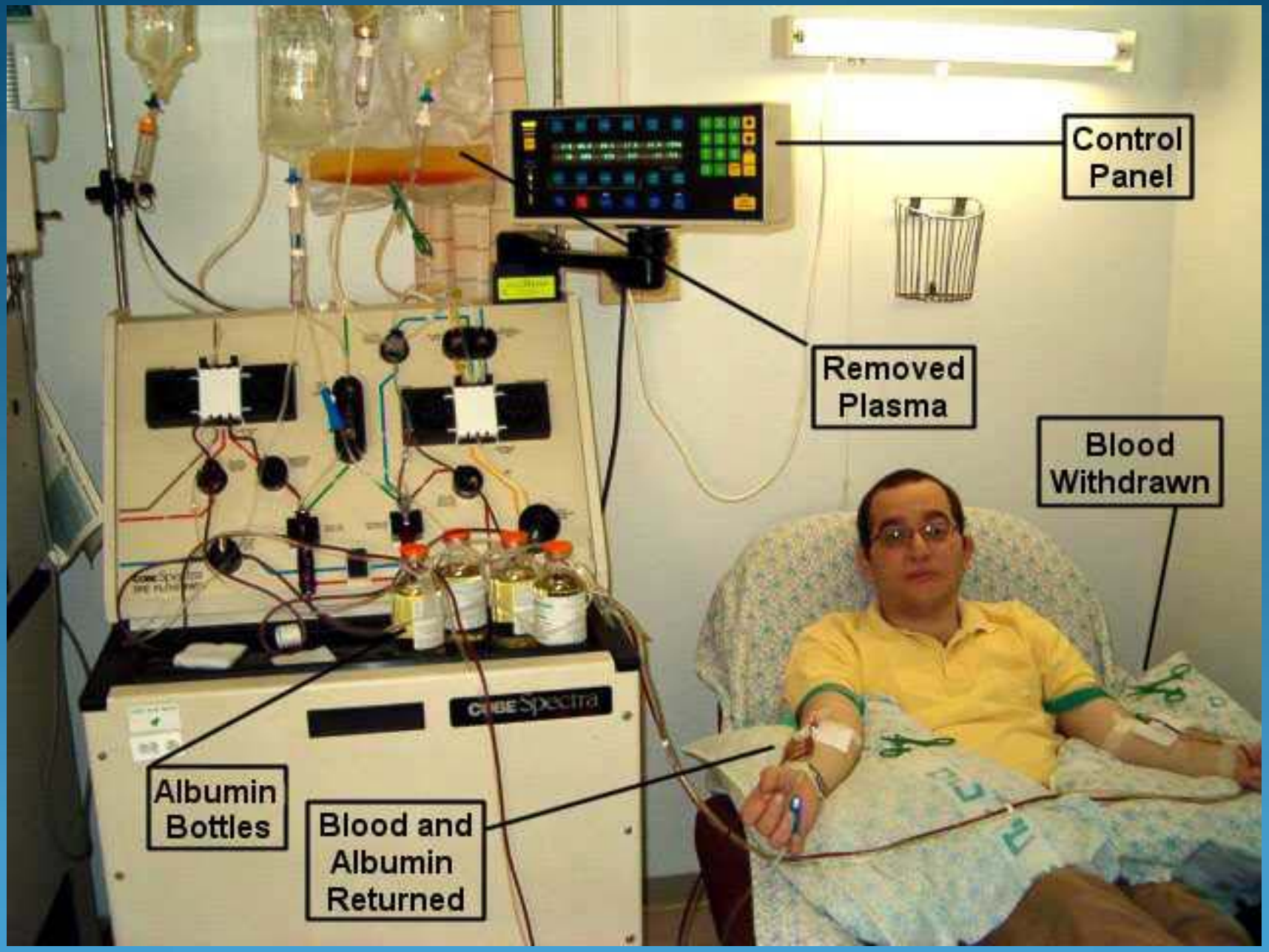
- Alkylates DNA → apoptosis
- Reduces B > T cells
- ↓ total antibody production
- Differentiated lymphocytes targeted
- Dosing: 2-3 mg/kg/d, single am dose
- Excellent adjuvant efficacy in pemphigus

Cyclophosphamide

Unfavorable safety profile

- Significant short term risks:
  - Myelosuppression → leukopenia
  - Hemorrhagic cystitis → aggressive hydration
- Long term risks:
  - Leukemia, lymphoma, bladder cancer
  - Amenorrhea; azoospermia → sterility



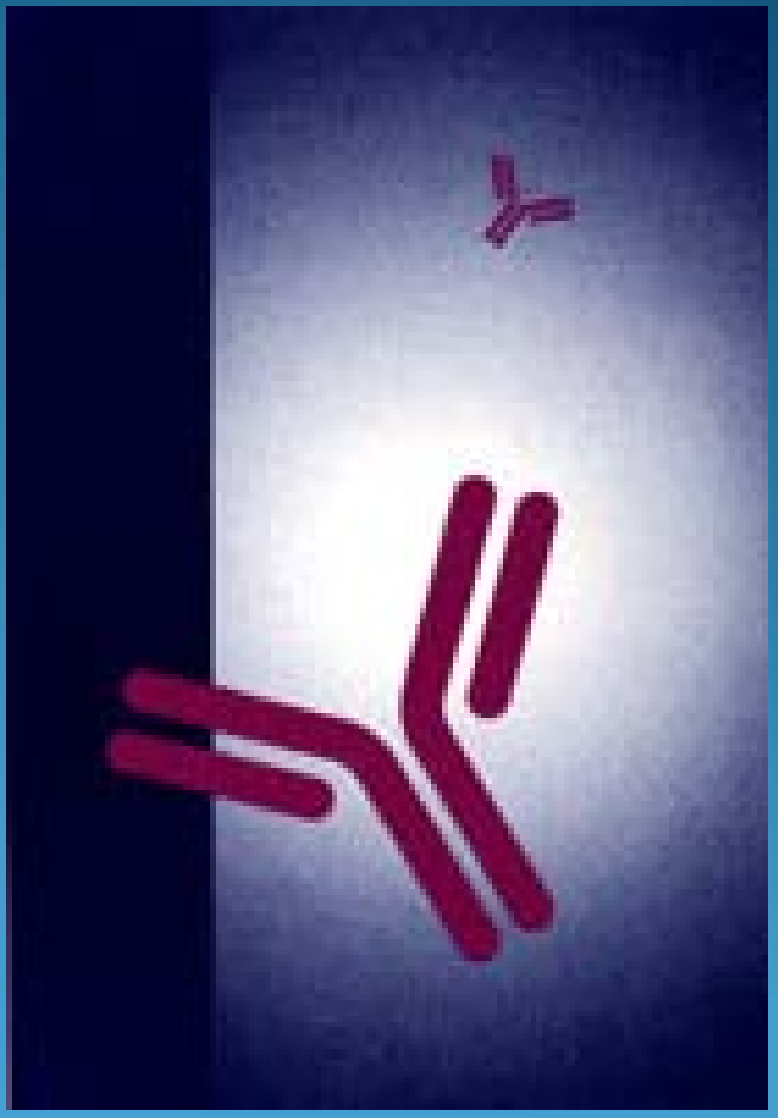

Control Panel
Removed Plasma
Blood Withdrawn
Albumin Bottles
Blood and Albumin Returned

Plasmapheresis

- Physically removes serum antibodies
- Efficacy is controversial
- Not recommended as 1st line therapy
- Results in rebound increase in antibodies
- Use *in combo* with an alkylating agent

Intravenous Immunoglobulin

- Purified human IgG from pooled plasma
- 2 g/kg/cycle
- 3 = doses over 3 days
- q month until remission +/- maintenance
- Exact MOA unknown
- Baseline labs/pre-Rx meds
- AE: thrombosis, anaphylaxis, infectious risk



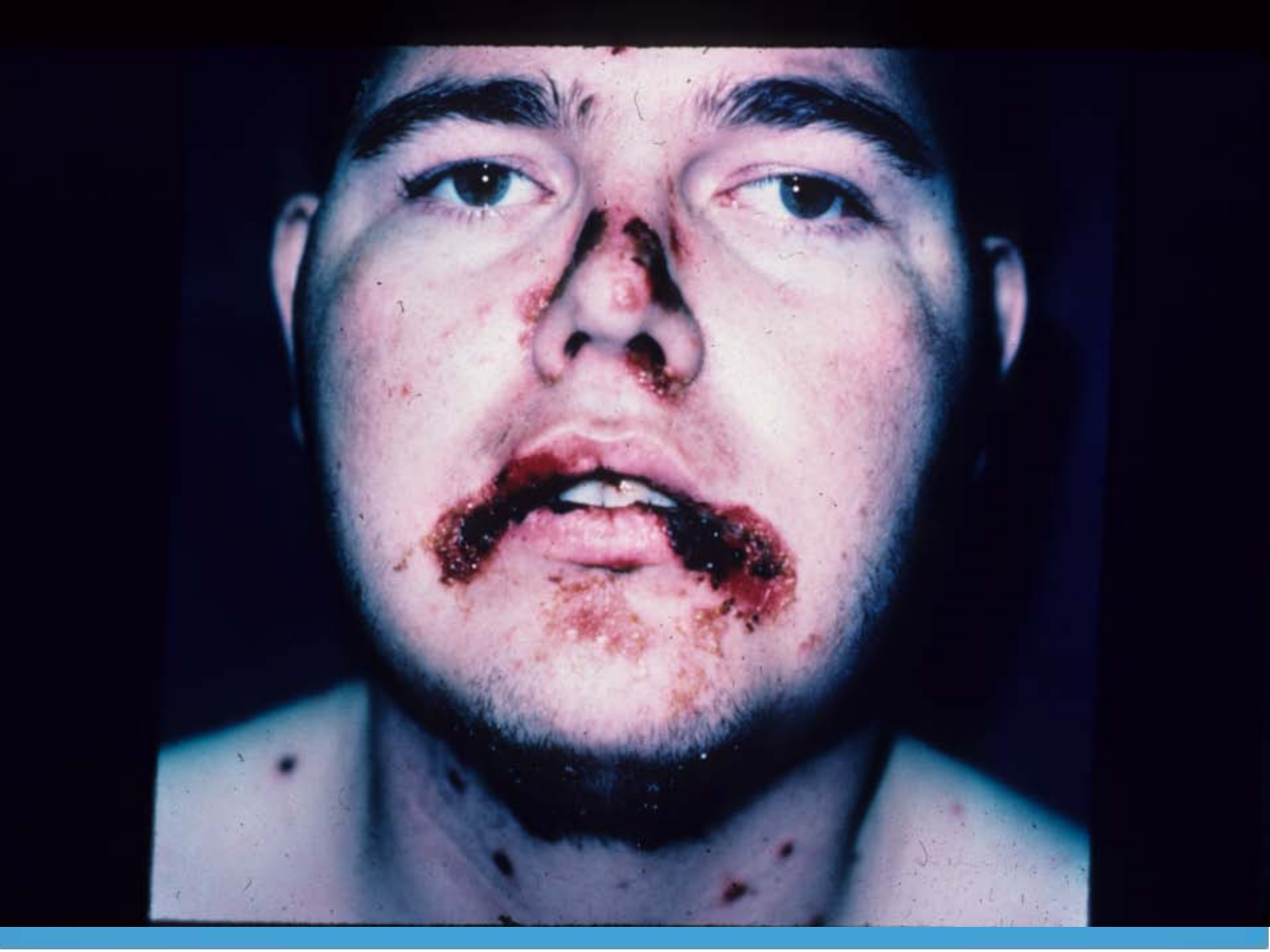
IVIg Indications

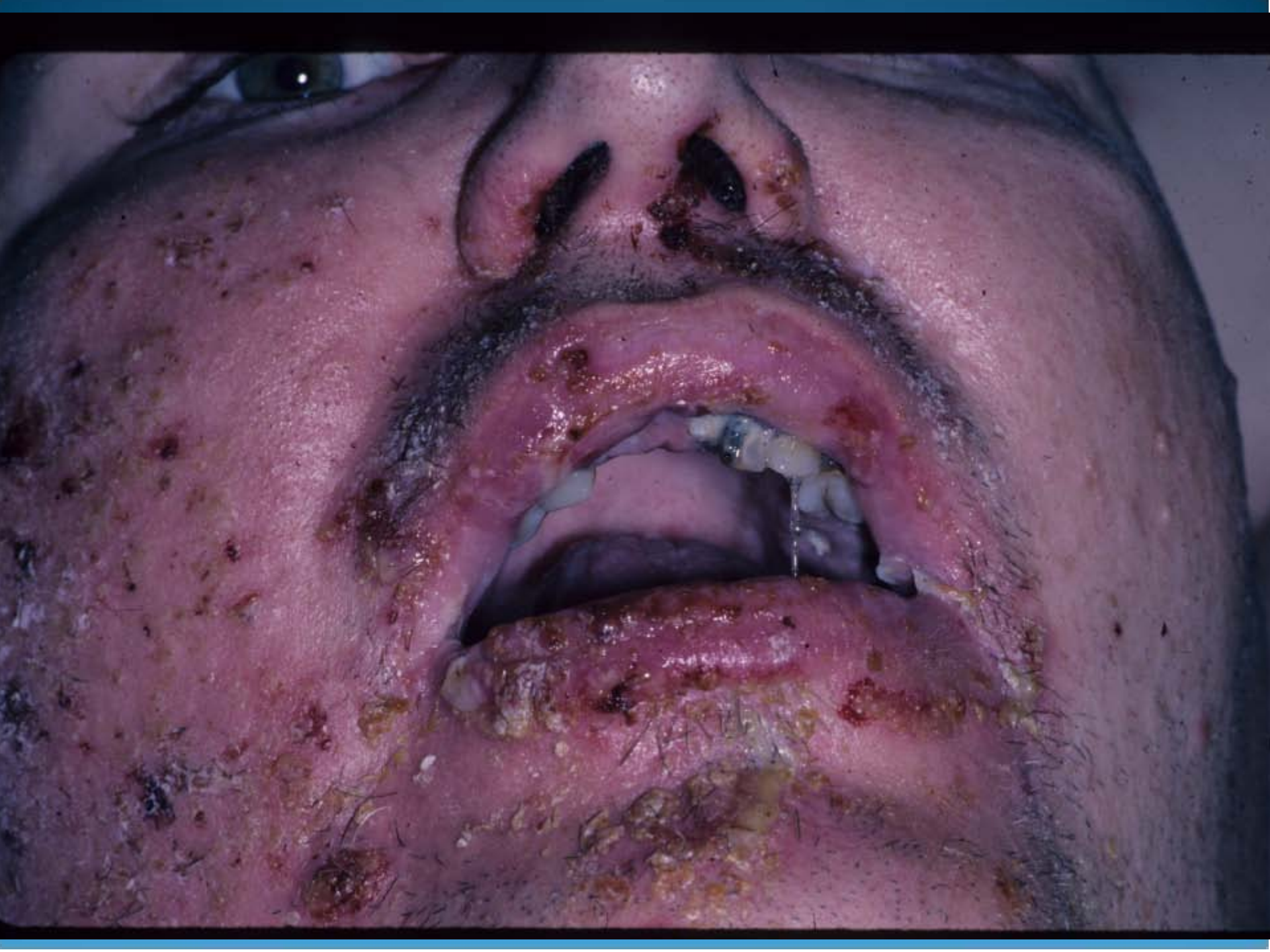
(Arch Dermatol. 2003;139:1051-1059)

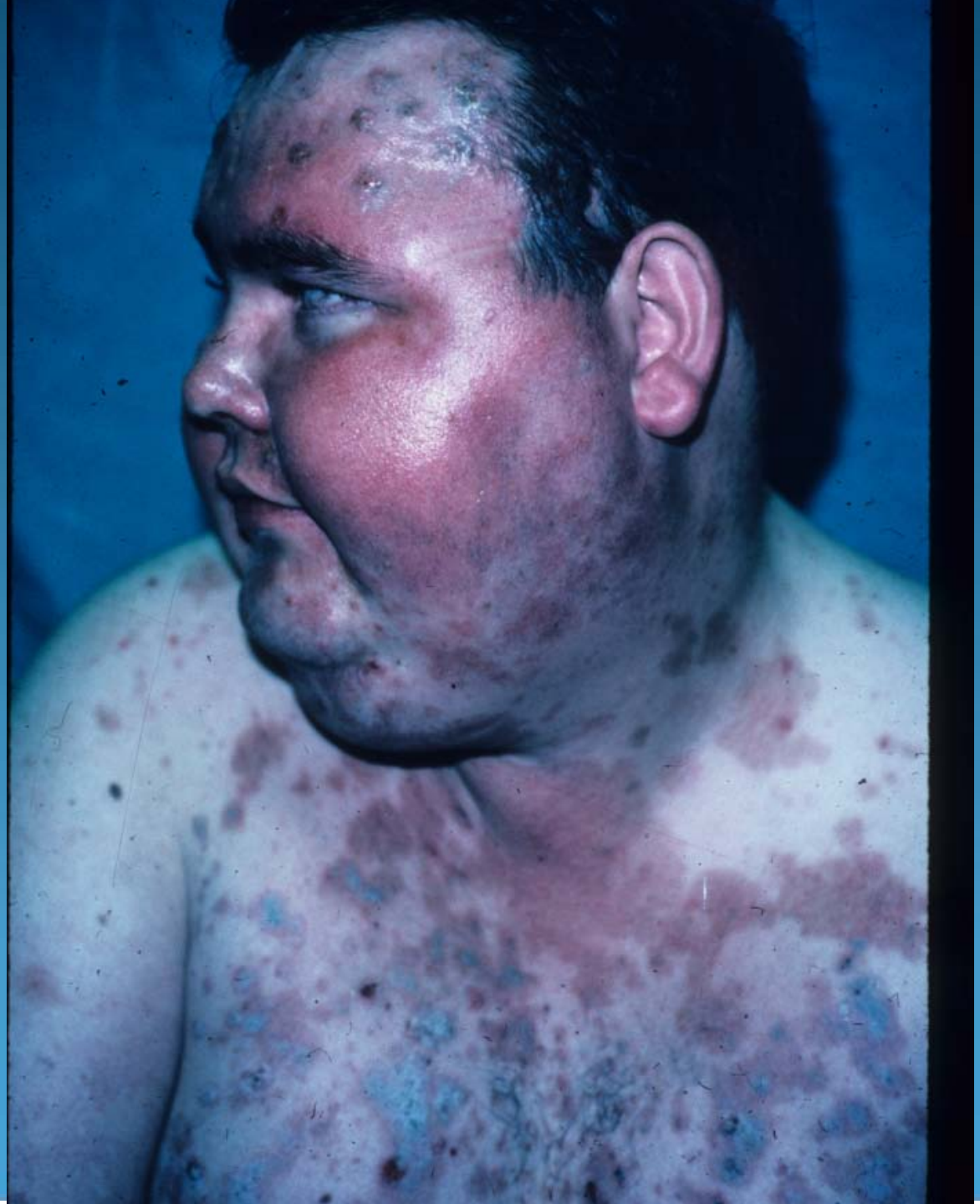
- Failure of conventional therapy
- Significant AE of conventional therapy
- Contraindications to conventional therapy
- Progressive or uncontrolled disease
- Age and pregnancy

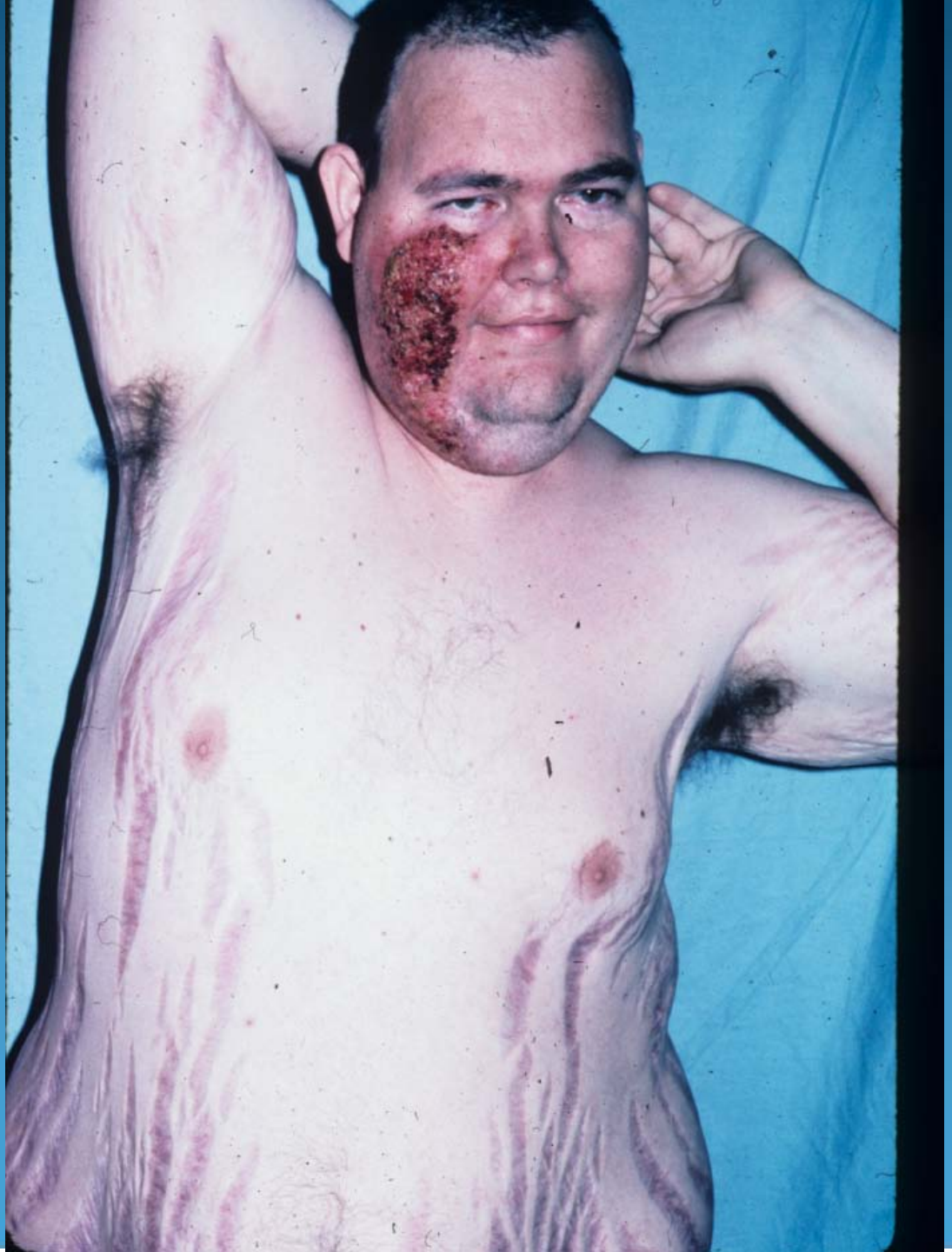
Other Agents

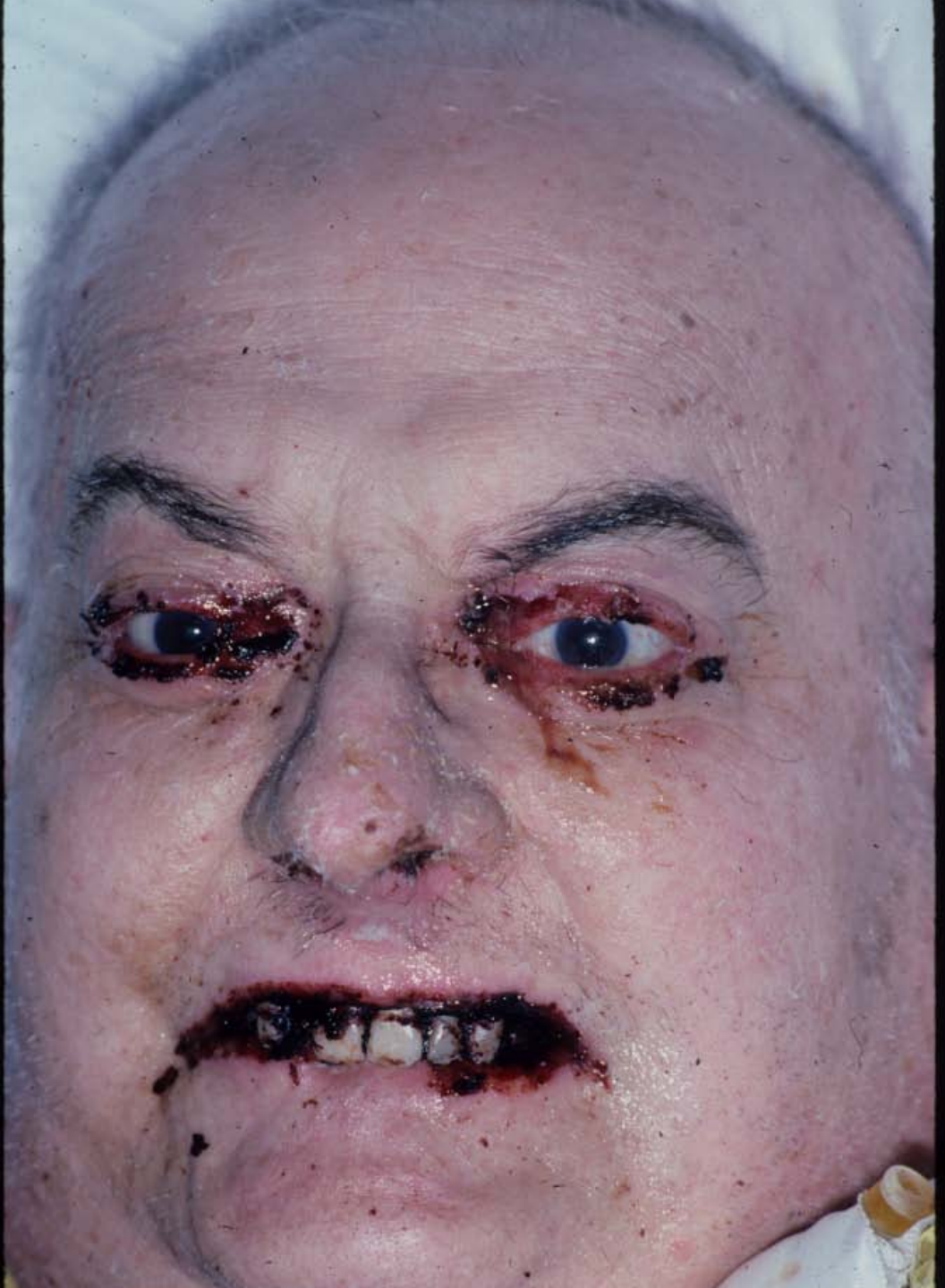
- Chlorambucil
  - Alkylating agent, toxic
- Methotrexate
  - Inconsistent, poor as monotherapy
- Cyclosporine
  - Adjuvant therapy
  - Jury is still out
- Immunoablative cyclophosphamide
- Gold
  - Inferior efficacy
  - No carcinogenicity/ infertility
- Dapsone
  - Fairly effective in PF
  - Unclear efficacy in PV
- Anti-CD20 mAb (rituximab)











Paraneoplastic Pemphigus

Autoimmune blistering disease associated with an underlying neoplasm

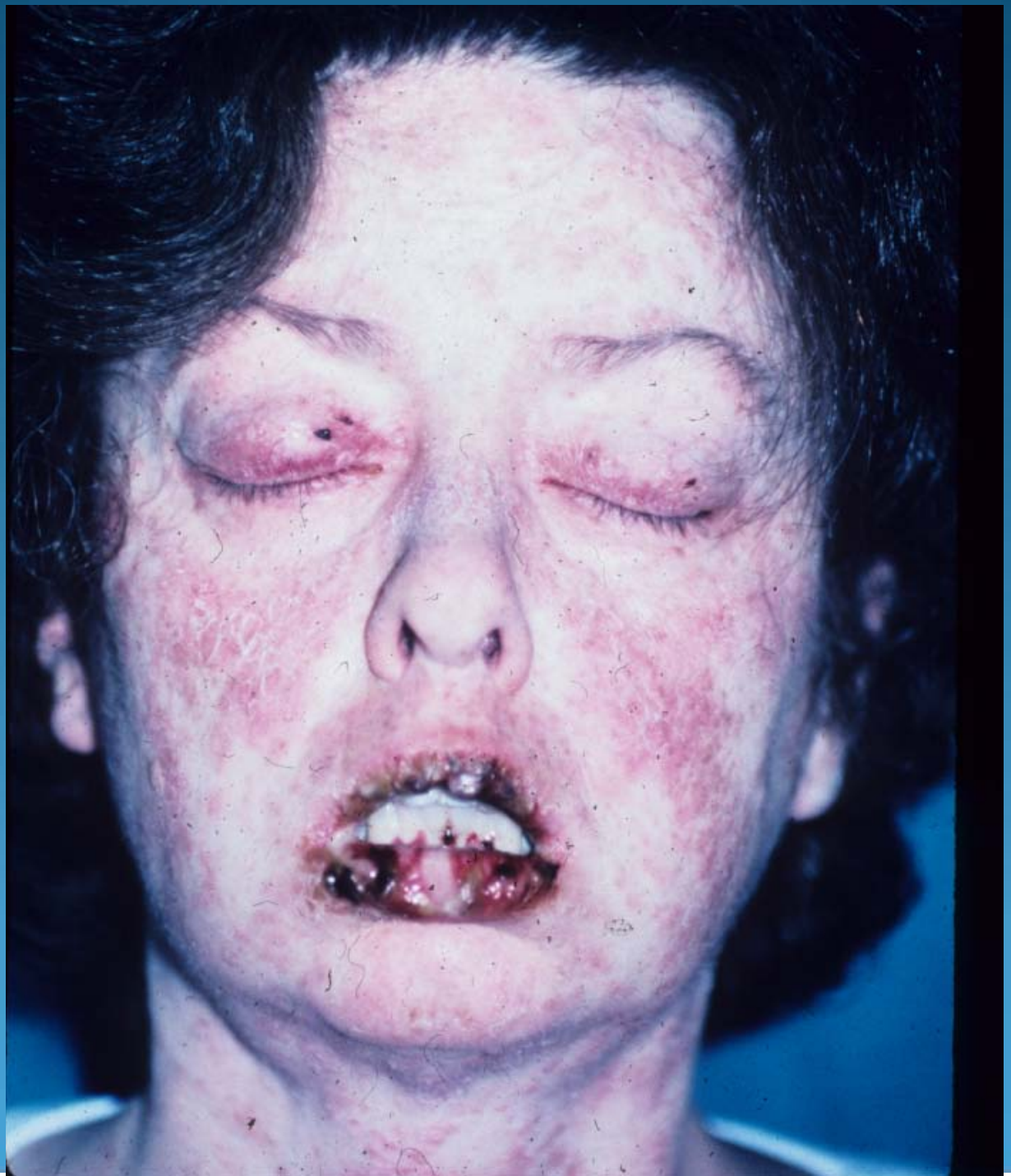
(B cell lymphoproliferative disorder)

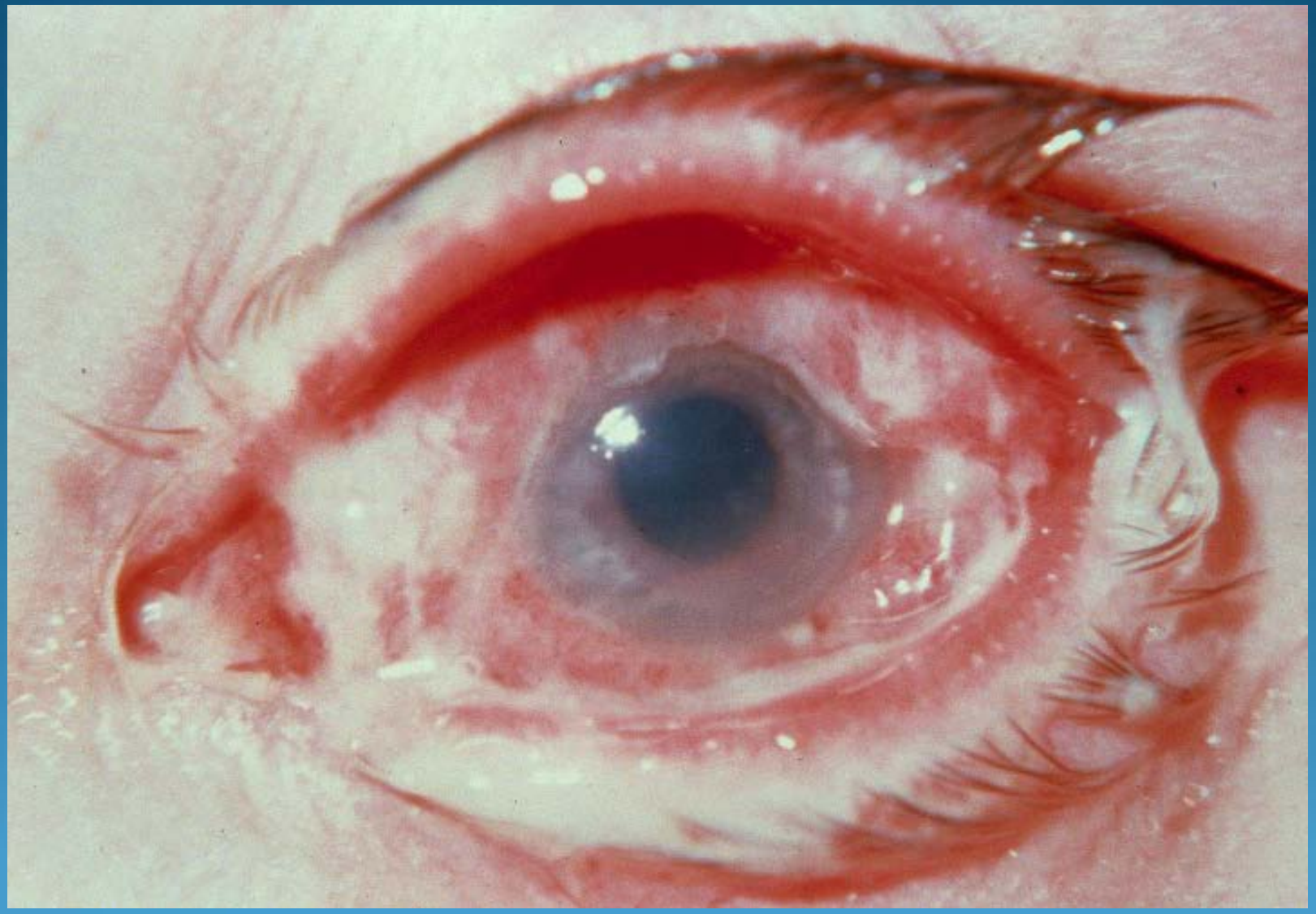
Mucocutaneous ulcerations

Polymorphous eruption

Mucosal Ulcerations

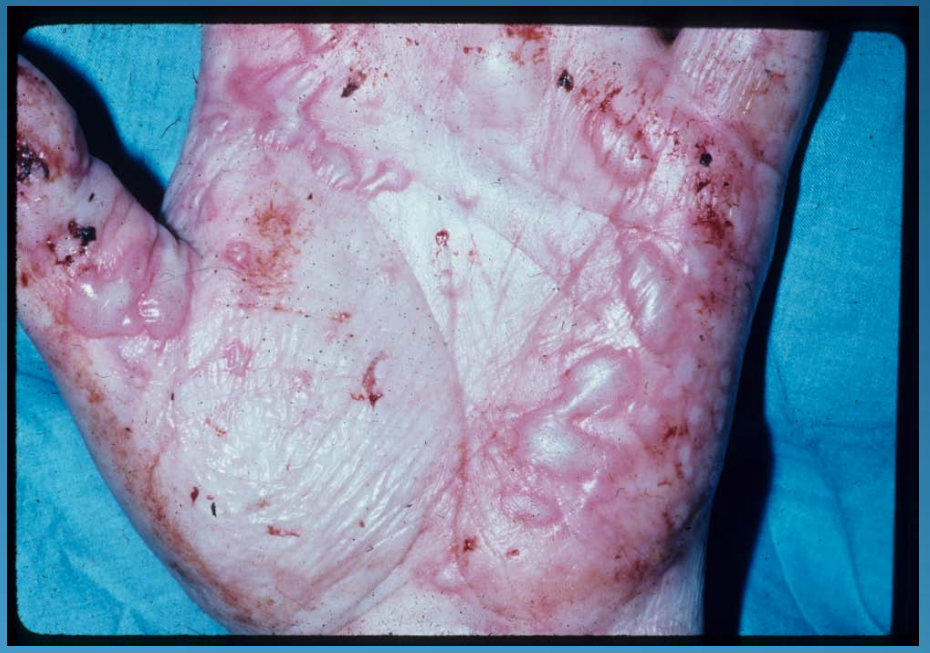
- Severe intractable stomatitis
- Pseudomembranous conjunctivitis
  - Scarring, obliteration of conjunctival fornices
- All mucosal sites are vulnerable
  - Esophageal, tracheobronchial $\Rightarrow$ morbidity

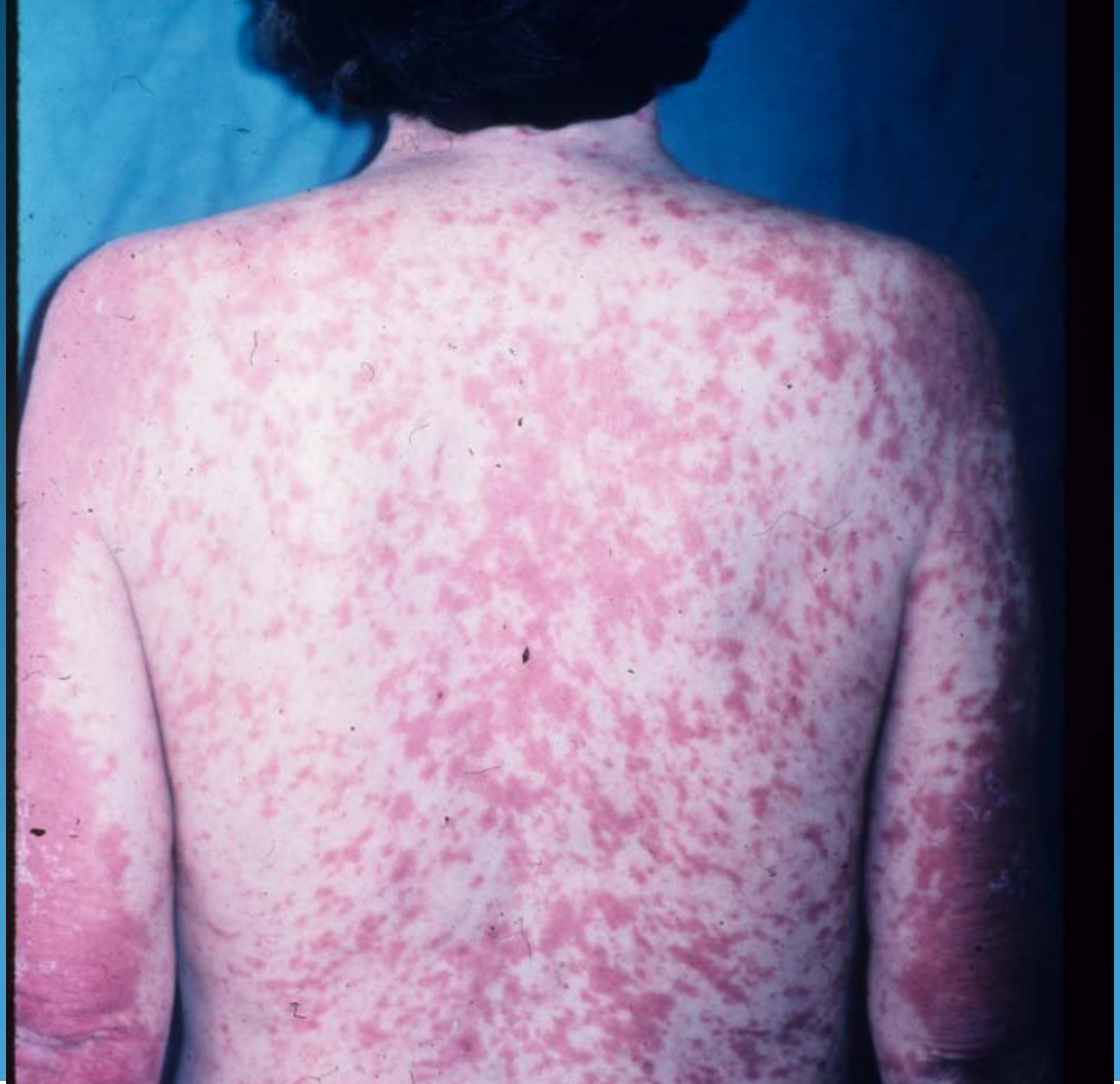


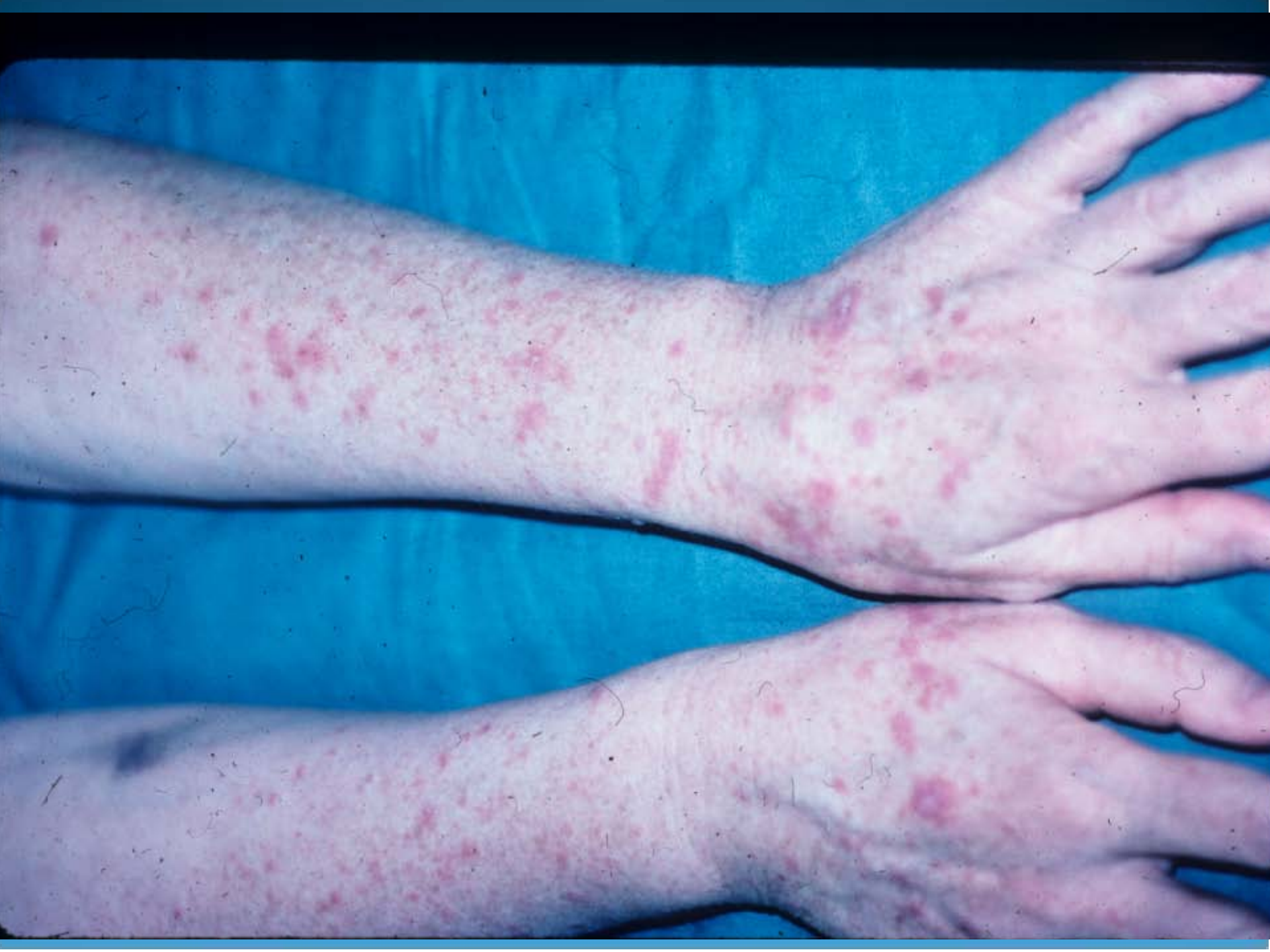


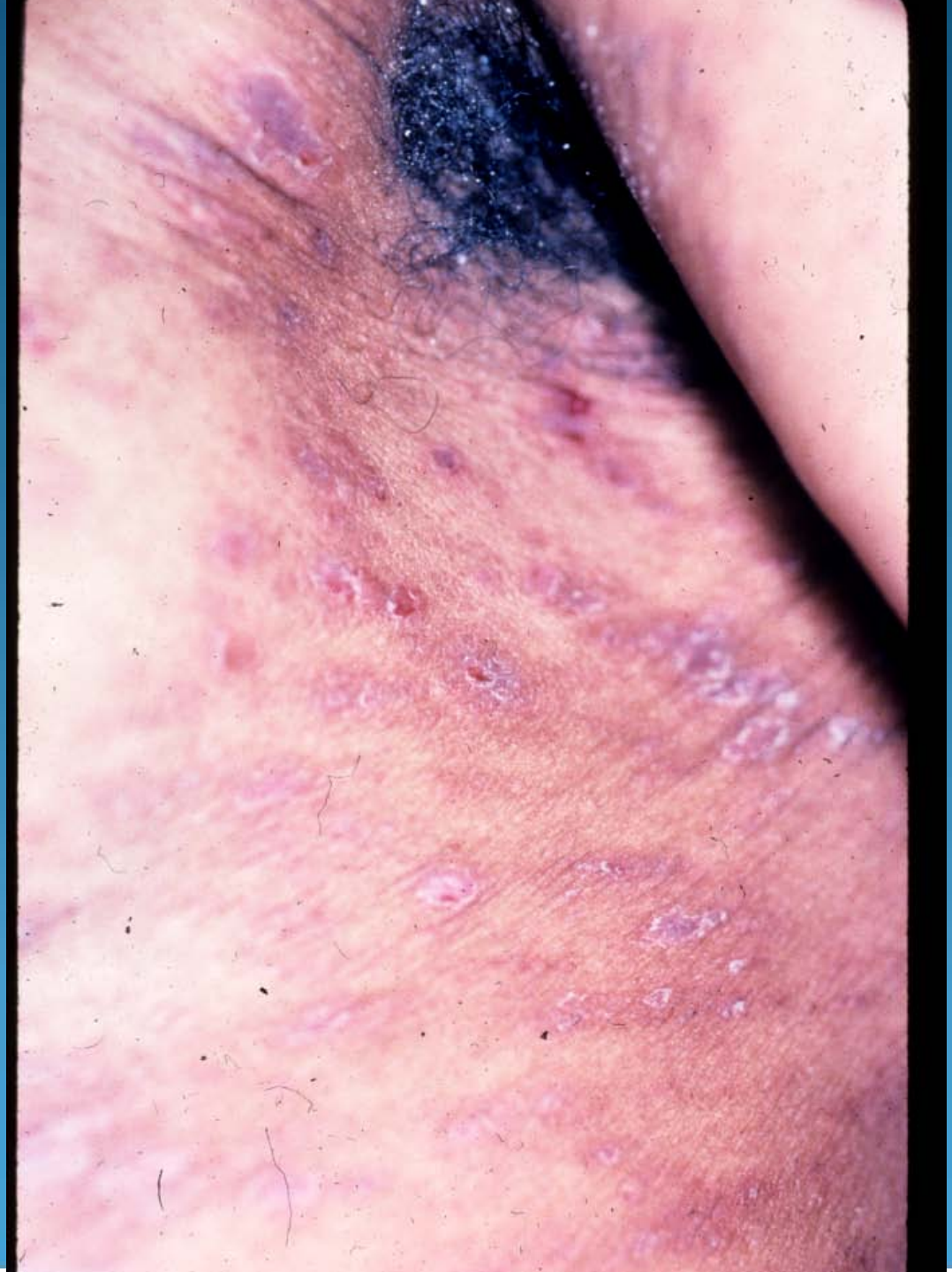
Polymorphous Skin Lesions

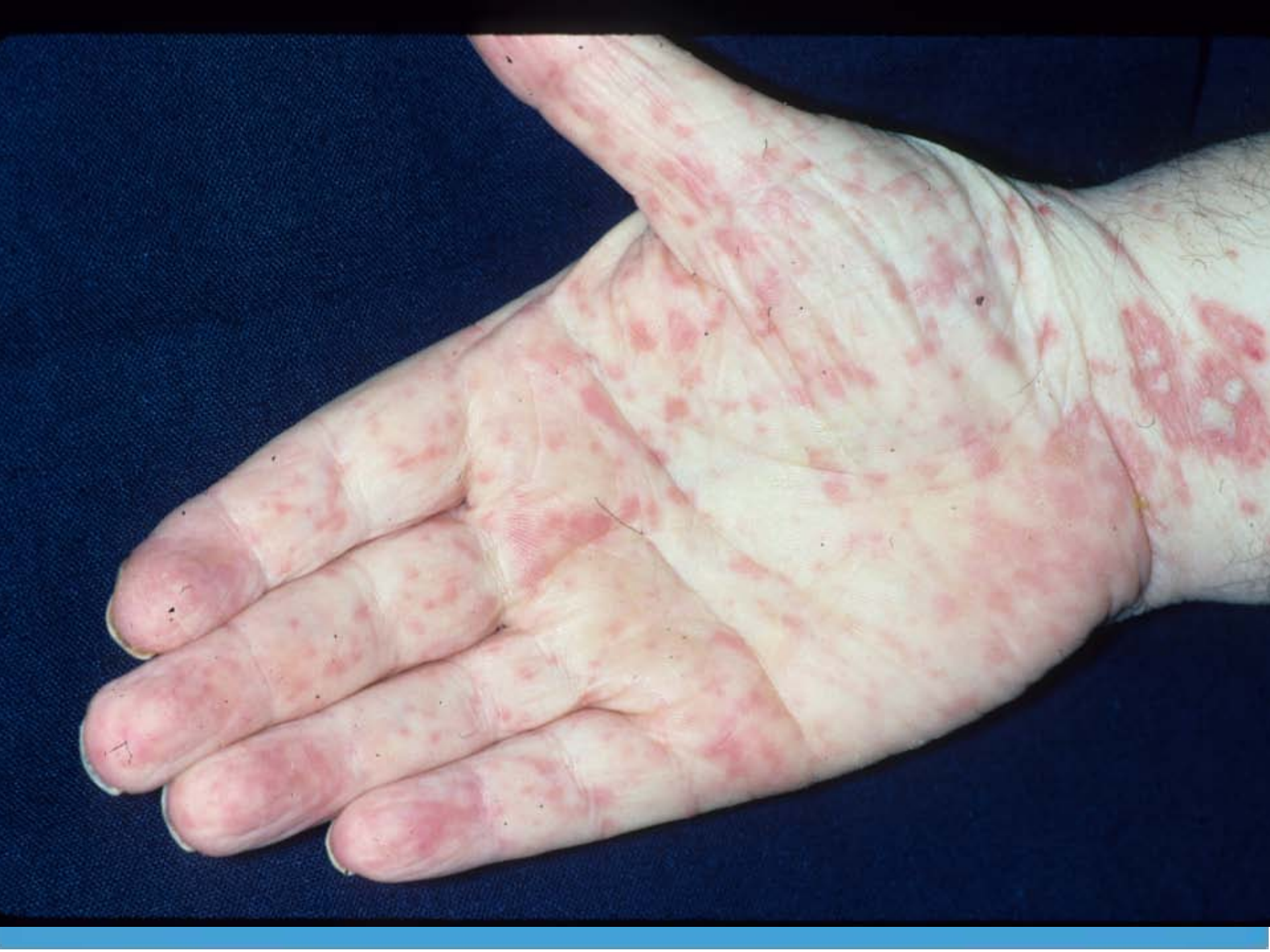
- Blisters and erosions
- Targetoid (EM-like)
- Lichenoid
- Palms and soles
  - distinguish PNP from PV
- Ulcerative paronychia

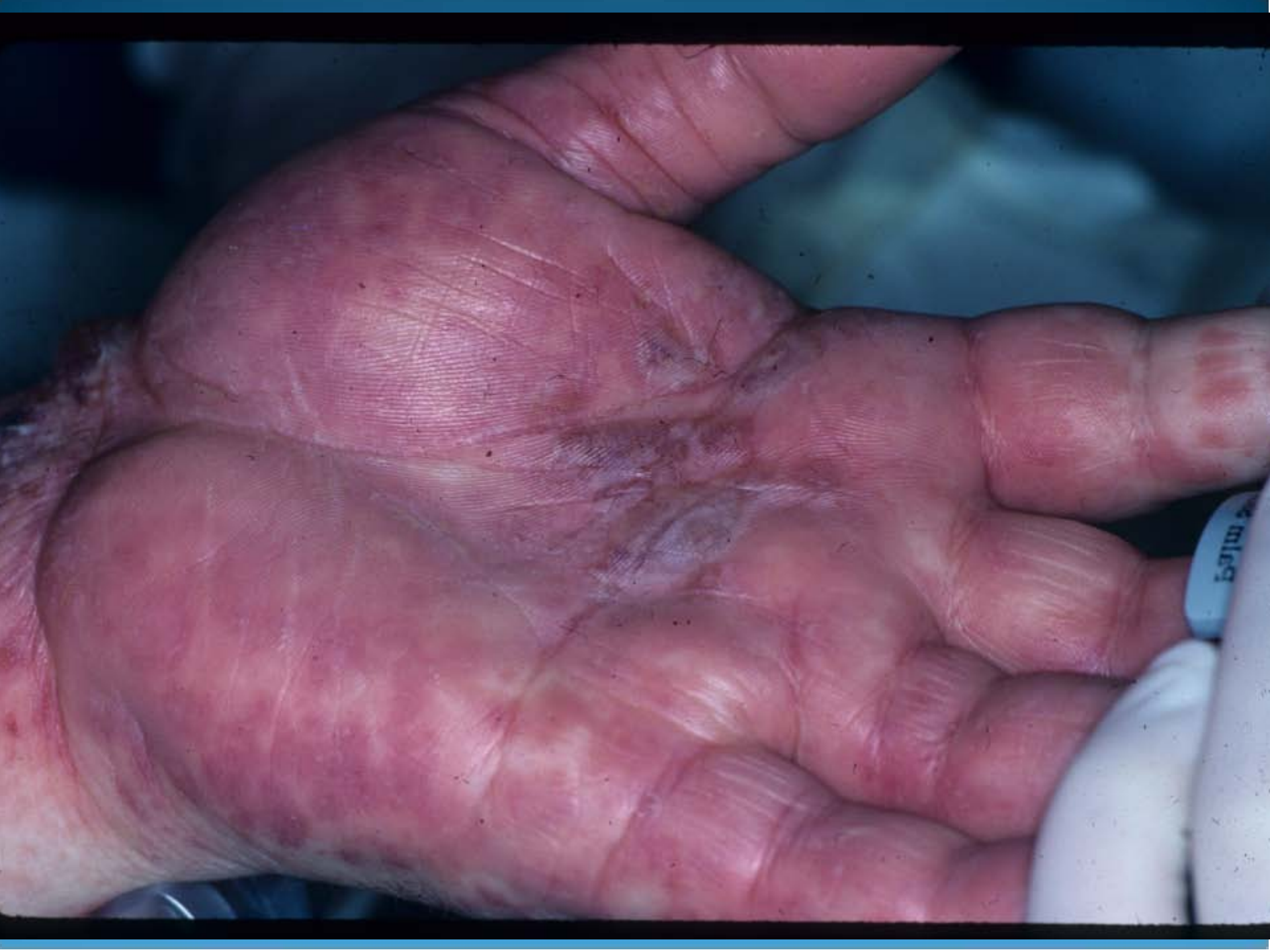


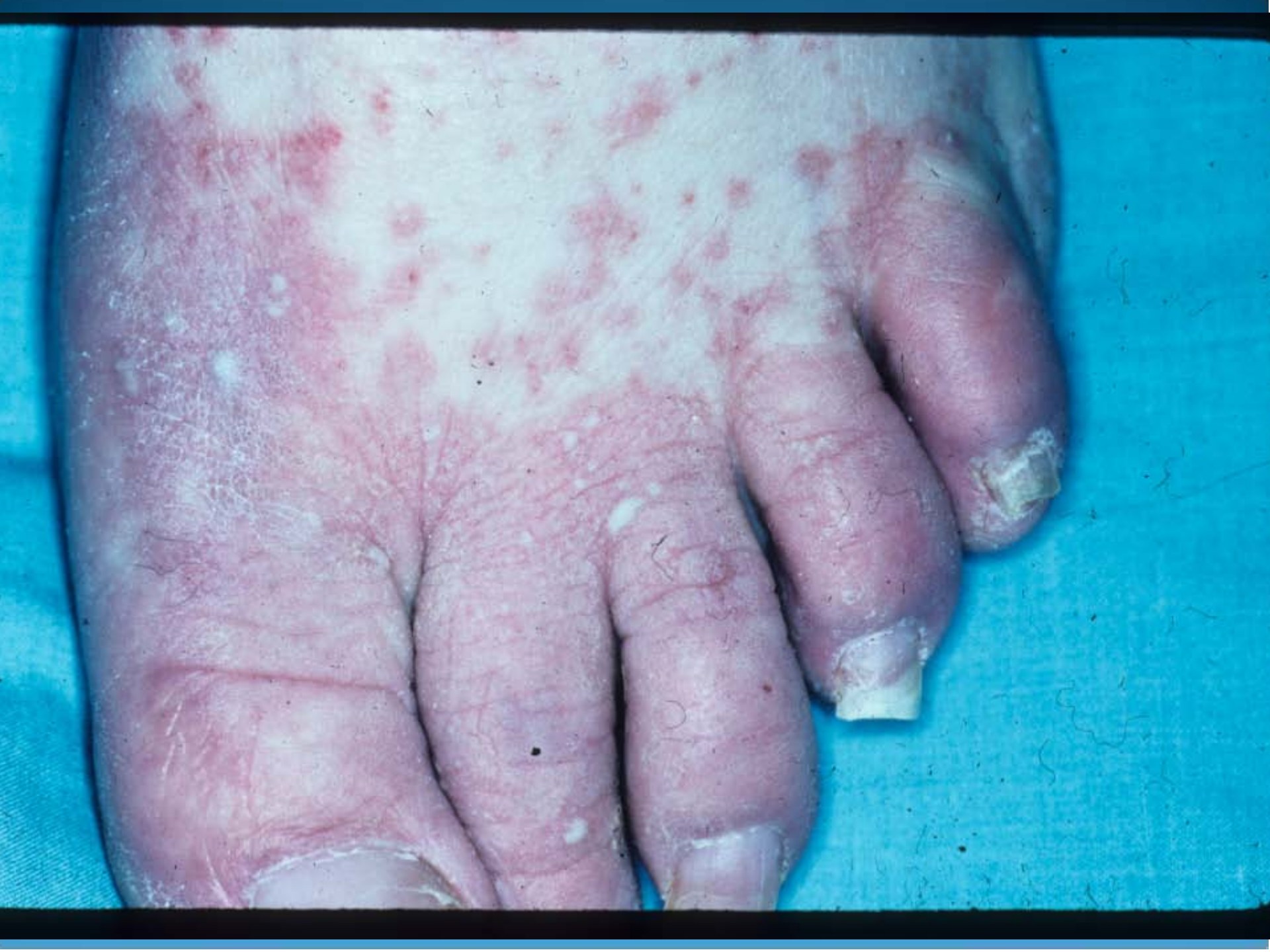












Associated Neoplasms

- 2/3: pre-existing neoplasm
- 1/3: neoplasm detected after presentation
- 3 most common neoplasms:
  1. Non-Hodgkin's Lymphoma (42%)
  2. Chronic Lymphocytic Leukemia (29%)
  3. Castleman's Disease (10%)

Associated Neoplasms

- Thymoma, malignant or benign (6%)
- Waldenstrom's Macroglobulinemia (6%)
- Spindle Cell Sarcoma (6%)

Striking absence of association with common tumors

Target Antigens

Plakin Gene Family

- 500 kd Plectin
- 250 kd Desmoplakin 1
- 230 kd BP Antigen 1
- 210 kd Envoplakin
- 190 kd Periplakin

Undetermined

- 170 kd transmembrane

Desmosomal Antigens

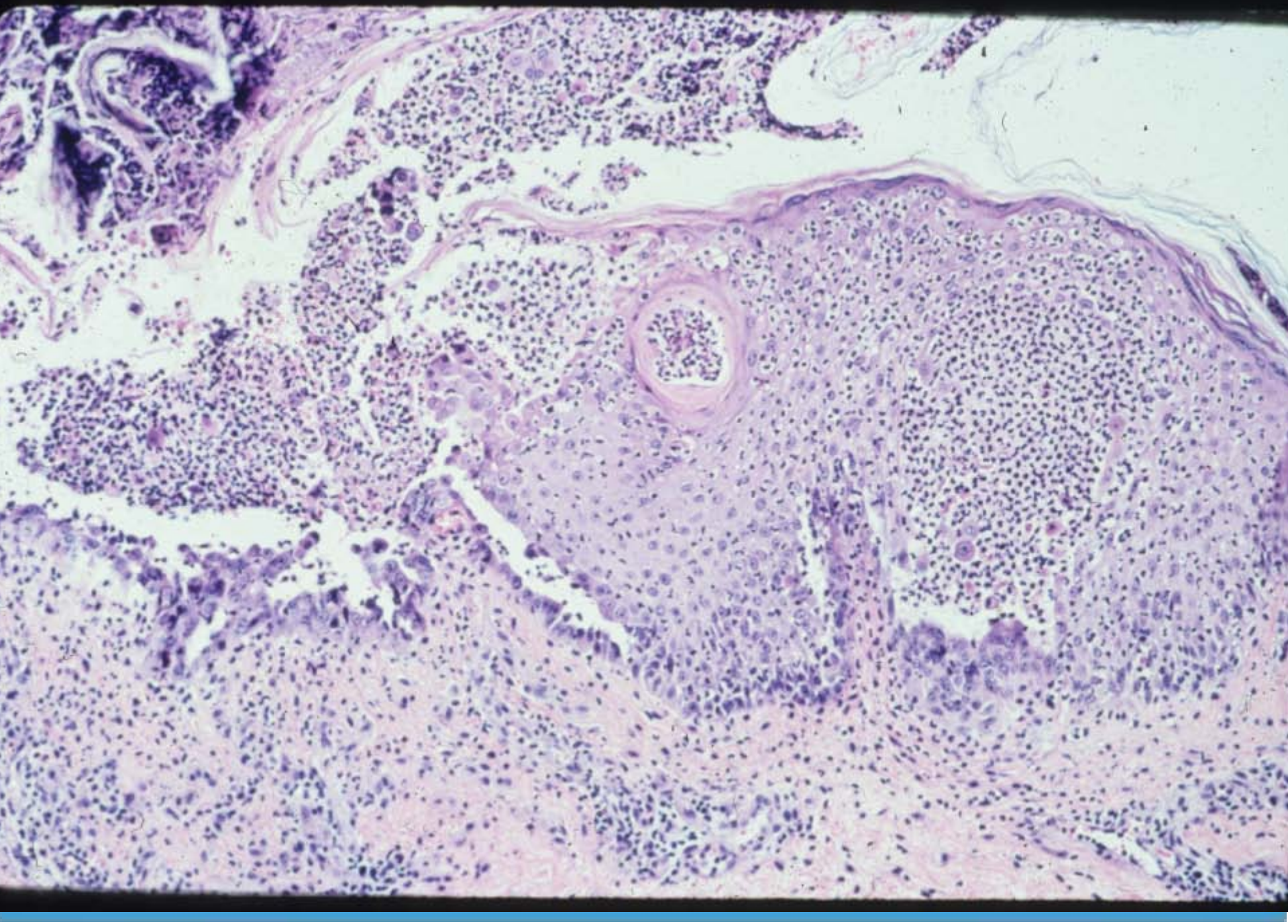
- 160 kd Desmoglein 1
- 130 kd Desmoglein 3

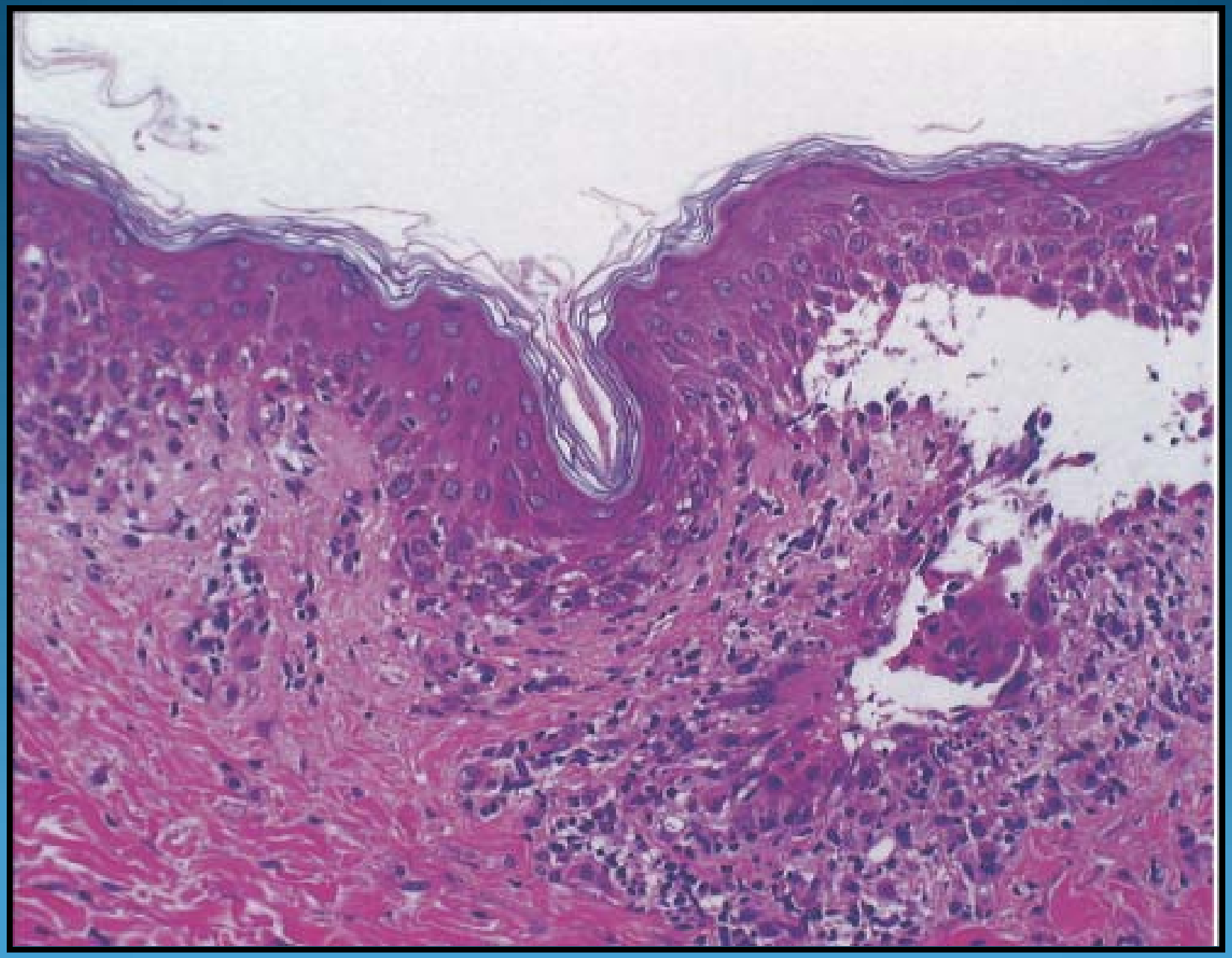
Theories of Pathogenesis

- Antitumor immune response cross reacts with epithelial proteins
- Cytokine secretion by tumor induces B cell differentiation and Ig production, resulting in autoimmunity

H&E: vesicular lesions

- Epidermal acantholysis
- Suprabasilar clefting
- Keratinocyte necrosis and dyskeratosis
- Vacuolar interface change in the basal layer
- Exocytosis of inflammatory cells



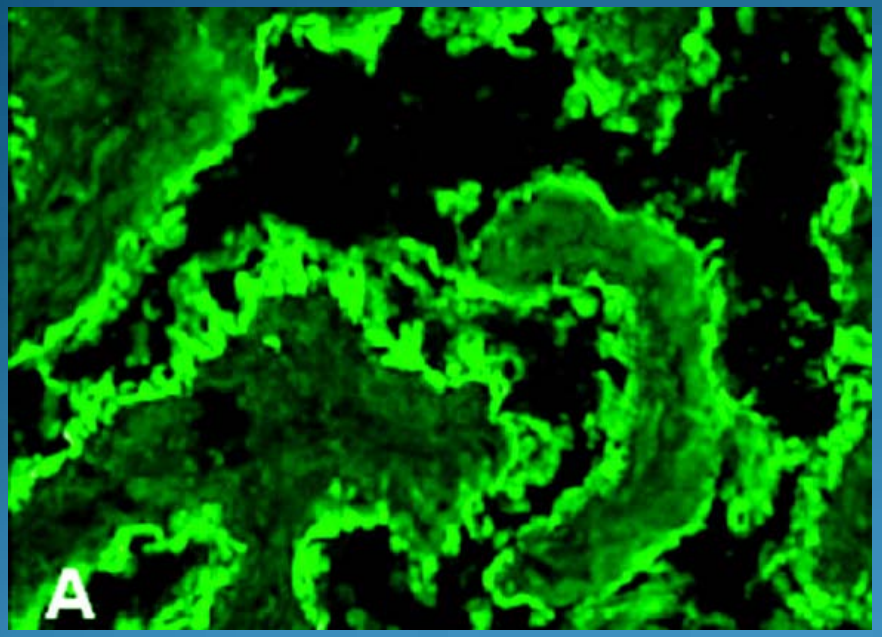


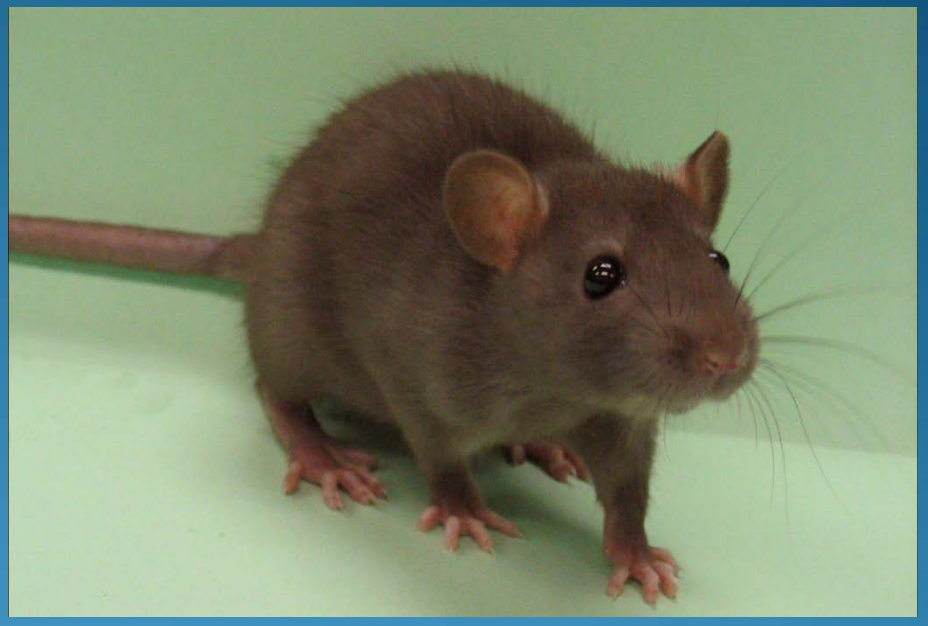
Direct Immunofluorescence

- Epidermal intercellular IgG/C3 ***and*** granular-linear complement along BMZ
- False negatives are common
  - Repeat biopsies are often necessary

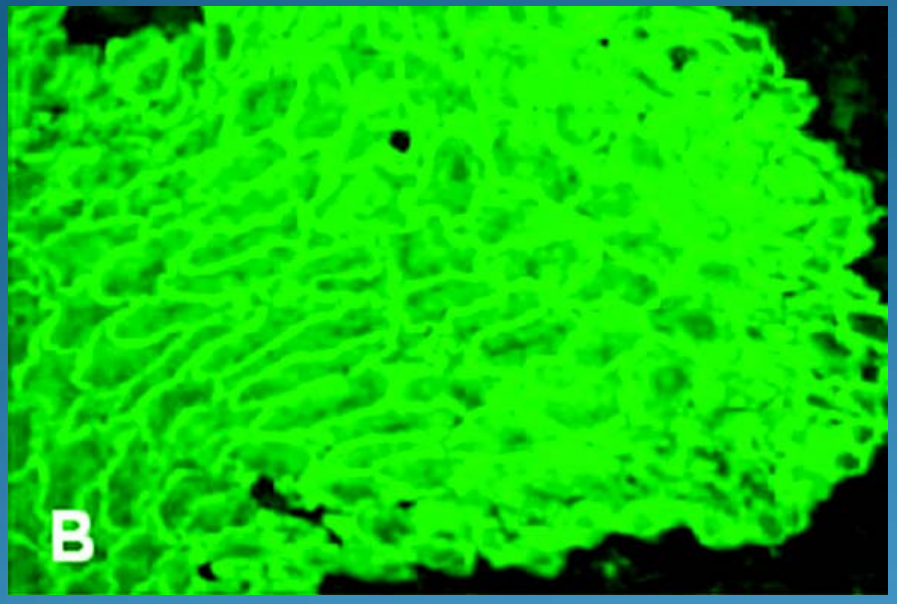
Indirect Immunofluorescence

- Circulating IgG binds SSE and non-SSE
- Substrates:
  - Monkey esophagus: SSE
  - Rodent bladder: NSSE





Lane, J. E. et al. Pediatrics 2004;114:e513-e516



Lane, J. E. et al. Pediatrics 2004;114:e513-e516

Diagnostic Criteria

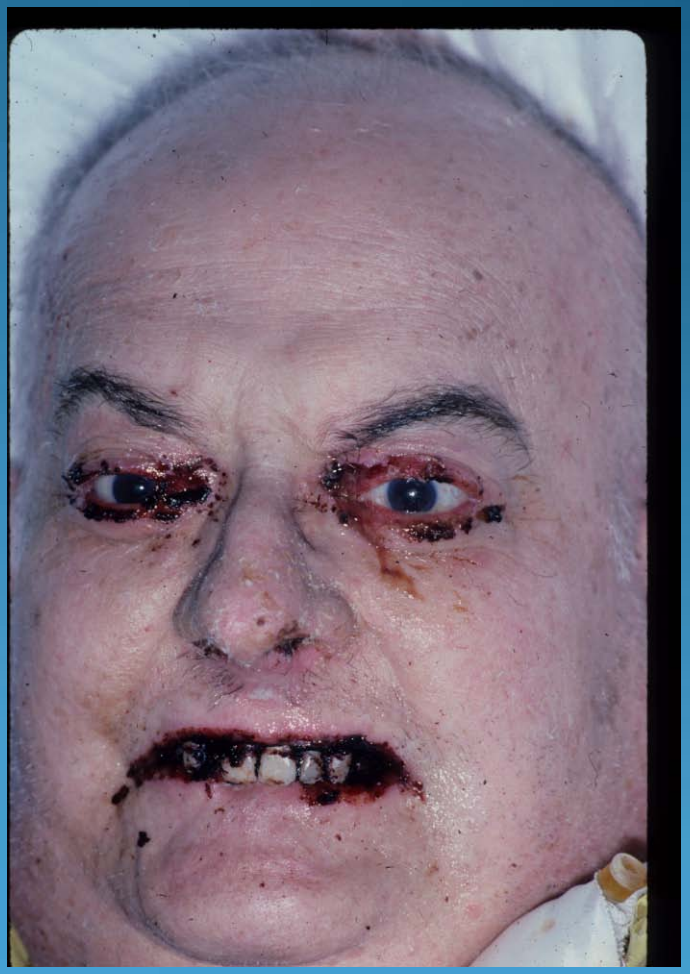
- Clinical findings
- Histopathology
- Pathogenic Autoantibodies

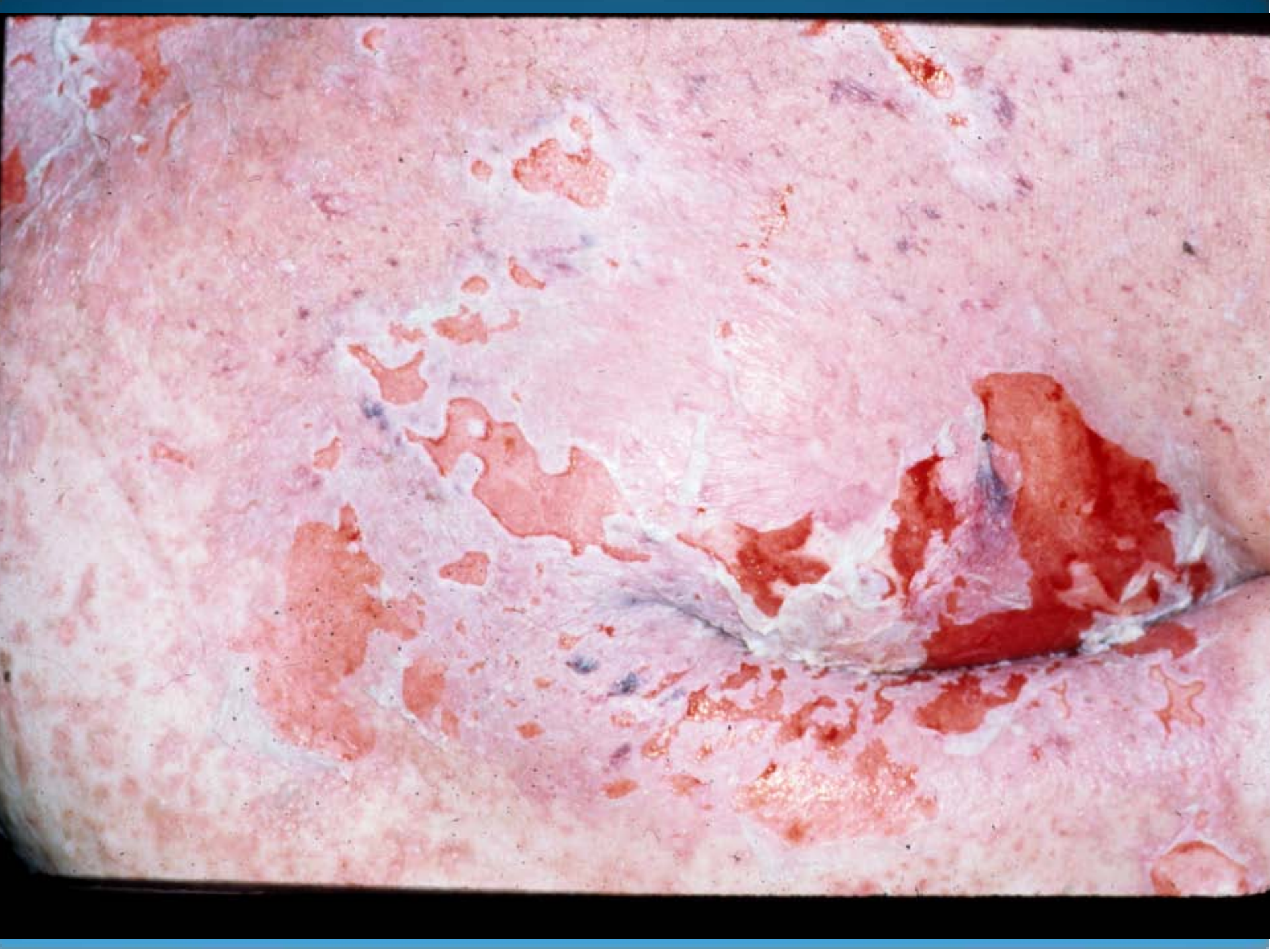
Paraneoplastic Pemphigus and Benign Neoplasms

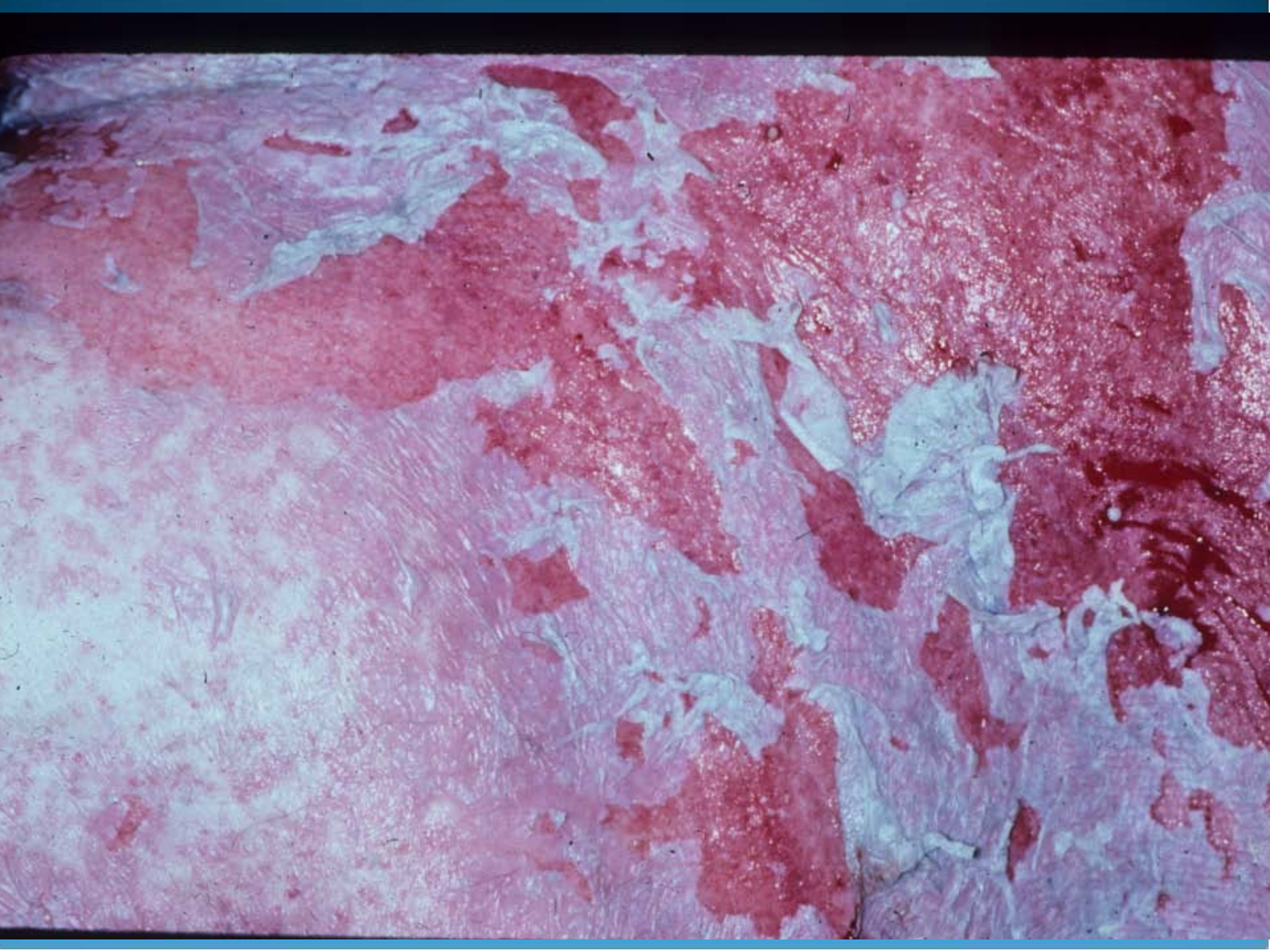
- Remove resectable neoplasms
- Substantial clearance or complete remission in the majority
- Time to clearance is variable (6-18 mos)

Paraneoplastic Pemphigus and Malignant Neoplasms

- Prognosis is grave
- 90% mortality despite aggressive Rx
- Course of autoimmunity ≠ malignancy
- Rx of neoplasm ≠ clearance of disease





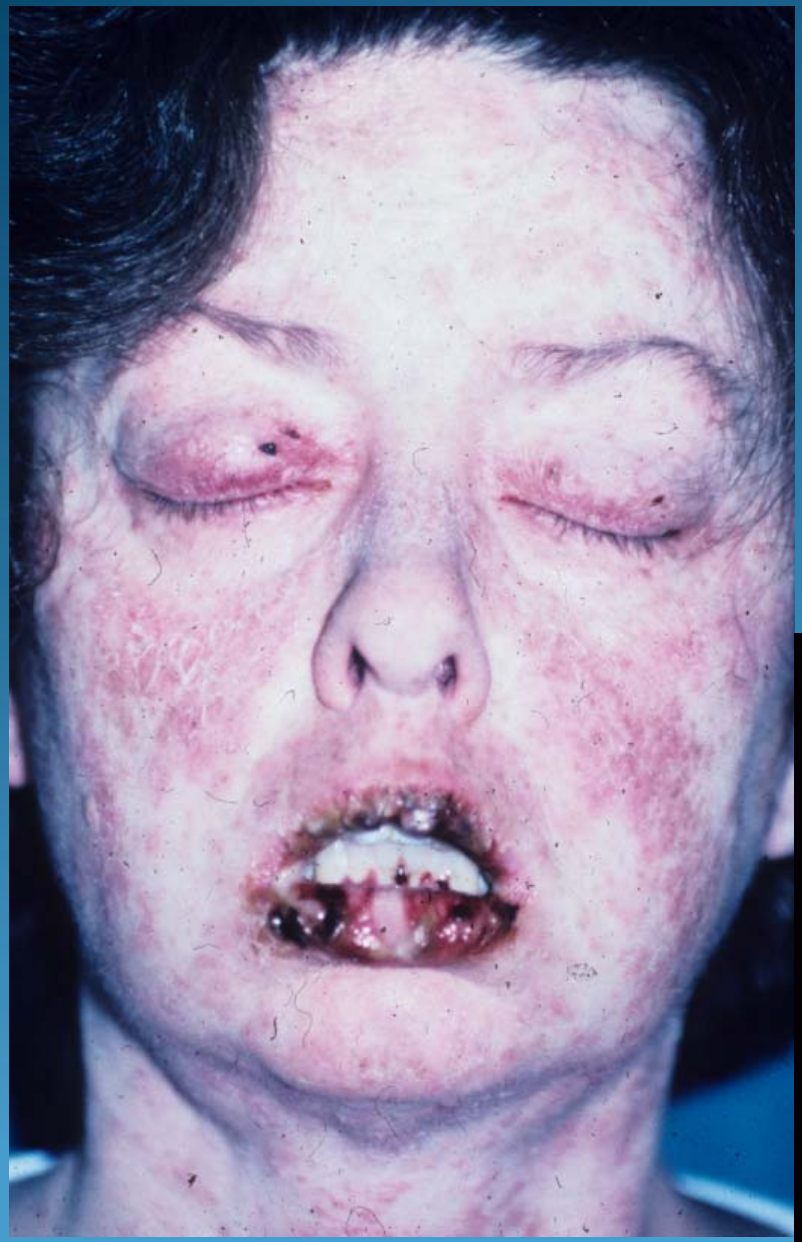


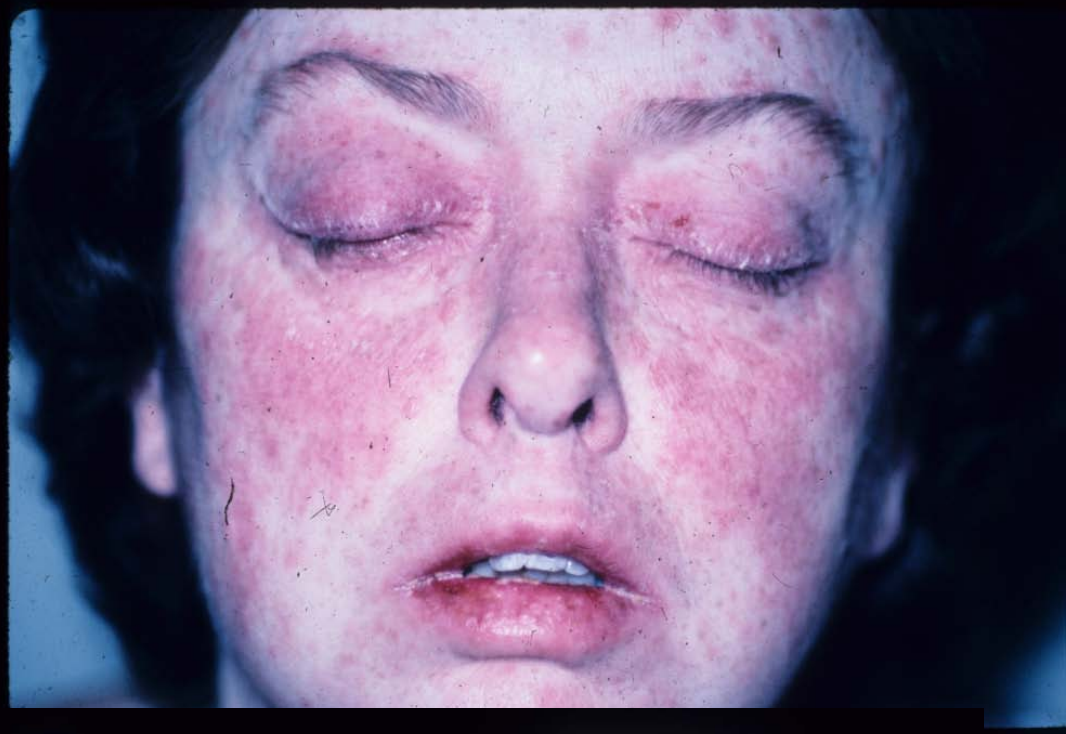
Paraneoplastic Pemphigus and Malignant Neoplasms

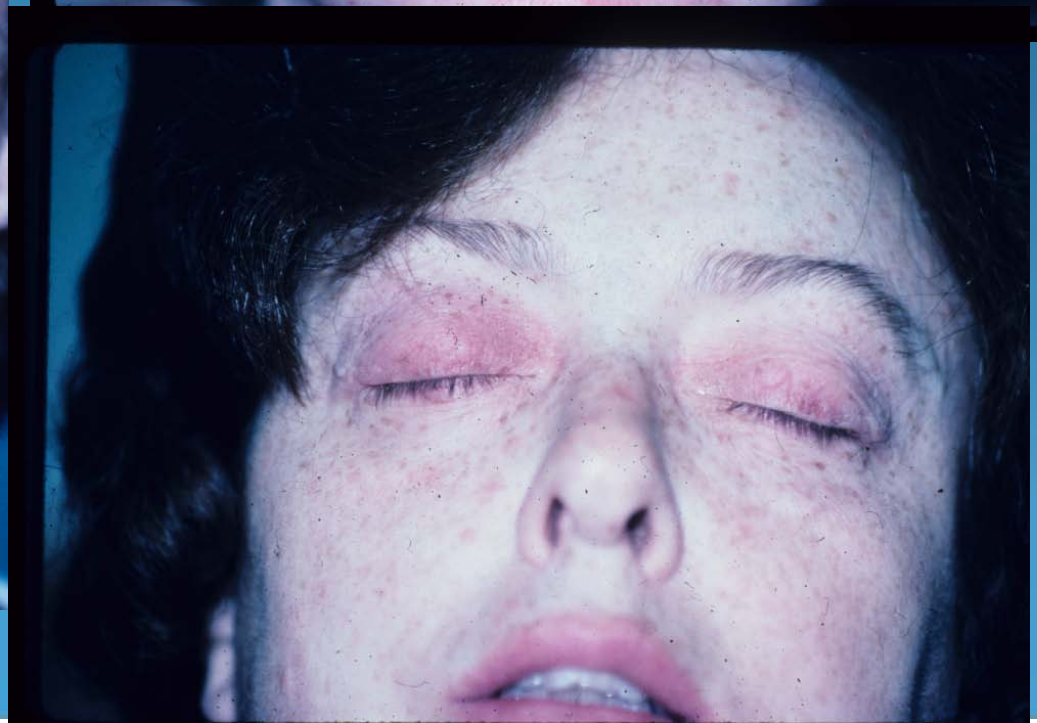
- Skin responds first
- Mucosal disease is particularly refractory
- Pulmonary involvement is prognostic
  - Progressive respiratory failure
  - Cause of death in ~30%

Paraneoplastic Pemphigus and Malignant Neoplasms

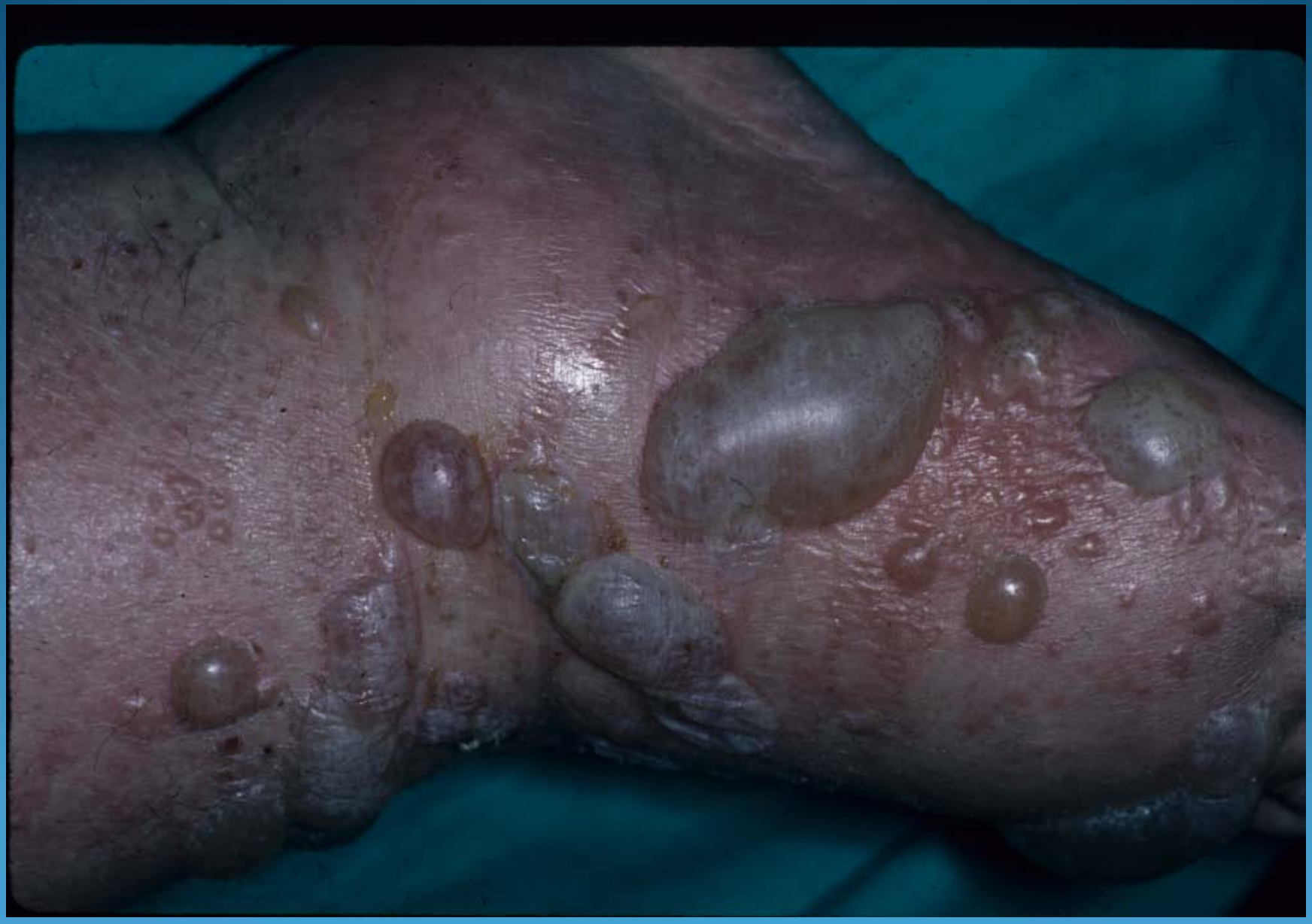
- Combination therapy is best
- Prednisone plus adjunctive agent
  - High dose immunoablative cyclophosphamide
  - Anti-CD20 mAb (rituximab)
  - Plasmapheresis







Bullous Pemphigoid



Bullous Pemphigoid

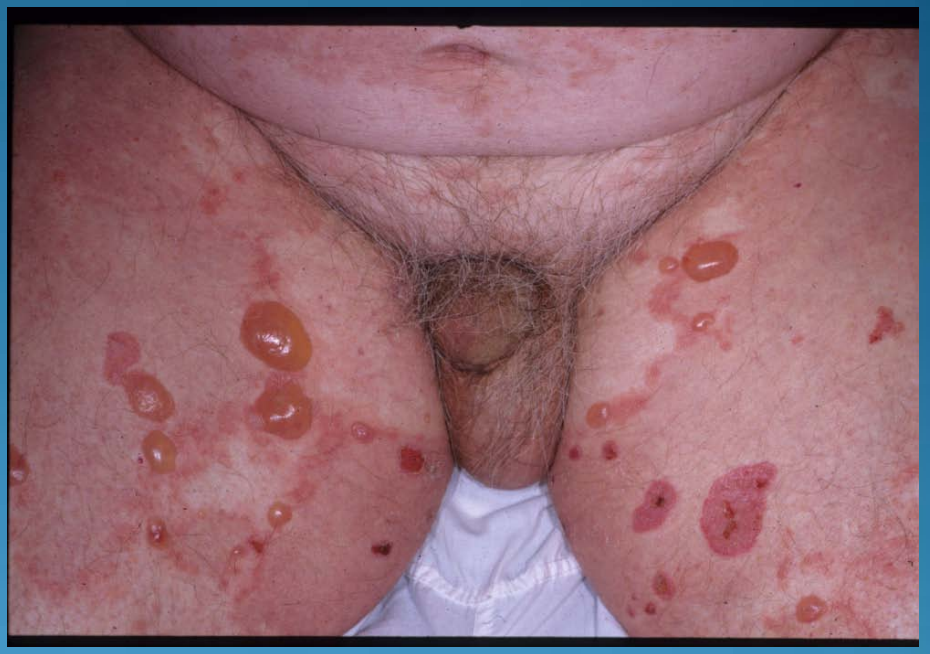
- Primarily affects the elderly
- Antibodies target hemidesmosomal proteins
- Subepidermal separation → tense bullae
- Wide clinical spectrum

Major Pemphigoid Variants

- Bullous Pemphigoid
- Gestational Pemphigoid
- IgA Pemphigoid
- Mucous Membrane Pemphigoid


Nikolsky Negative

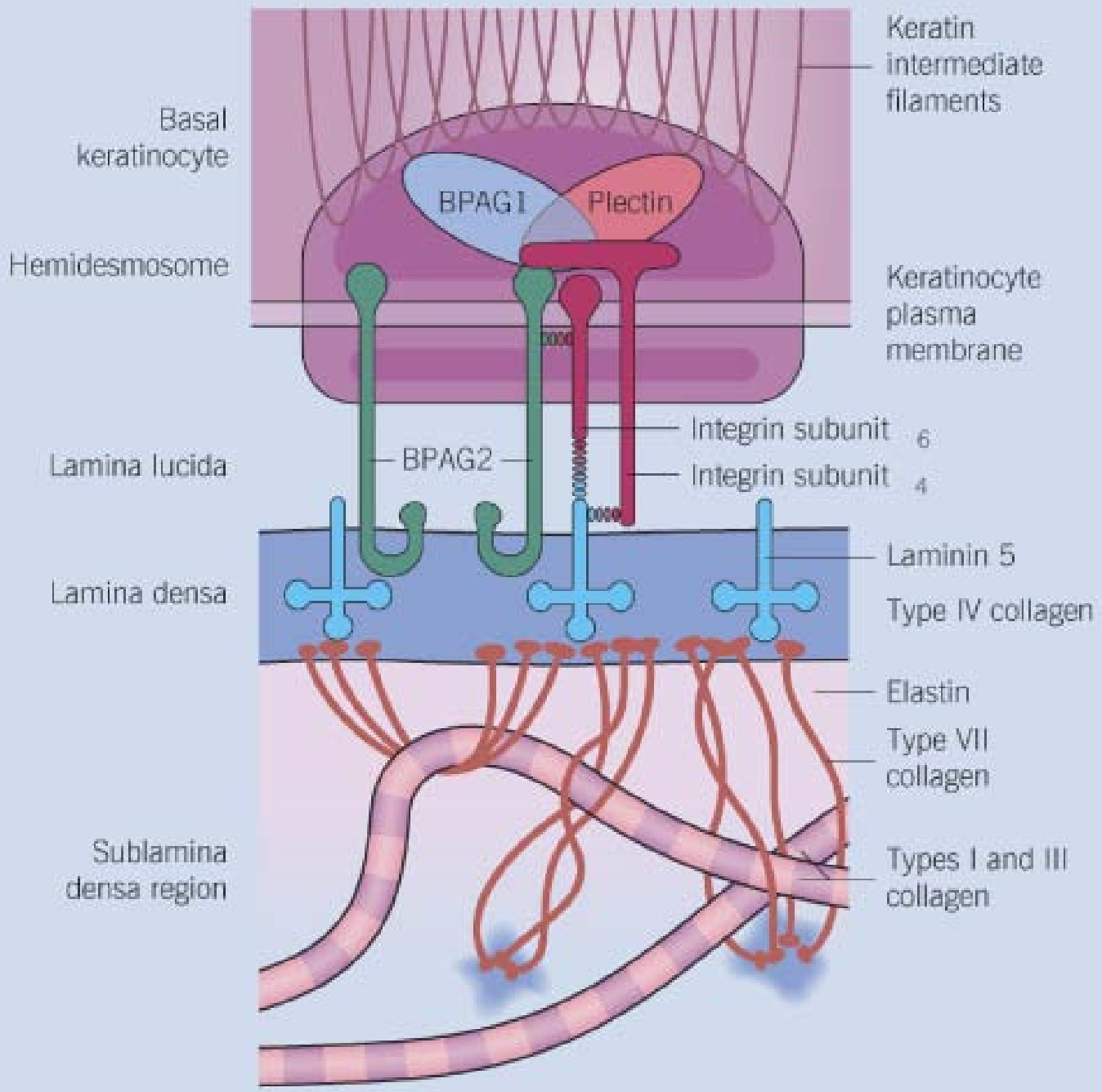
- Most common AIBD
- Onset typically after 60
- Rarely in children
- No geographic nor gender predilection
- HLA Class II alleles may predispose



Antigenic Targets

- Components of the hemidesmosome
  - Mediate epithelial-stromal adhesion

1. BP Ag 1, 230 kd
   - Cytoplasmic protein, plakin family
2. BP Ag 2, 180 kd (type XVII collagen)
   - Transmembrane protein with a collagenous extracellular domain


Basal keratinocyte
Hemidesmosome
Lamina lucida
Lamina densa
Sublamina densa region
Keratin intermediate filaments
BPAG1
Plectin
Keratinocyte plasma membrane
Integrin subunit 6
Integrin subunit 4
BPAG2
Laminin 5
Type IV collagen
Elastin
Type VII collagen
Types I and III collagen

Pathogenesis

Humoral and cellular immune responses

- Autoreactive $CD4+$ T cells respond to BP 180
- Cytokine cascade stimulates B cells
- Plasma cells $\rightarrow$ pathogenic autoantibodies

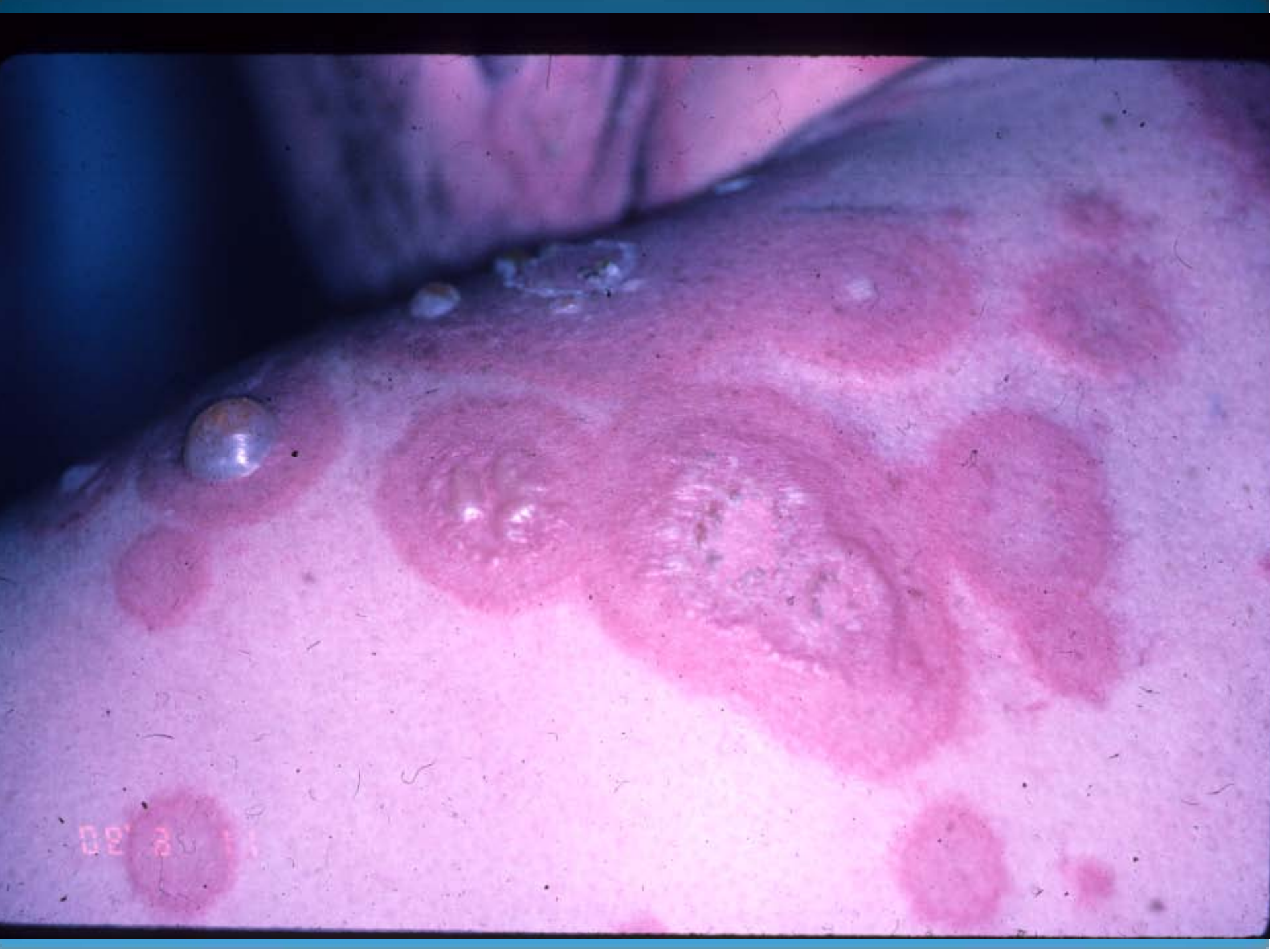
Pathogenesis

- Circulating autoantibodies bind:
  - BP Ag 2, NC16A domain (extracellular)
  - BP Ag 1, C-terminal region (intracellular)

- Complement activation → inflammatory cascade → tissue disadhesion → blistering

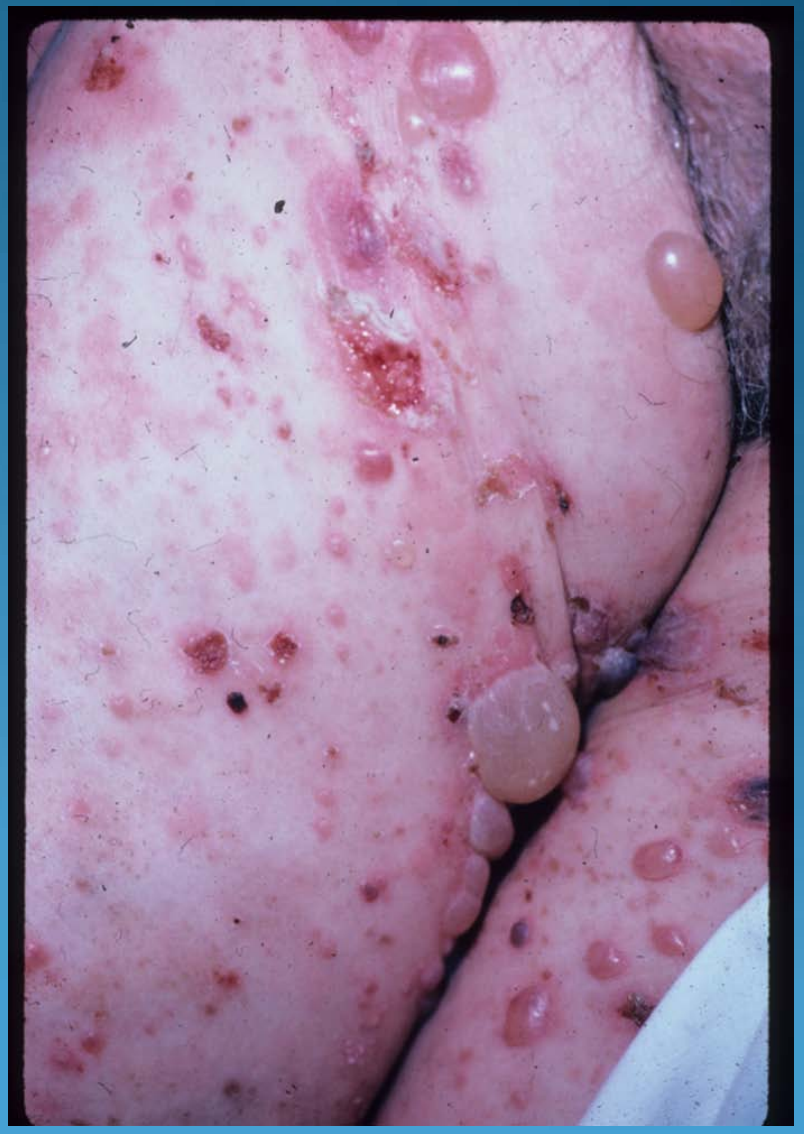
Non-bullous Phase

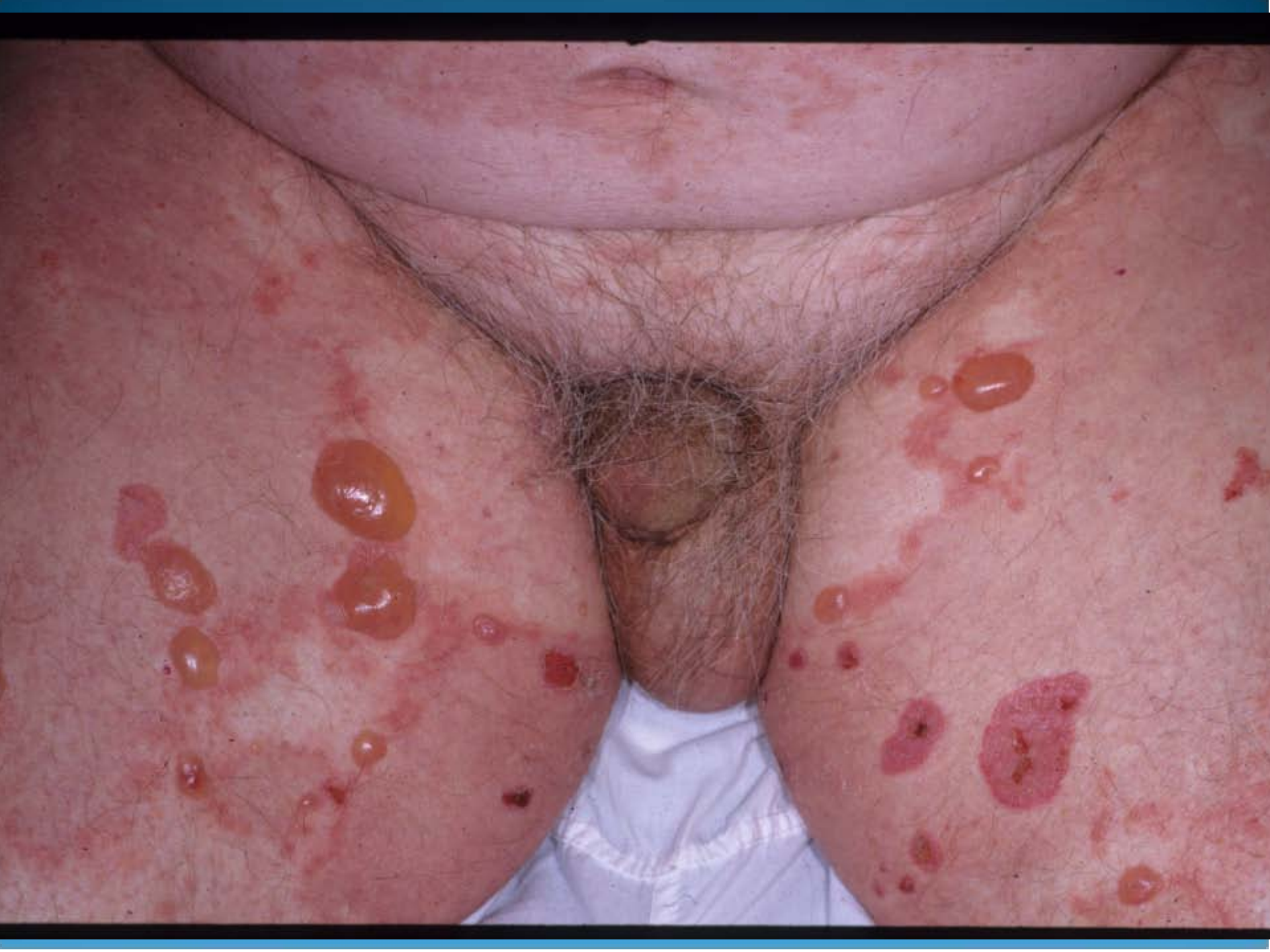
- Nonspecific and of variable duration
- Intractable pruritus is common
- Wide spectrum of clinical presentations
- Urticarial, eczematous, or papular lesions
- May remain as sole disease manifestation



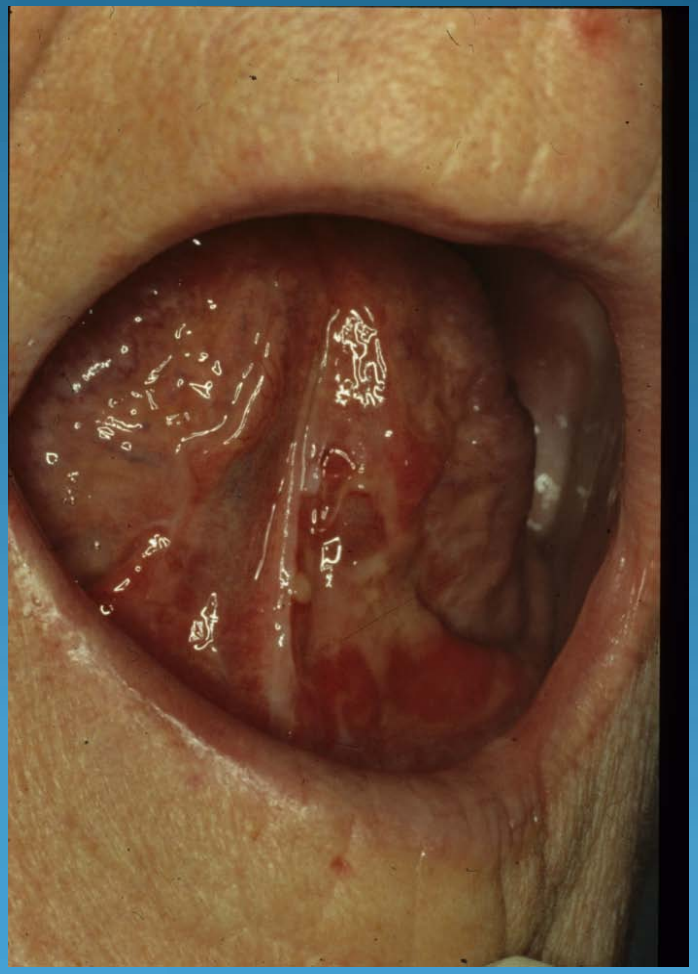
Bullous Phase

- Tense bullae on nl or inflamed skin
- Flexures, lower trunk, thighs, legs
- Urticarial and infiltrated papules/plaques
- Annular or figurate patterns



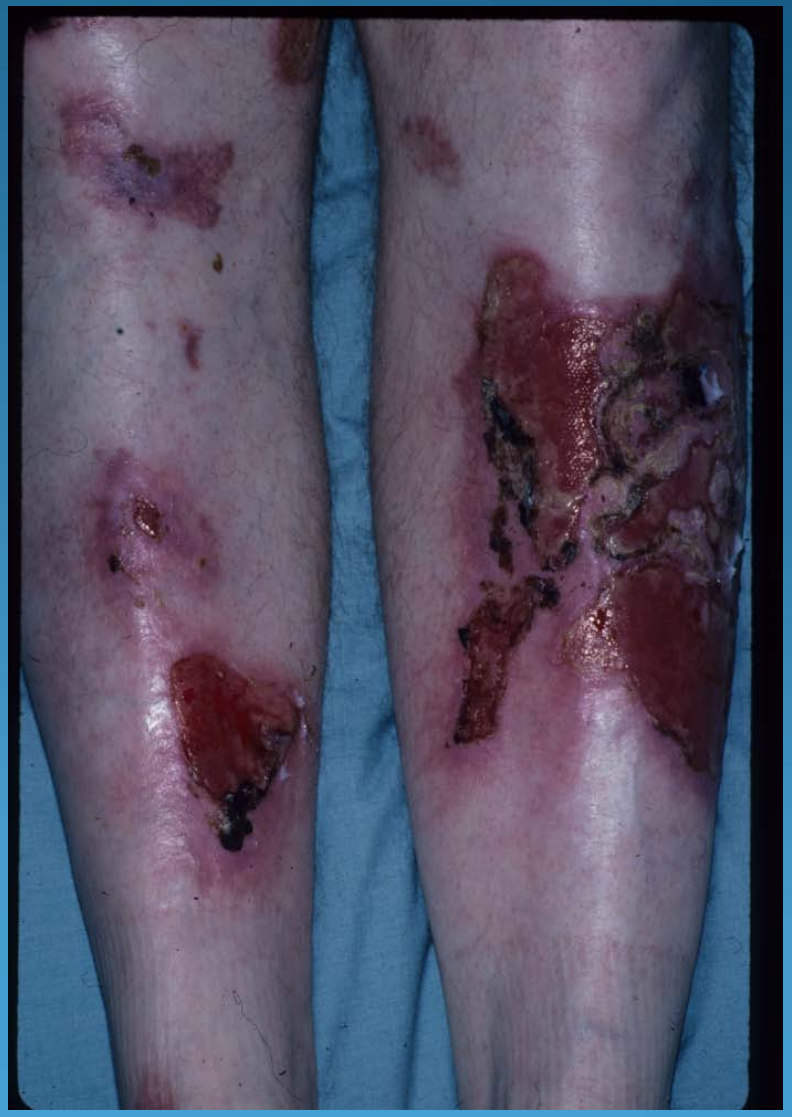


- Oral mucosa involved in ~10-30%
- Other mucosal sites rarely involved
- Peripheral blood eosinophilia in ~50%



Clinical Variants

- Localized
- Dyshidrosiform
- Vesicular
- Pemphigoid Nodularis
- Erythrodermic
- Gestational
- Childhood



Disease Associations

Malignancy

- Likely related to advanced age
- Screen if symptomatic/atypical presentation

Autoimmune Disorders

- Genetically predisposed?

Disease Associations

Chronic Inflammation/Trauma/Burns

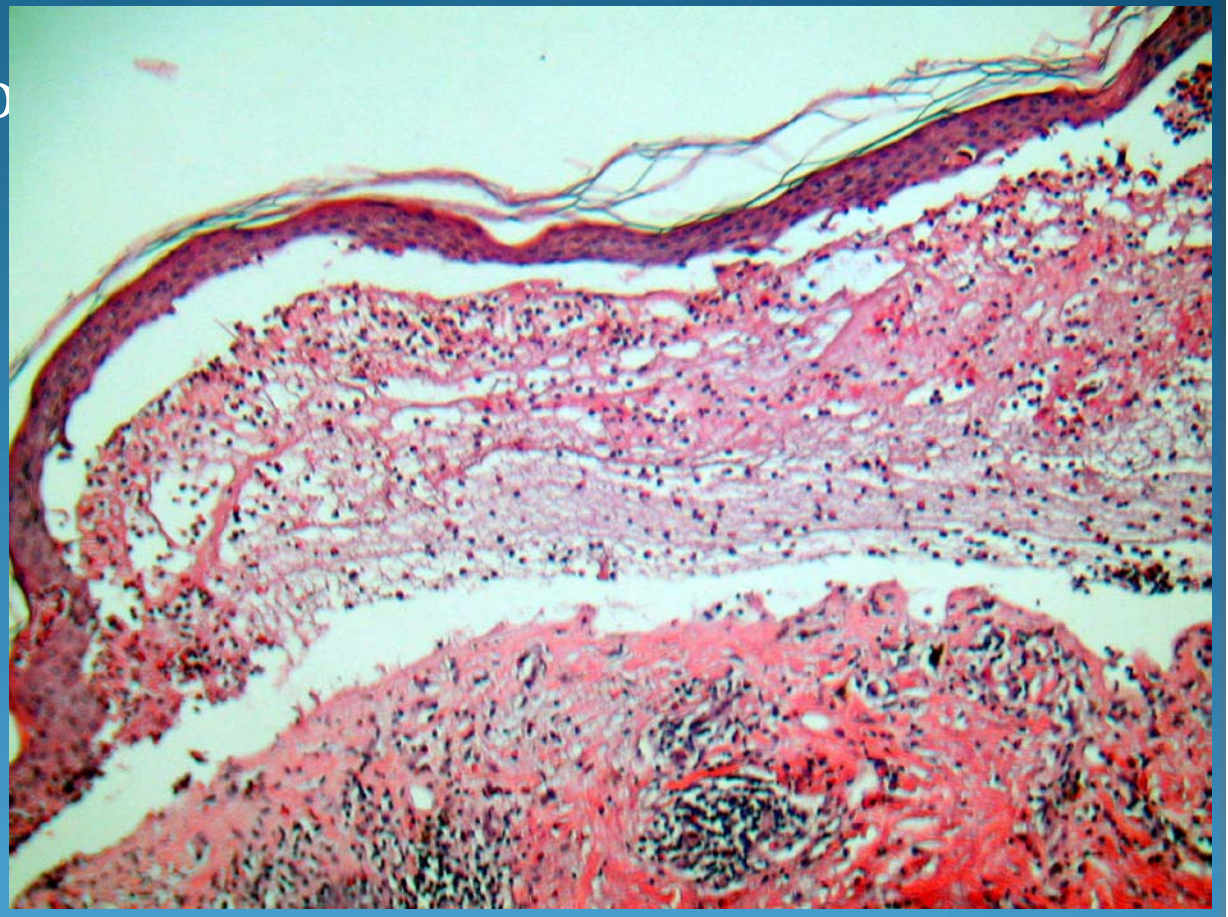
- Epitope spreading

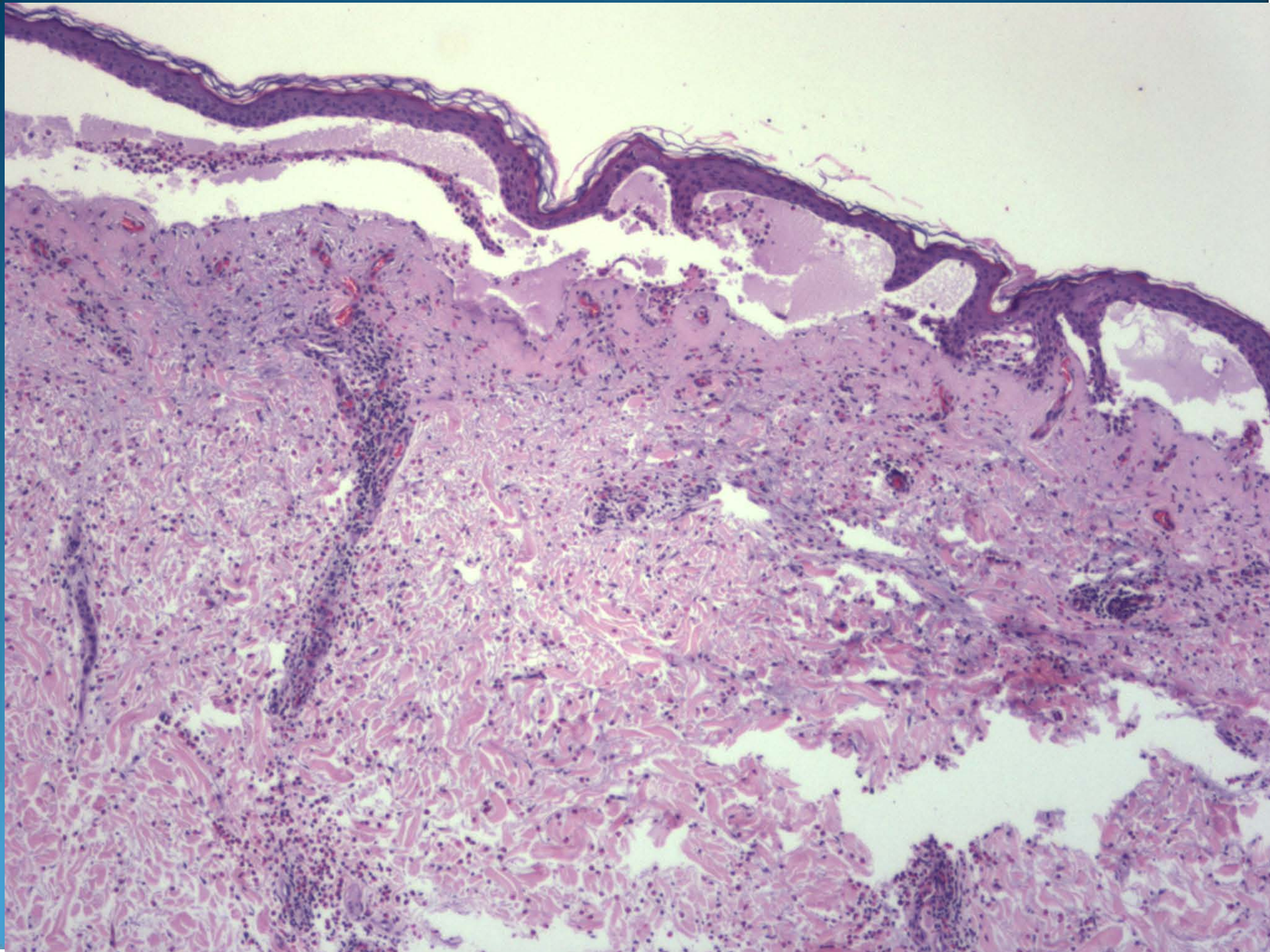
Drugs

- Trigger in genetically predisposed?
- Modify immune response or alter antigens

H&E

- Eosinophilic spo
- Subepidermal
- Blister cavity:
  - Fibrin/variable
  - Eosinophils
- EM:
  - split occurs at the *lucida*

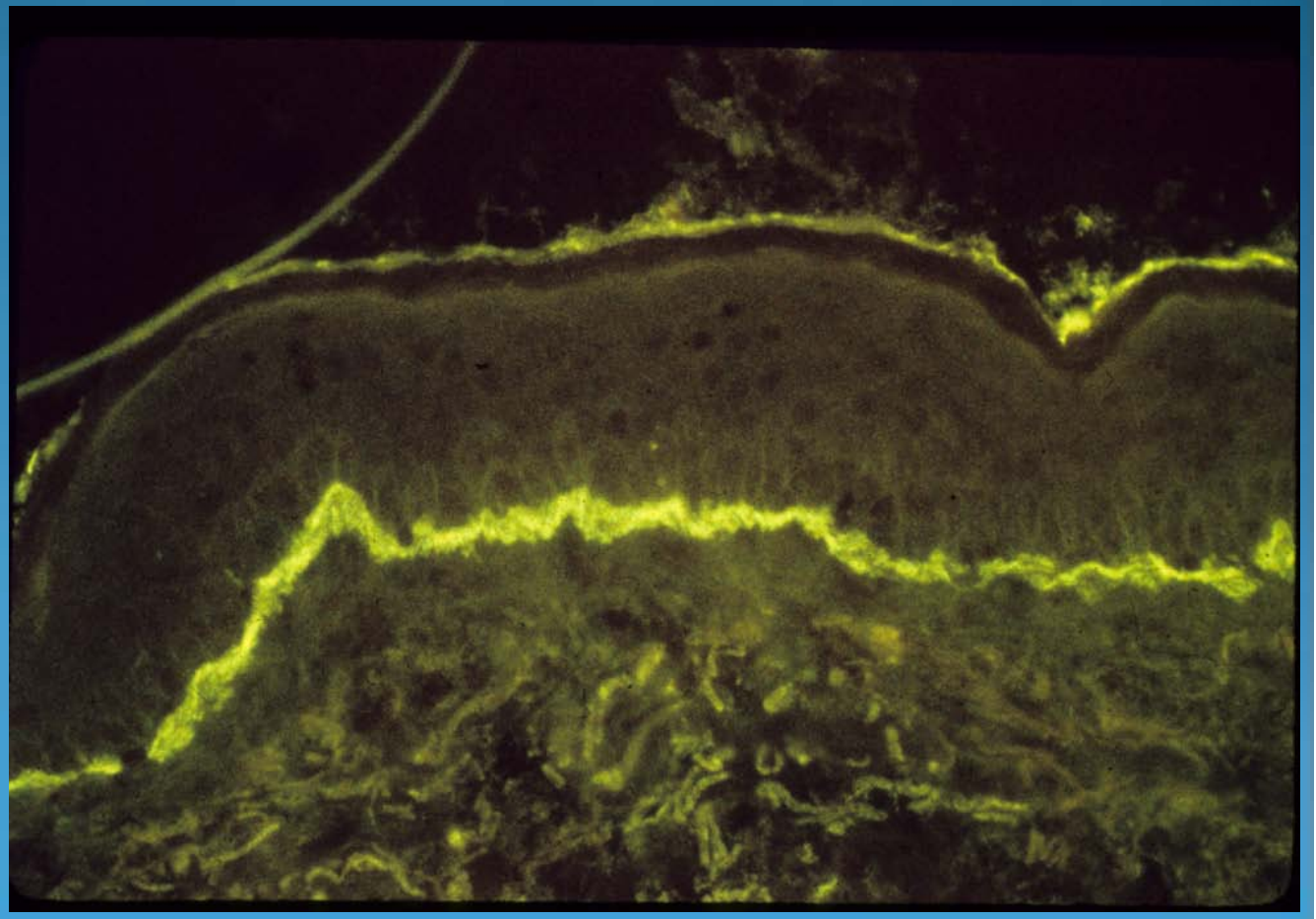




Direct Immunofluorescence

Perilesional skin

- Linear IgG and/or C3 along BMZ



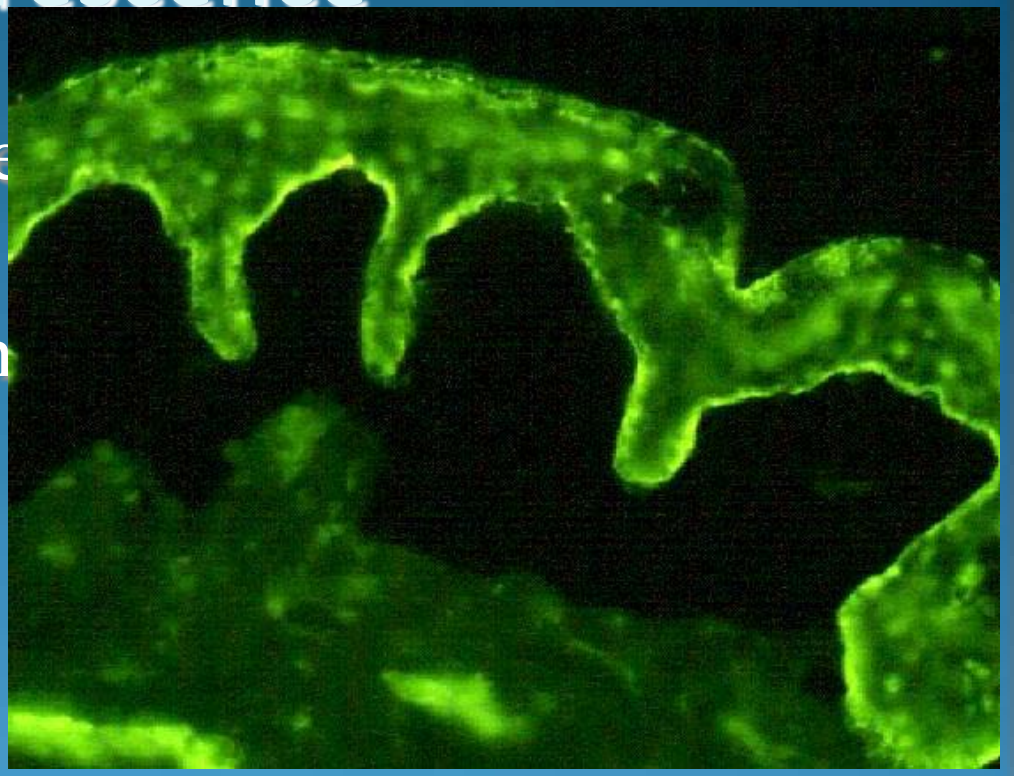
Indirect Immunofluorescence

Serum:

- 60-80% have detectable circulating IgG / C3
- Variable correlation with clinical disease

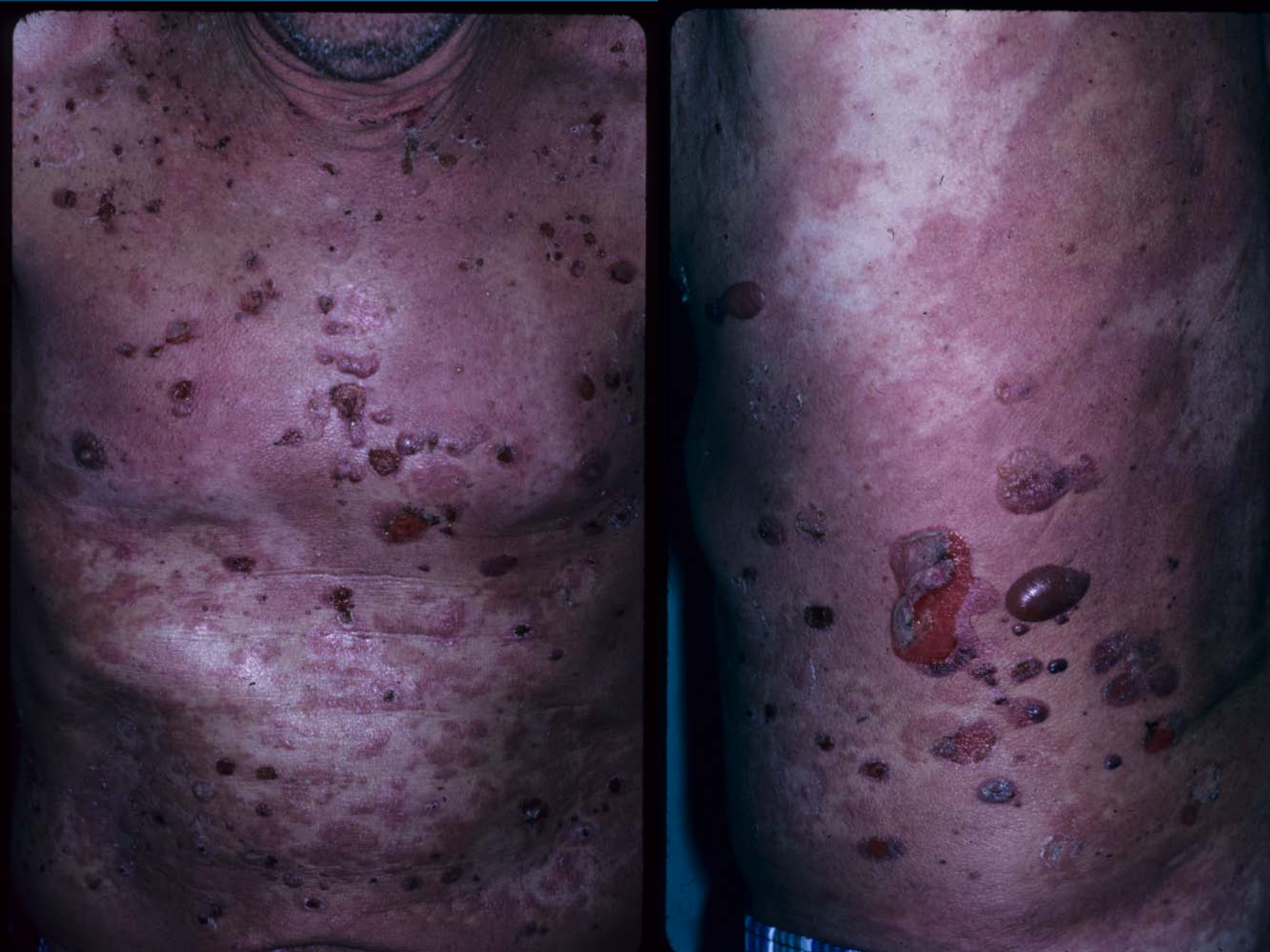
Salt split nl human skin:

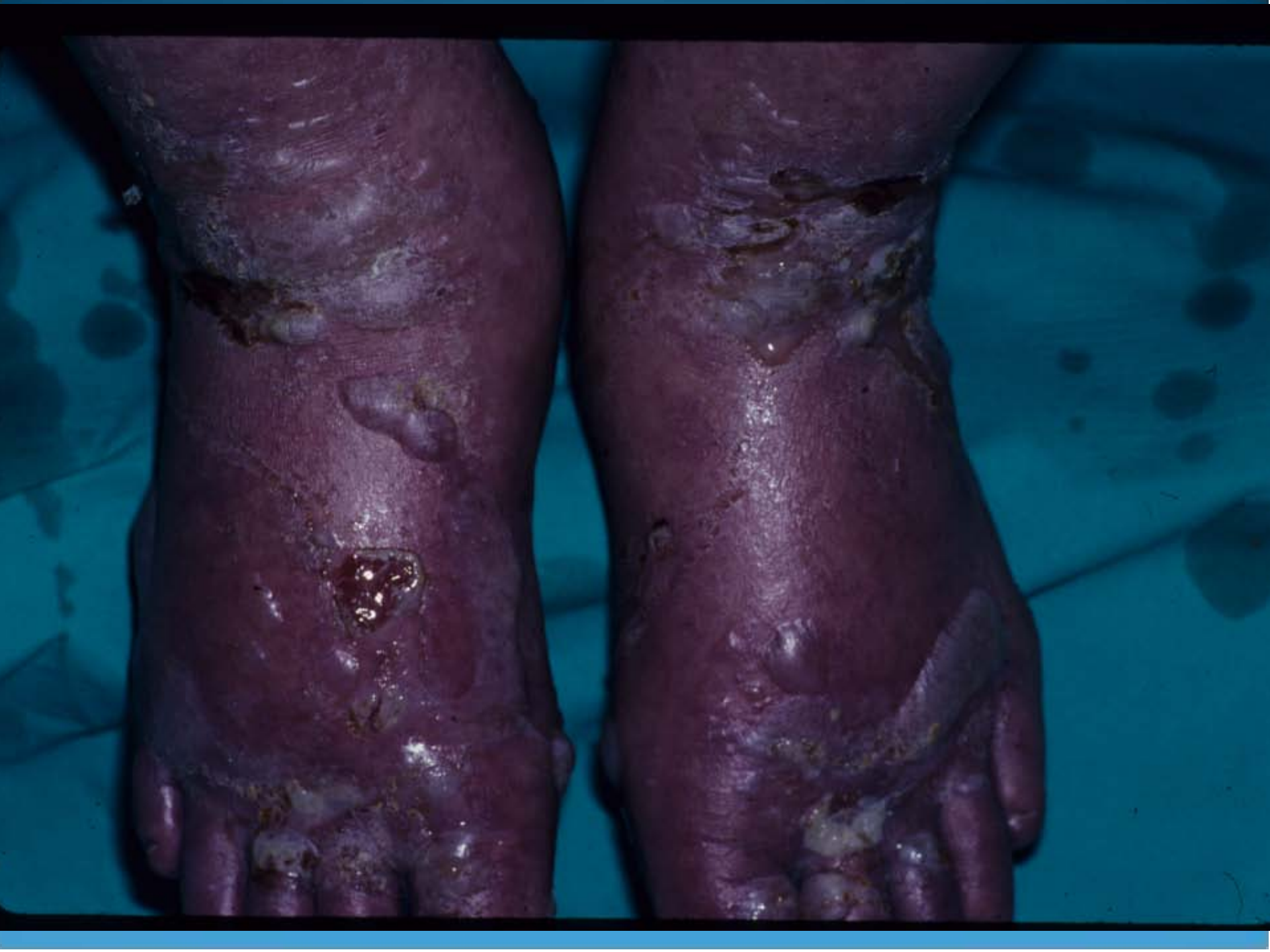
- *Substrate of choice*
- Ab bind epidermal side



Course & Prognosis

- Chronic with exacerbations/remissions
- Self-limited, remits within 5-10 years
- Morbidity limited but *can* be significant
  - Intractable pruritus, impetiginization, fluid/electrolytes
  - Quality of life
- Mortality
  - Estimated mortality during 1st year: 10-40%
  - Age and drug-related side effects contribute





Treatment Principles

- Consider the patient
- Aggressive vs. conservative approach
- Balance risk to benefit ratio of therapies
- Aim for reduction, not complete suppression
- Inflammation is a key pathogenic element
- Utilize synergistic mechanisms
  - Decrease antibody synthesis
  - Decrease inflammation

Treatment Options

Corticosteroids: 1st line

- Anti-inflammatory & immunosuppressive
- Intralesional
- Topical
- Systemic
  - 0.5-1 mg/kg/d (lean body weight)

If disease is limited or steroids are not tolerated/ contraindicated

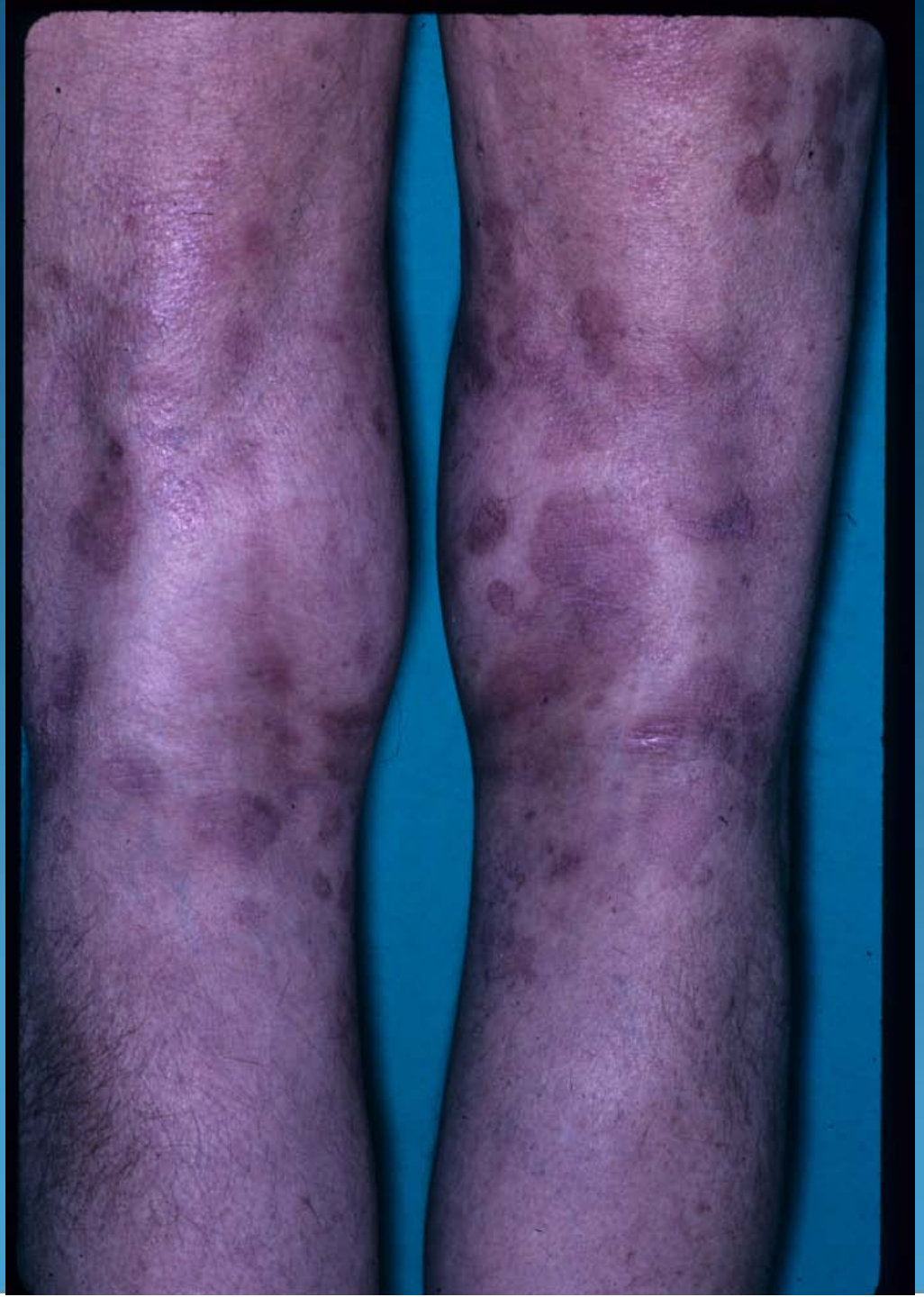
Non-steroidal anti-inflammatory drugs:

- Antimetabolites (methotrexate)
- Calcineurin Inhibitors (cyclosporine)
- Antibiotics (tetracycline, erythromycin)
- Dapsone

Good Response:

- Healing of lesions
- Cessation of new blisters

Begin steroid taper

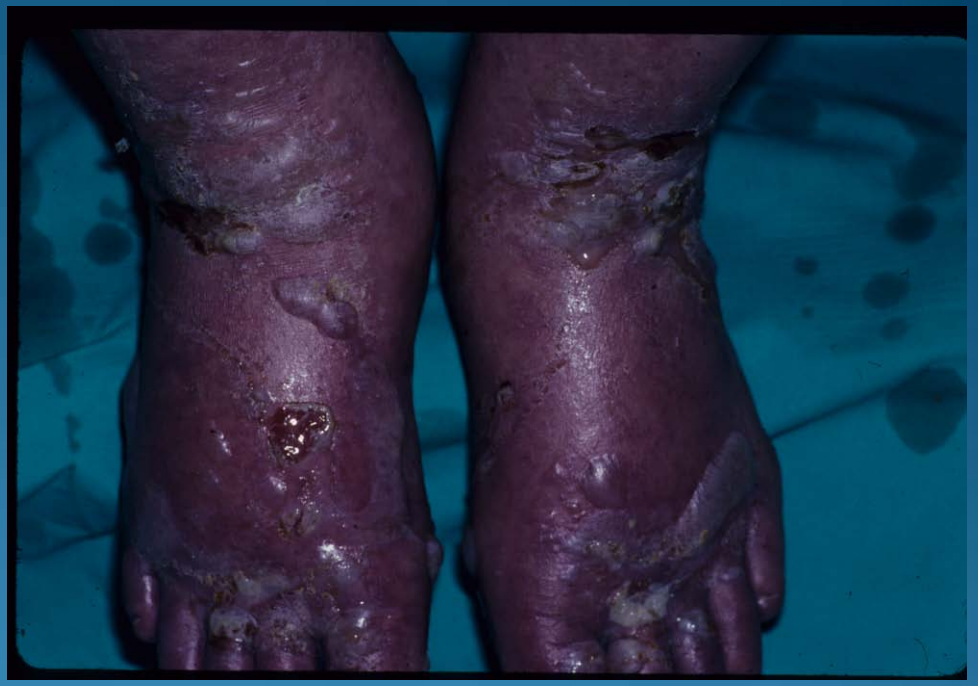


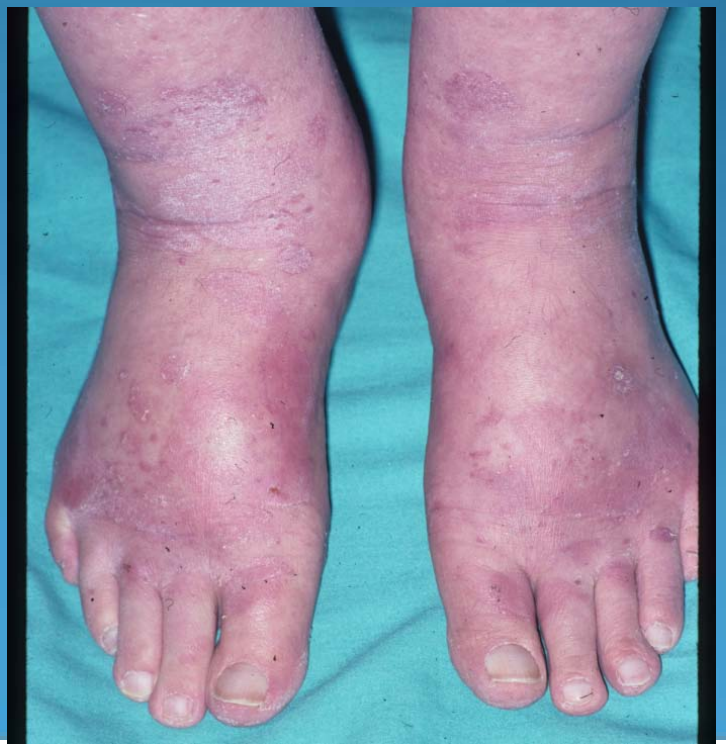
Poor Response:

- Persistent or progressive

Continue steroid
add steroid sparing agent

- MMF
- Azathioprine
- Alkylating agents rarely





Monitoring and Follow-Up

- Until remission is achieved and off all meds
- Frequently to review efficacy/adverse effects
- Clinical is best, IF is of limited value