Cutaneous Deposition Diseases-Part 2

Cutaneous Deposition Disorders

Group of unrelated conditions characterized by the presence of endogenous or exogenous substances within the dermis or subcutis

Endogenous Cutaneous Deposition Disorders

- **Lipoid Proteinosis**
- **Porphyria**
- Amyloidosis
- Colloid Milium

Lipoid Proteinosis

Hyalinosis Cutis et Mucosae

Urbach-Wiethe Disease

Lipoid Proteinosis

- Autosomal Recessive
- **ECM-1**: Extracellular Matrix Protein 1
- South Africa
- Hyaline-like material deposited in skin, mucous membranes, brain, and viscera
- Cause is unknown

Lipoid Proteinosis: Pathogenesis

- Hyaline-like material:
  - deposited in blood vessel walls and free in the papillary dermis
  - deposits consist of 2 substances:
    - True hyaline of fibroblast origin
    - Reduplicated basement membranes

Lipoid Proteinosis: Presentation

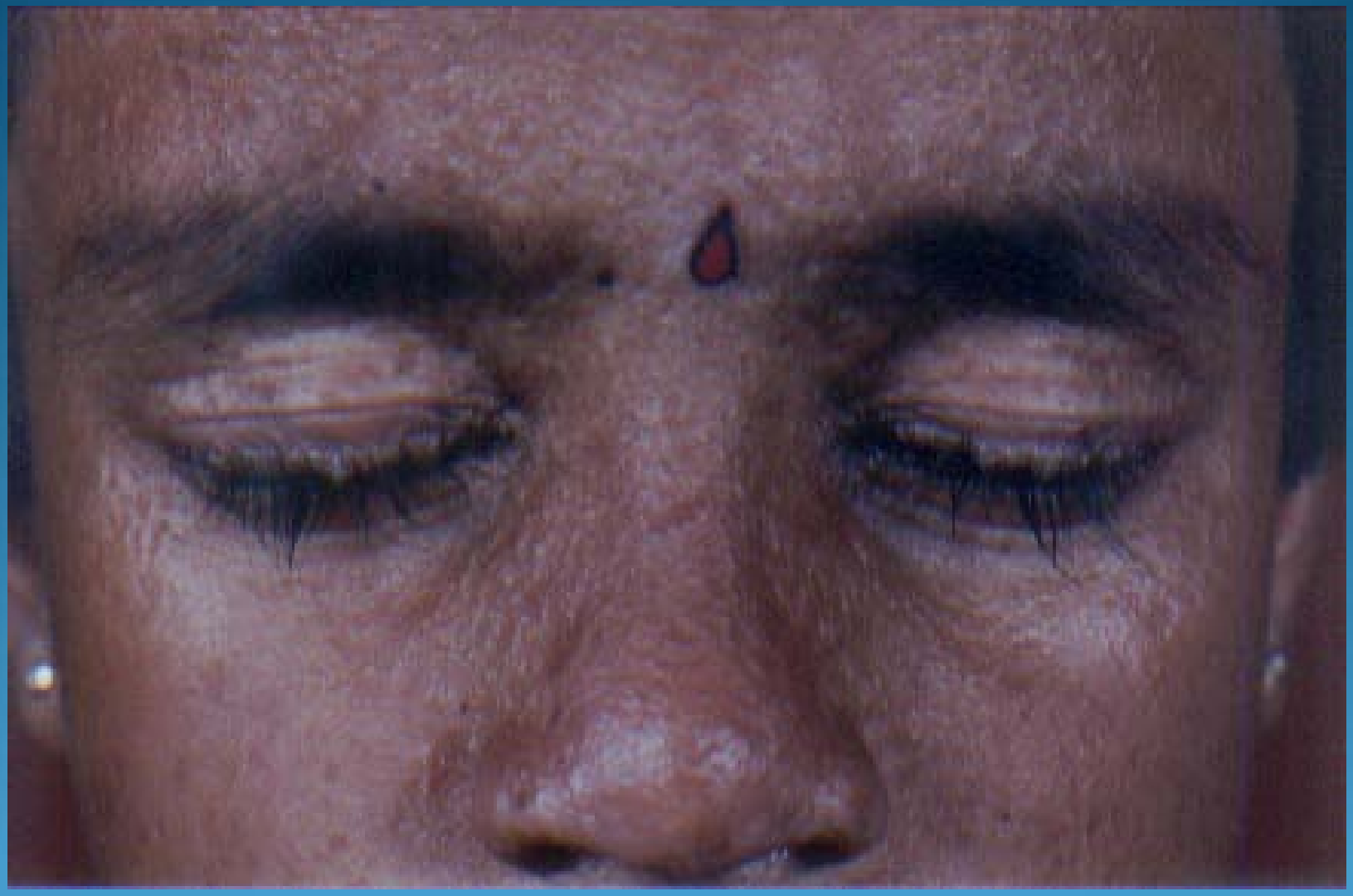
- **Hoarse cry at birth / infancy**
- **Hoarseness throughout life**

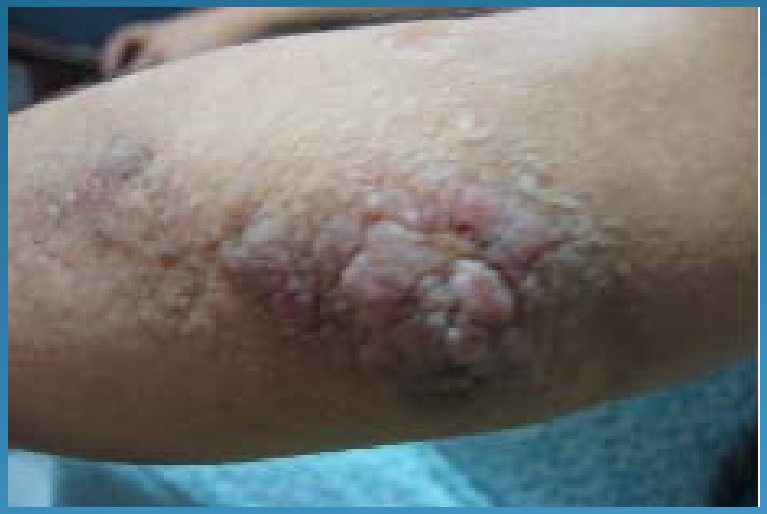
Lipoid Proteinosis: Clinical Features

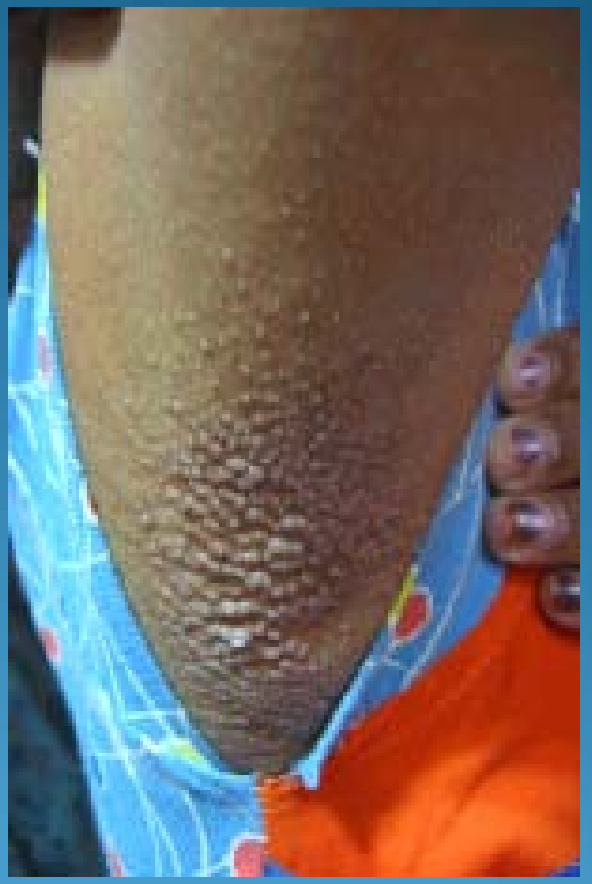
- Skin lesions appear during the first two years of life as 2 overlapping stages
- **Stage 1: Inflammatory**
  - Lasts through teens
  - Vesiculobullous and crusted erosions of the skin, mouth and throat
  - Resolve with atrophic, ice-pick scars on face

Lipoid Proteinosis: Clinical Features

- **Stage 2: Infiltrative**
  - Deposits increase in the dermis
  - Thick, yellow, waxy skin
  - Papules/plaques/nodules on face, extremities
  - Verrucous nodules on elbows, knees, hands
  - Generalized hyperkeratosis/infiltration may occur







Lipoid Proteinosis: Clinical Features

- Eyes:
  - **Moniliform blepharosis (beaded papules)** on the palpebral margins
- Lips:
  - **Pebbling of lip mucosa**
- Tongue:
  - **Infiltration of frenulum**, fixed to the mouth floor
  - Firm and woody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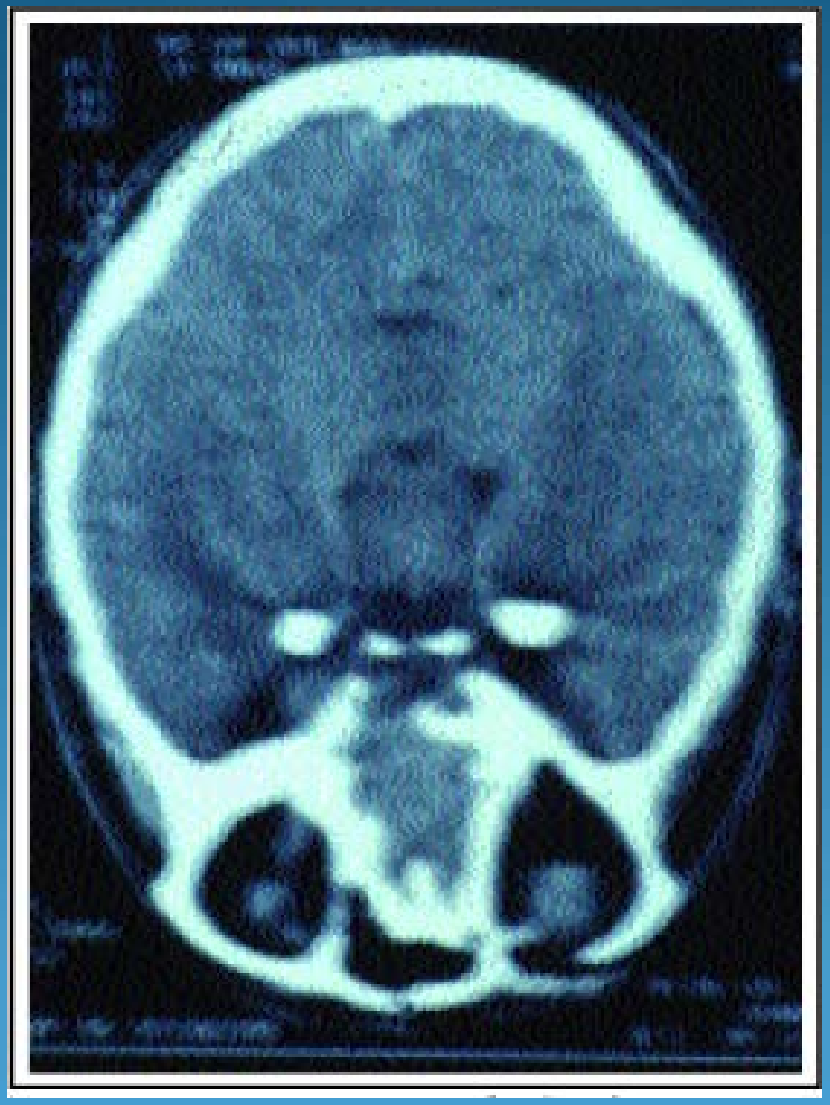
Lipoid Proteinosis: Clinical Features

- **Bilateral, intracranial, sickle-shaped calcifications** in the temporal lobe
  - Seizures, memory loss, rage attacks



Lipoid Proteinosis: Clinical Features

- Patchy or diffuse alopecia
- Hypo- or aplasia of teeth
- Multiple organ systems may be affected but rarely result in significant clinical symptoms

Lipoid Proteinosis: Clinical Course

- Stable or slowly progressive
- Normal life span
- Slightly increased infant mortality rates due to **respiratory complications**
- Adults are at risk for laryngeal obstruction and may require **tracheostomy**

Lipoid Proteinosis: Differential Diagnosis

- Xanthomatosis
- Amyloidosis
- Colloid milium
- Papular mucinosis
- Myxedema

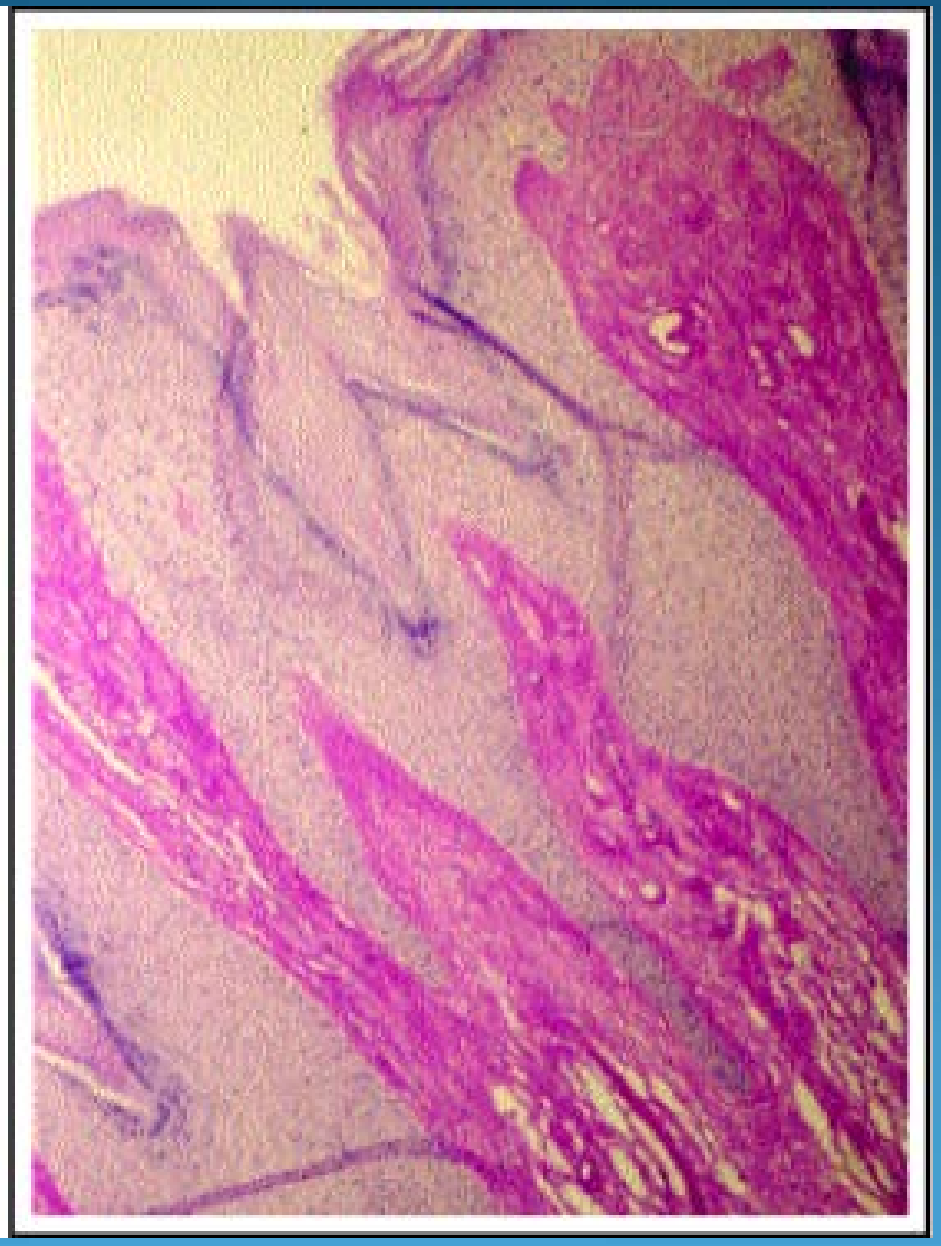
Lipoid Proteinosis: laboratory findings

- There are no consistent lab abnormalities
- ESR, serum lipids, calcium, bone marrow biopsies, and chromosomal studies are either inconsistent or inadequately studied

Lipoid Proteinosis: Histology

Figura 2: PAS 100X - Derme superficial com deposição de substância PAS-positiva e diástase-resistente

Figure 2: PAS 100X - superficial dermis with deposition of a PAS-positive and diastase-resistant substance



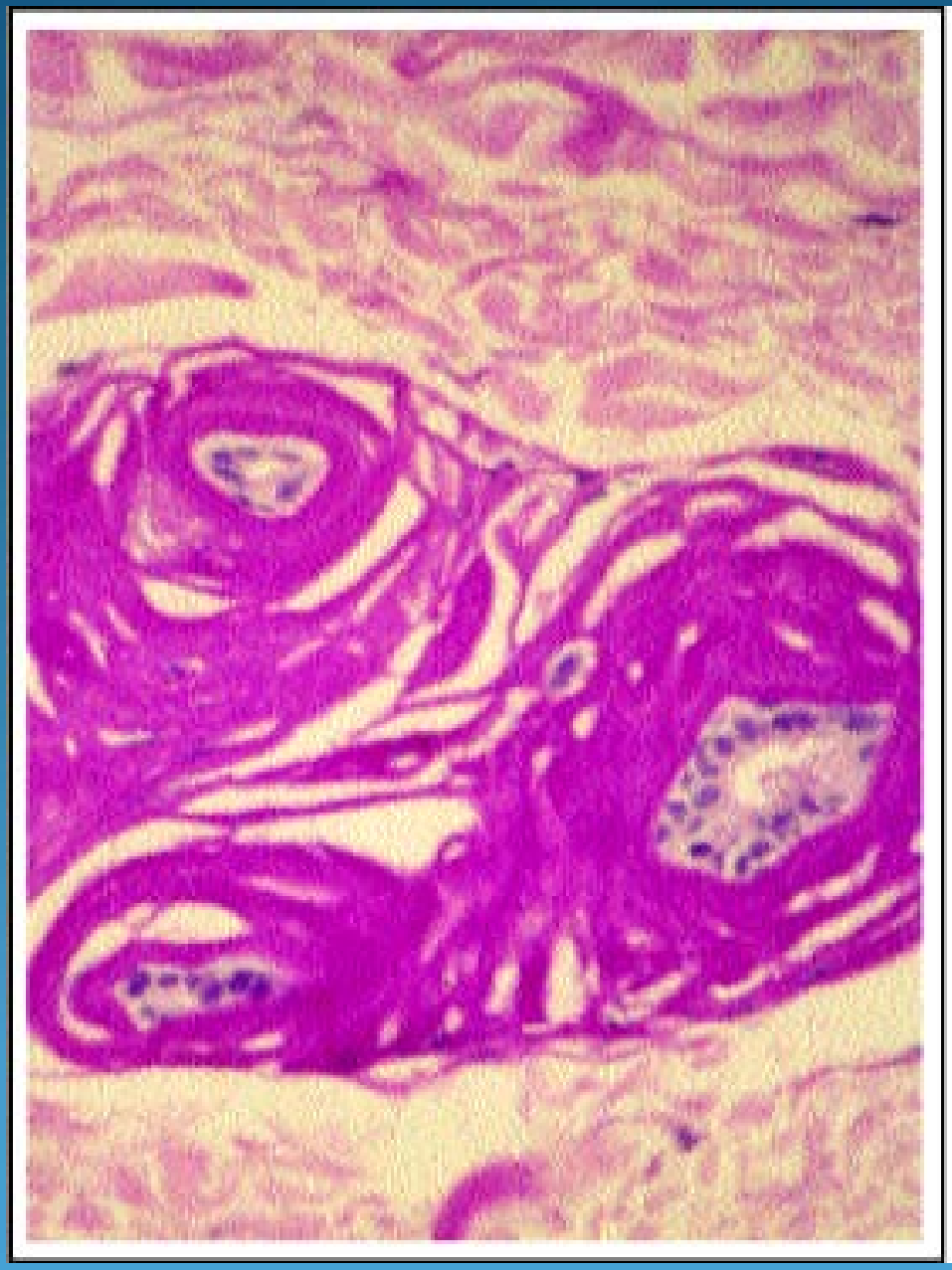


Figura 3:
PAS 400X -
Depósito
de material
ao redor
de glândula
écrina
Figure 3:
PAS 400X -
material
deposited
around
the eccrine
gland

Lipoid Proteinosis: Histology

- Early: pale pink hyaline-like thickening of the papillary dermal capillaries
- Later: hyperkeratosis, papillomatosis, and a thick dermis with diffuse bundles of pink hyaline oriented perpendicularly to the DEJ
- Hyaline mantles surround or replace eccrine glands

Lipoid Proteinosis: Staining Pattern

- The hyaline is PAS positive, diastase resistant:
  - indicating neutral mucopolysaccharides
- Alcian Blue and Hyaluronidase:
  - reveal hyaluronic acid

Lipoid Proteinosis: Treatment

- No known cure
- All therapy is based on anecdotal reports
  - Oral DMSO
  - Dermabrasion
  - Surgical resection of vocal cord plaques
- Supportive treatment (anticonvulsants)

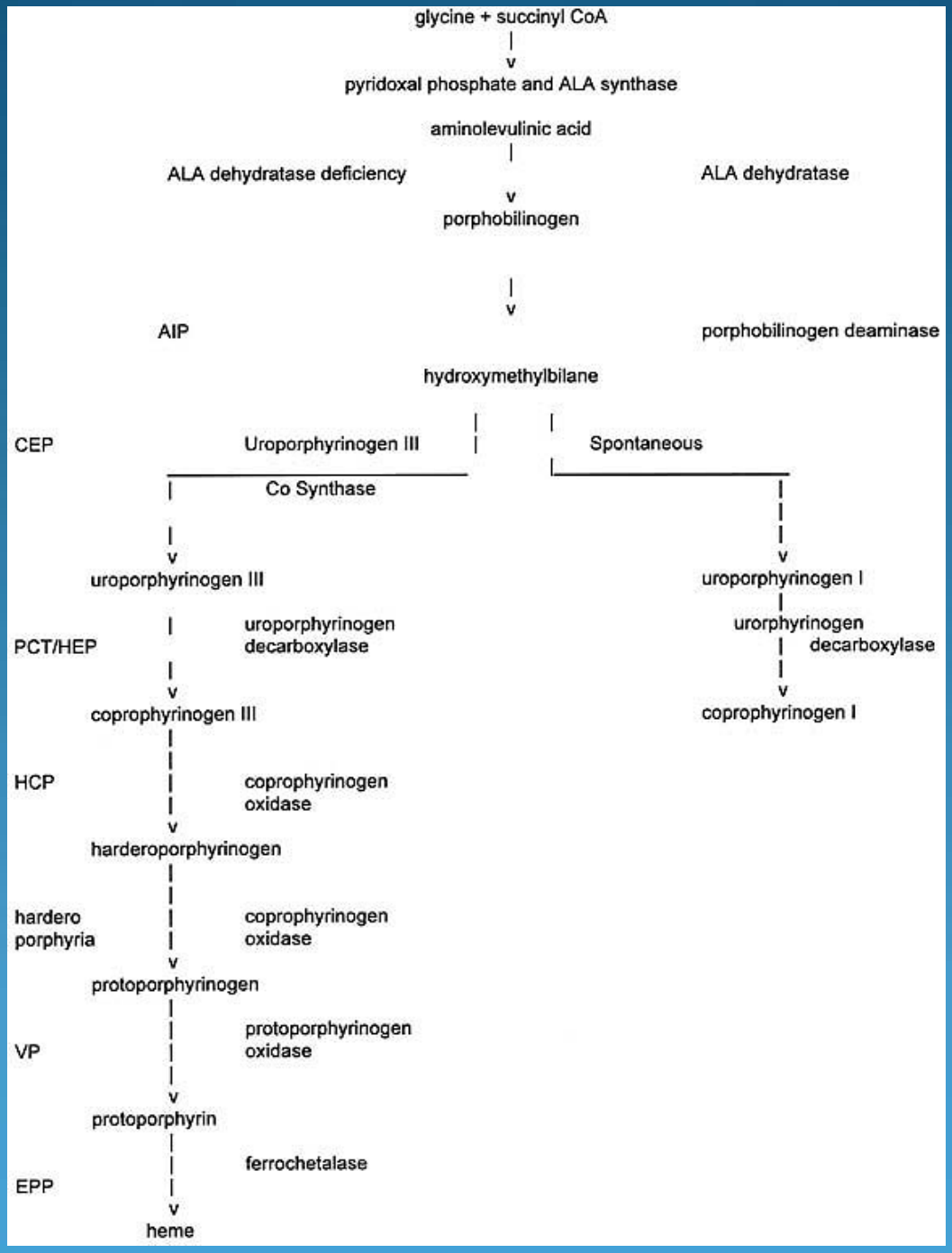
Porphyria

The Porphyrias

- A group of inherited or acquired disorders resulting from excessive production of porphyrins or their precursors during heme synthesis
- The synthesis of heme occurs primarily in the *liver and bone marrow*

Porphyria Classification

- Erythropoietic
  - Congenital Erythropoietic Porphyria (CEP)
- Hepatic
  - Porphyria Cutanea Tarda (PCT)
  - Acute Intermittent Porphyria (AIP)
  - Variegate Porphyria (VP)
  - Hereditary Coproporphyria (HCP)
- Erythrohepatic
  - Hepatoerythropoietic Porphyria (HEP)
  - Erythropoietic protoporphyria (EPP)


glycine + succinyl CoA
pyridoxal phosphate and ALA synthase
aminolevulinic acid
ALA dehydratase deficiency
ALA dehydratase
porphobilinogen
AIP
porphobilinogen deaminase
hydroxymethylbilane
CEP
Uroporphyrinogen III
Co Synthase
Spontaneous
uroporphyrinogen III
uroporphyrinogen I
PCT/HEP
uroporphyrinogen decarboxylase
urorphyrinogen decarboxylase
coprophyrinogen III
coprophyrinogen I
HCP
coprophyrinogen oxidase
harderoporphyrinogen
hardero porphyria
coprophyrinogen oxidase
protoporphyrinogen
VP
protoporphyrinogen oxidase
protoporphyrin
EPP
ferrochetalase
heme

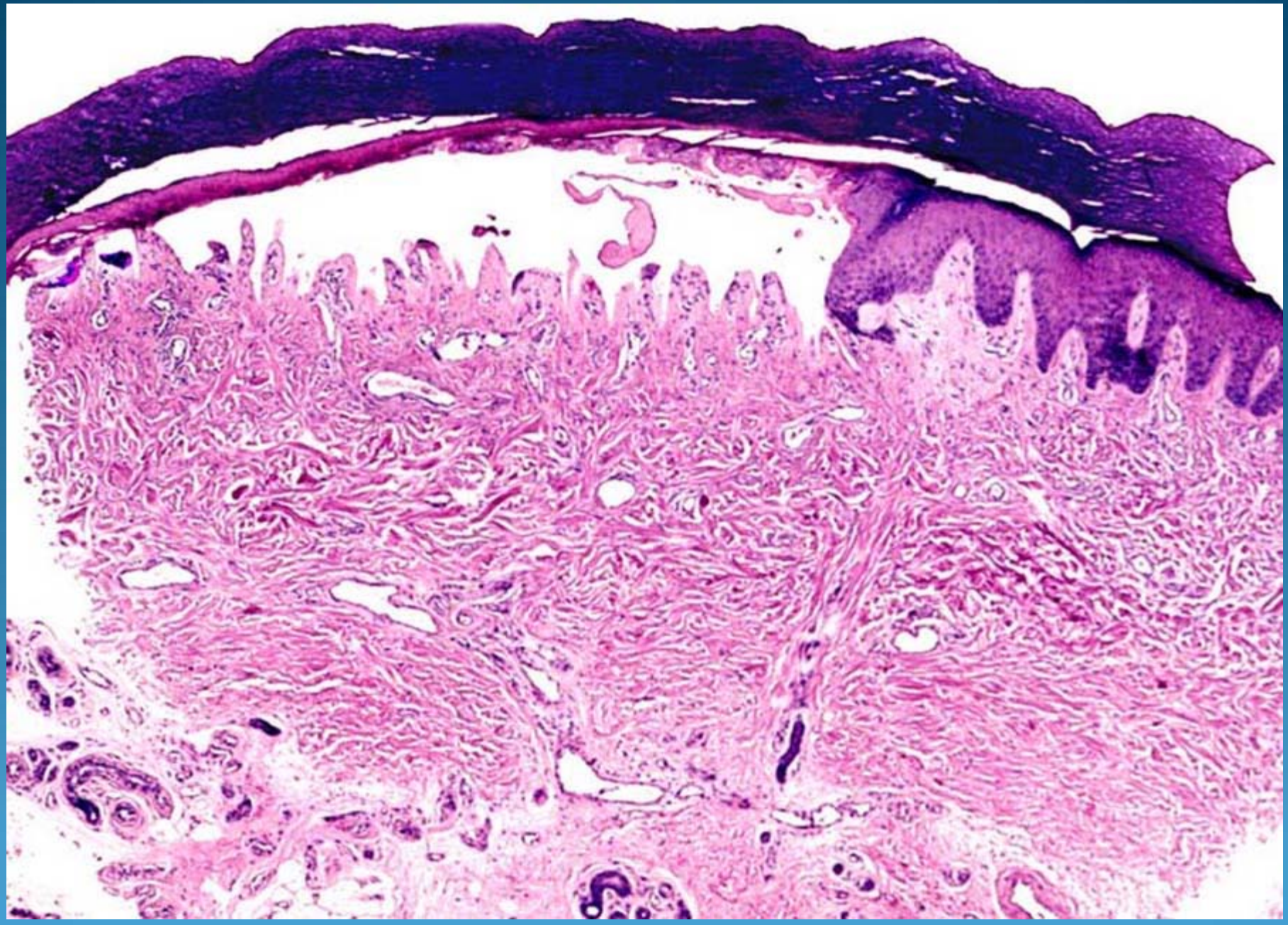
Pathogenesis

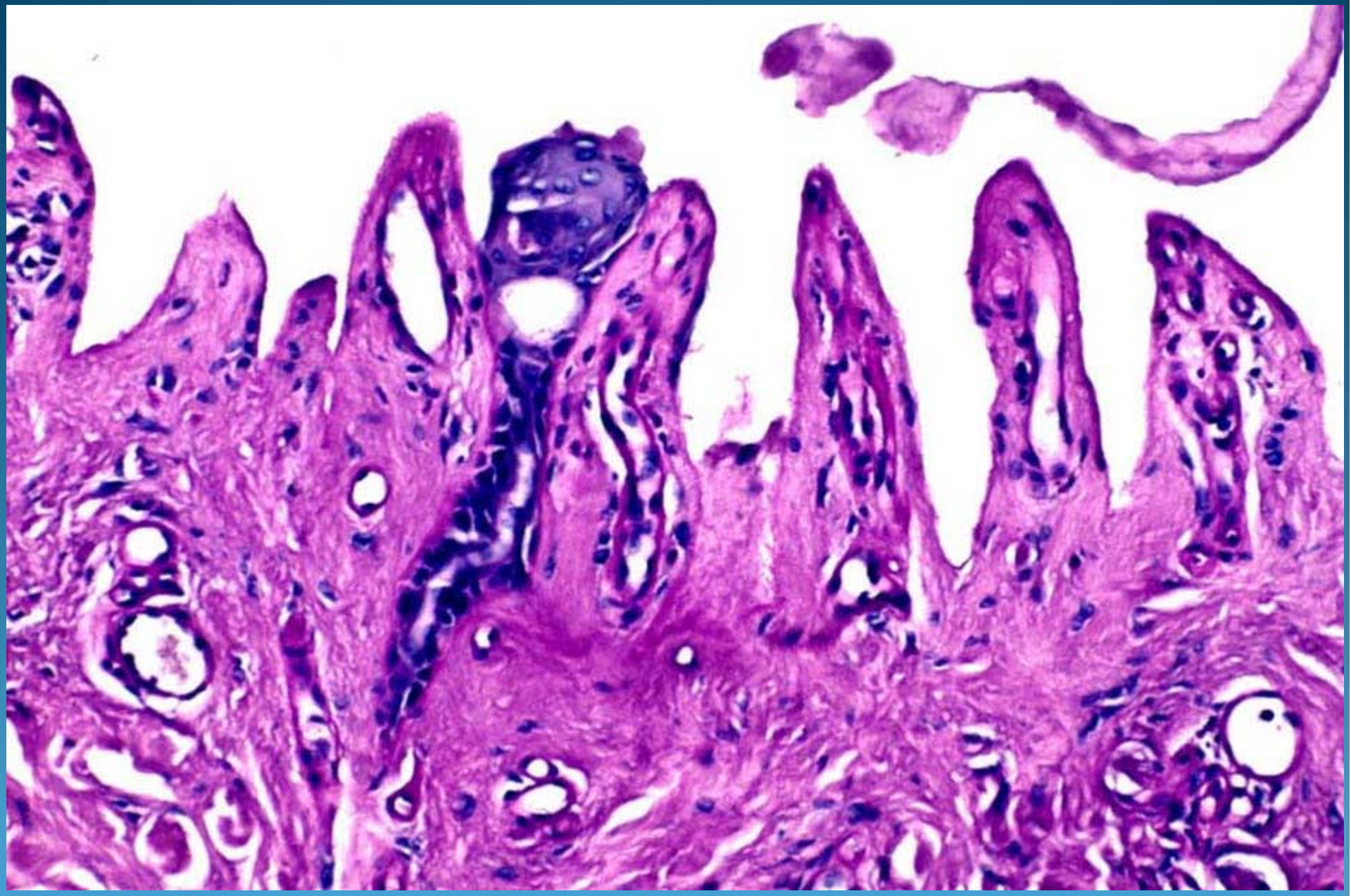
- Enzyme defects in the heme synthetic pathway result in elevated intermediates called *porphyrinogens*
- Porphyrinogens are oxidized to photosensitizing *porphyrins*
- Porphyrins absorb radiation in the **Soret Band (400-410 nm)**

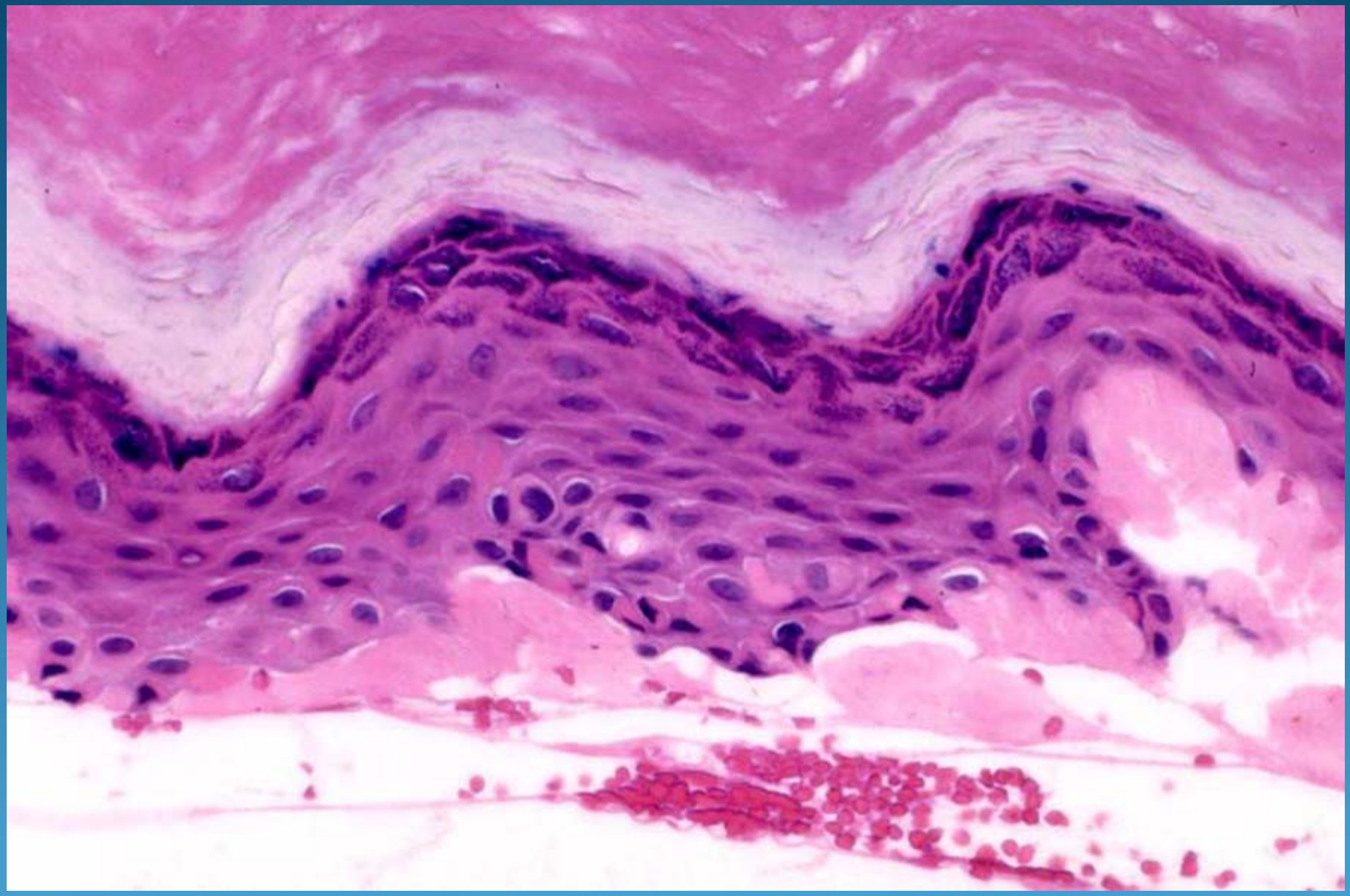
Pathogenesis

1. Porphyrins become excited/unstable
2. Transfer energy to oxygen
3. Oxygen free radicals are created
4. Free radicals transfer energy to cells and DNA
5. Tissue damage: skin, liver, and RBC

Porphyria Histology







Congenital Erythropoietic Porphyria:

Gunther's Disease

Congenital Erythropoietic Porphyria

- Mom comes into office with pink diapers
- Baby cries and screams when outside
- Baby has red teeth

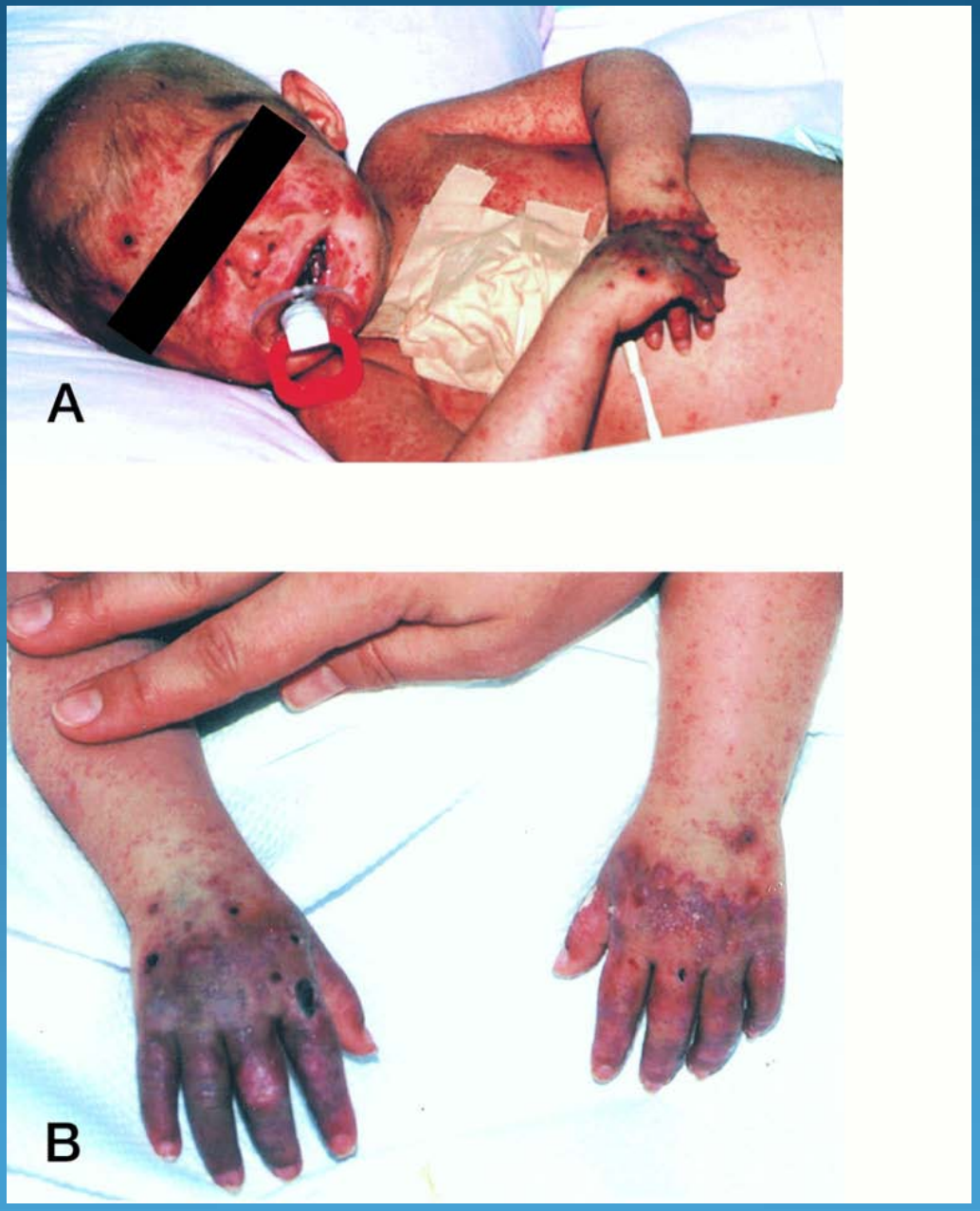
Congenital Erythropoietic Porphyria

- Autosomal Recessive
- **Uroporphyrinogen III Cosynthetase**
- Very rare: < 200 case reports

Congenital Erythropoietic Porphyria

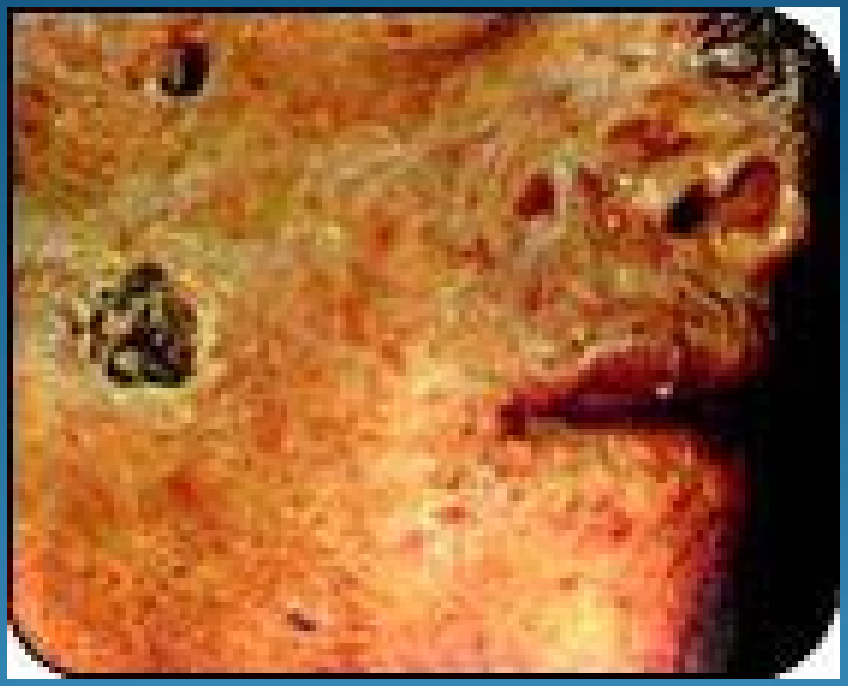
- Presents in early childhood (birth-5 years)

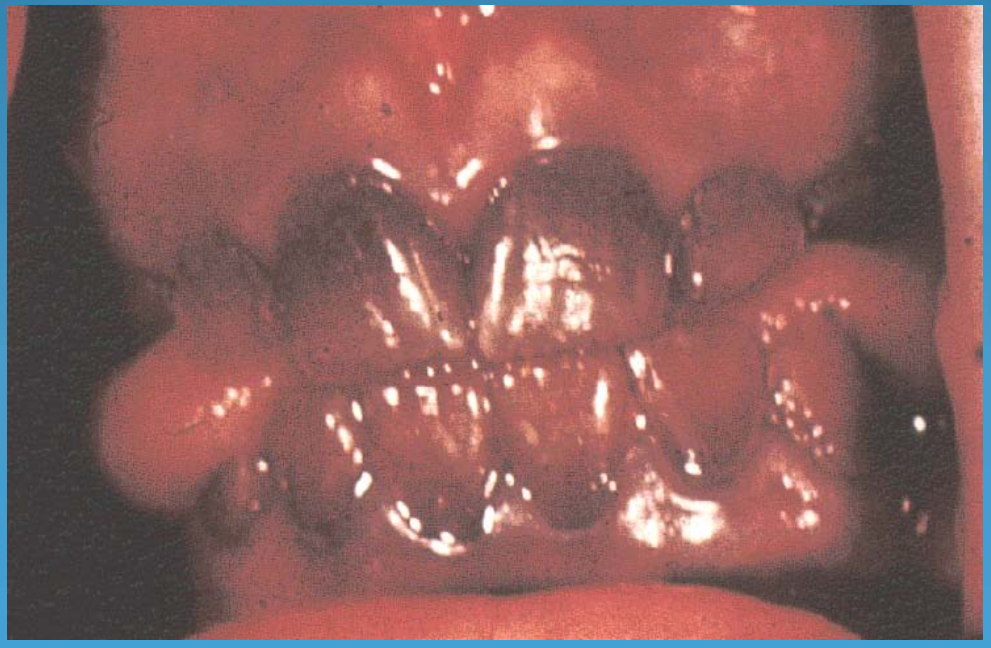
- **Early:**
  - Immediate photosensitivity with burning, edema, erythema and blistering after UV exposure
- **Late:**
  - Mutilating, deforming scars of nose, ears, fingers
  - Scarring alopecia, dyspigmentation, sclerodermoid changes

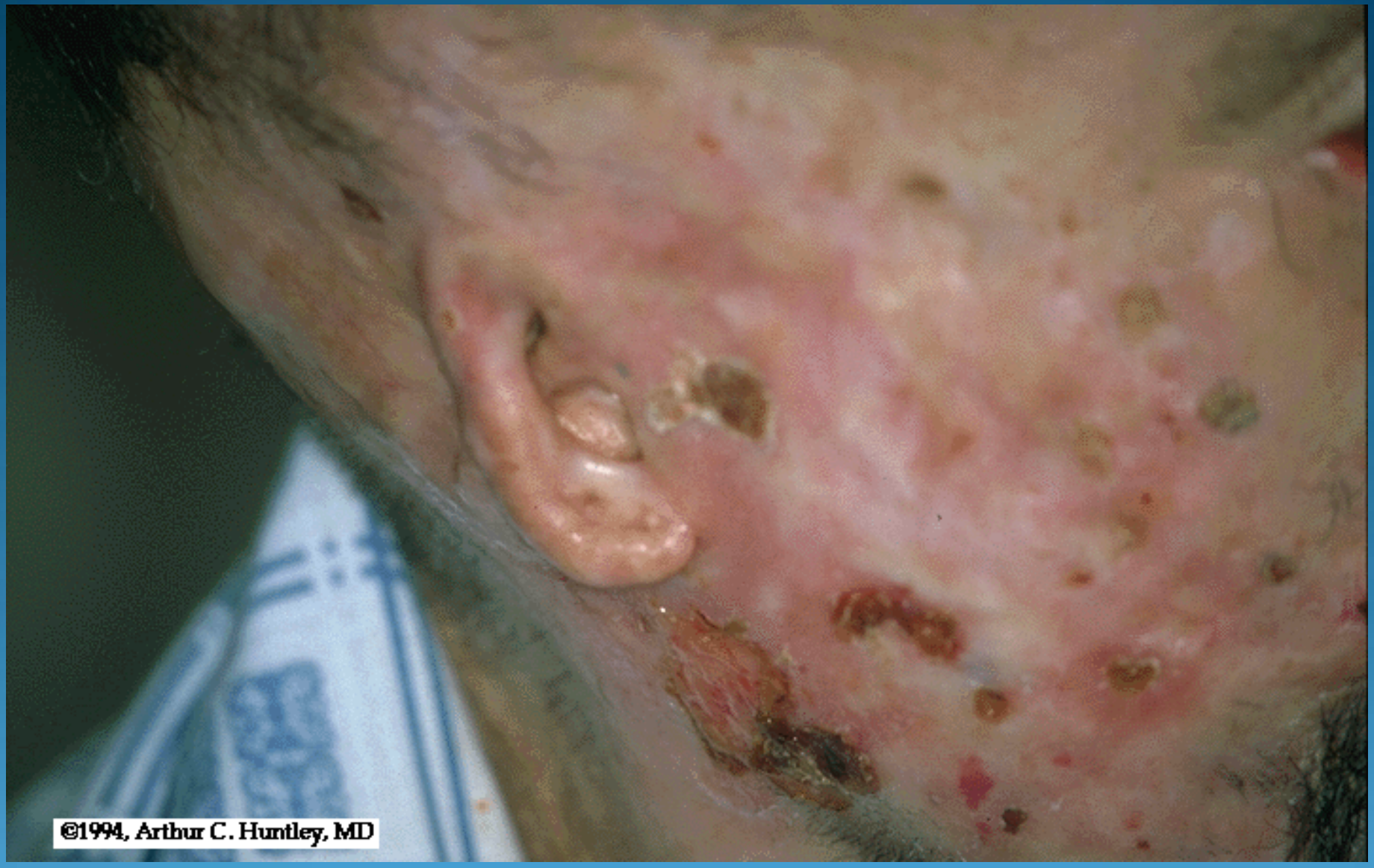

A
B

Congenital Erythropoietic Porphyria

- Hypertrichosis w/ lanugo hair over face/neck/extr.
- Photophobia, ectropion, corneal scars, blindness
- **Erythrodontia**
- Hemolytic anemia
- Splenomegaly
- “wherewolves”



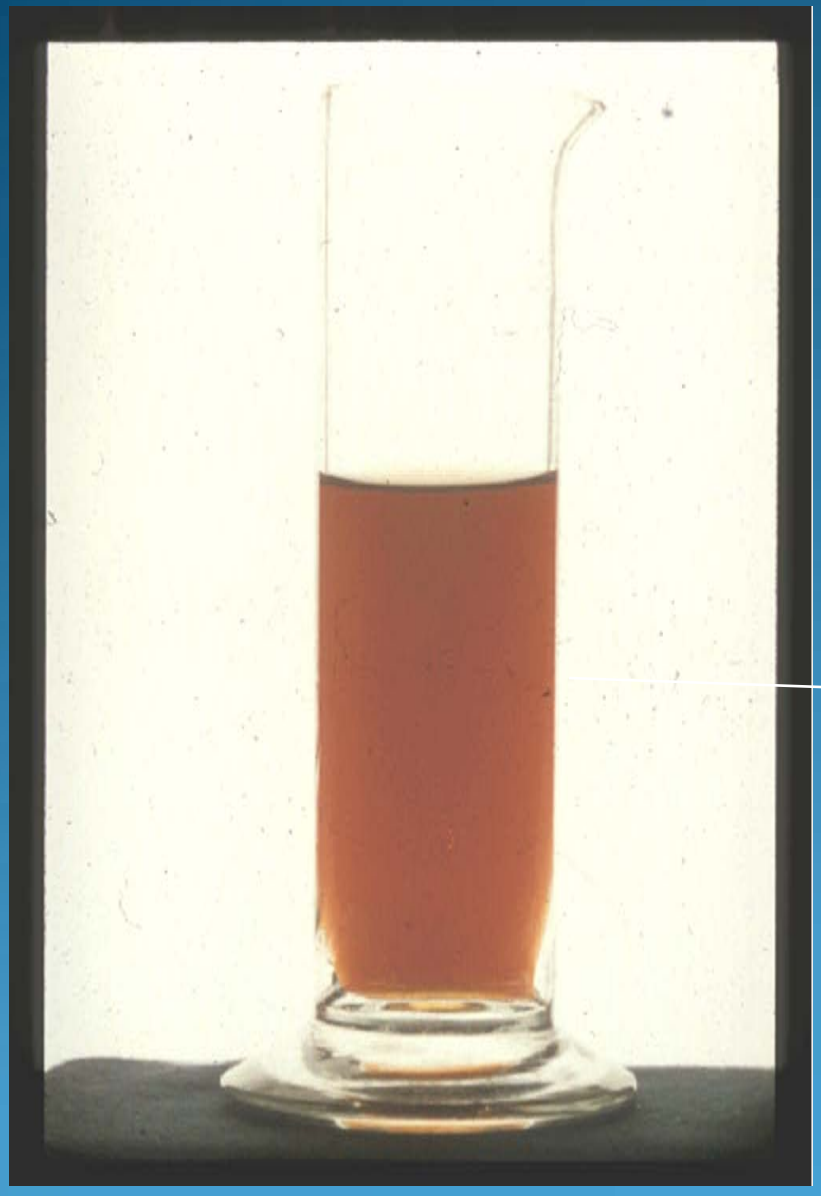




Congenital Erythropoietic Porphyria

Congenital Erythropoietic Porphyria

- **Uroporphyrinogen III Cosynthetase**
- Uroporphyrin and coproporphyrin accumulate in urine, feces, plasma, RBC, bone
- Uroporphyrin I in erythrocytes leads to **hemolysis**
- Hemolysis turns the urine pink (**stains diapers**)

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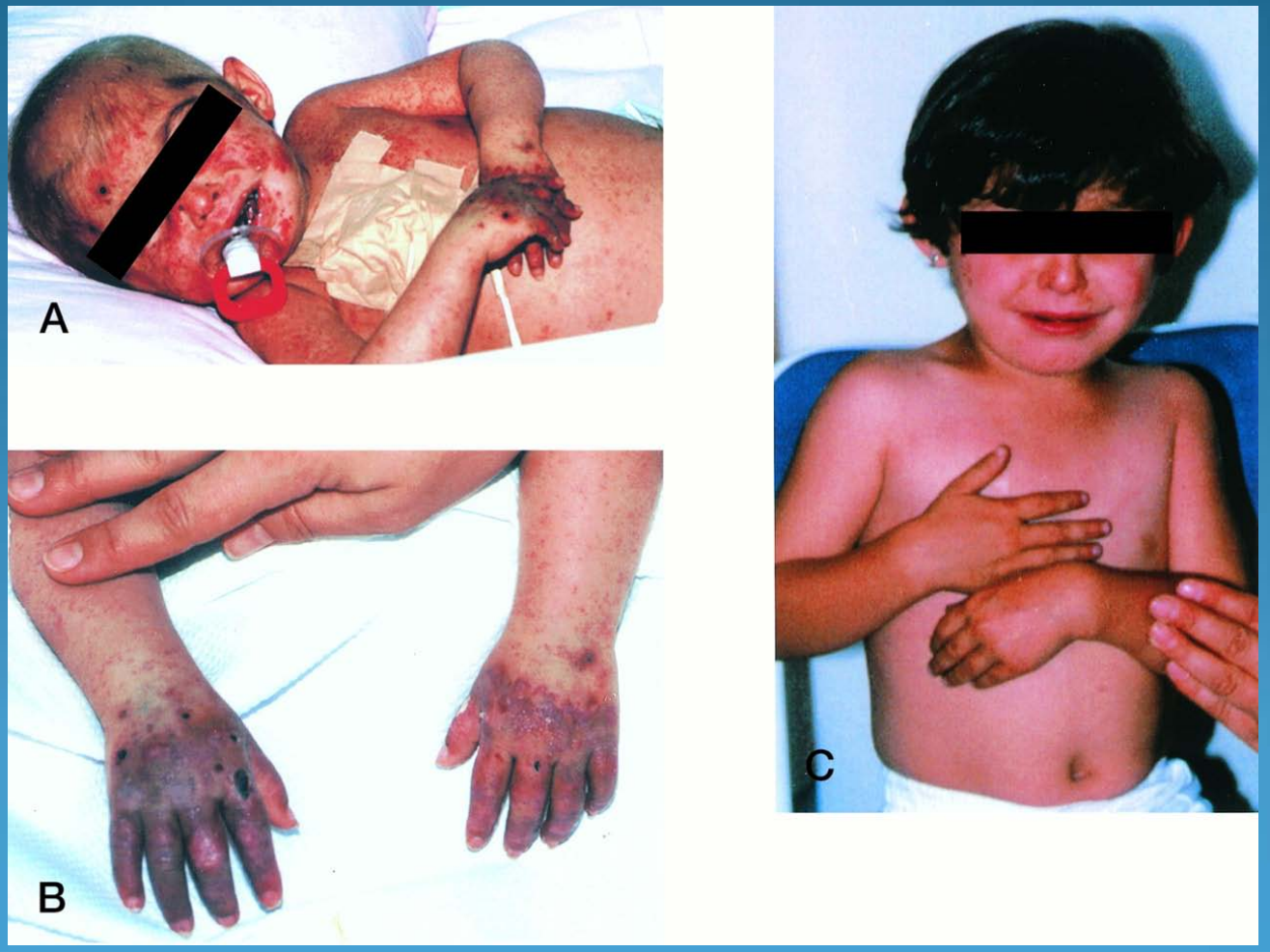
CEP: Labs

- CBC: Hemolytic anemia (schistocytes)
- Urine, RBC, Plasma: Uroporphyrin
- Stool: Coproporphyrin

CEP: Management

- Photoprotection (even bili lights!)
- Transfusions
- Beta-carotene
- Splenectomy
- Hydroxyurea: suppress BM heme synthesis
- Bone Marrow Transplant
- If detected early…normal life span

CEP successfully treated with BMT



Hepatic Porphyrias

- Acute Intermittent Porphyria
- Variegate Porphyria
- Hereditary Coproporphyria
- Porphyria Cutanea Tarda

} Acute Attack Porphyrias

Porphyria Cutanea Tarda

- Most common porphyria
  - Autosomal Dominant (Familial)
  - Acquired
- **Uroporphyrinogen decarboxylase**
  - Familial: deficient in RBC and hepatocytes
  - Sporadic: deficent in hepatocytes only

Porphyria Cutanea Tarda

- All acquired forms are precipitated by an inducer
- Inducers:
  - Alcohol, estrogen, hepatic tumors
  - Iron, Hemodialysis
  - HCV, HBV, HIV
- Inducers may unmask familial cases
- **C282Y** gene: predisposes to HC and PCT

Porphyria Cutanea Tarda

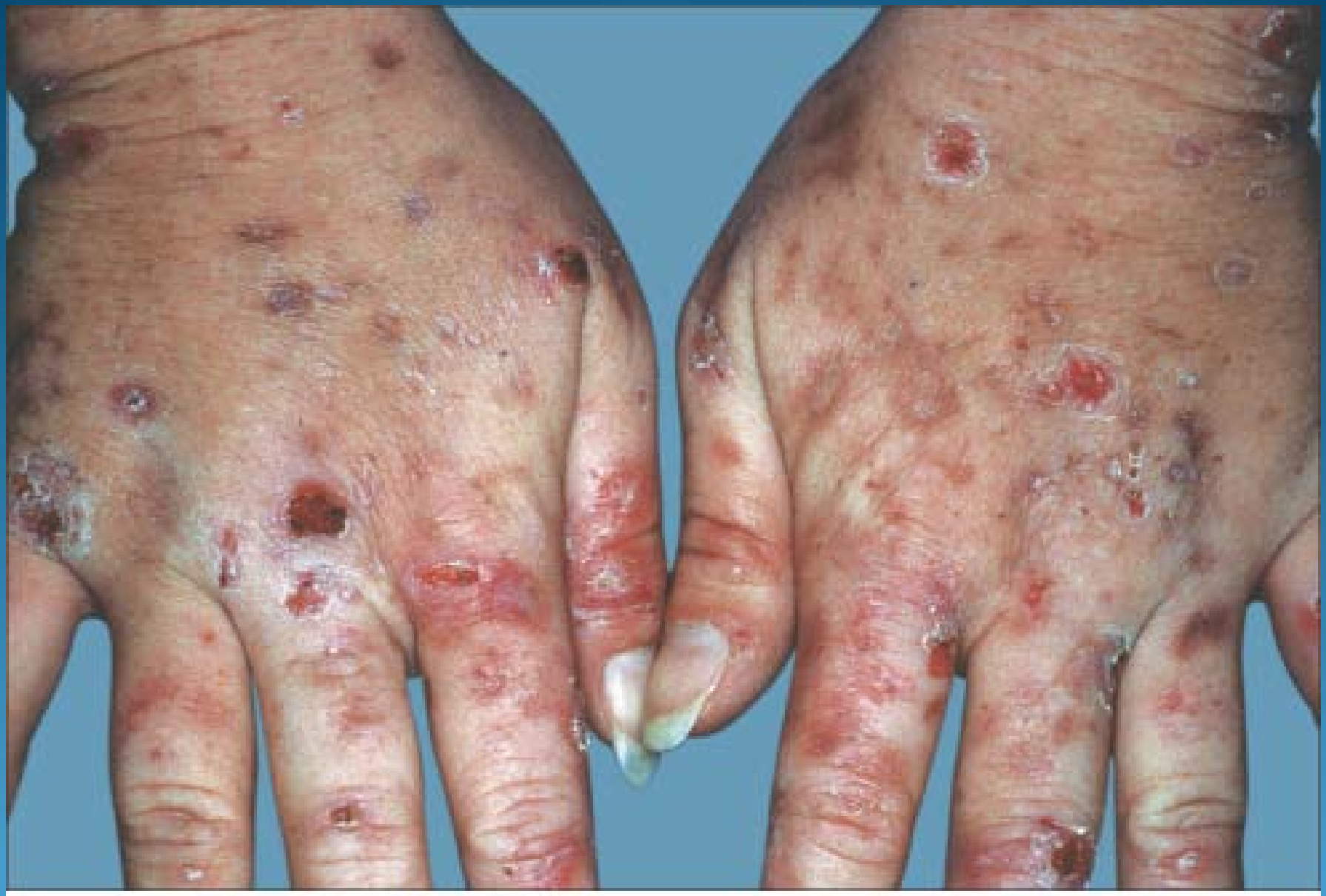
- **Homozygous inherited form**:
  - Hepatoerythropoietic Porphyria (HEP)
  - erythrocyte *and* hepatic enzymes are deficient

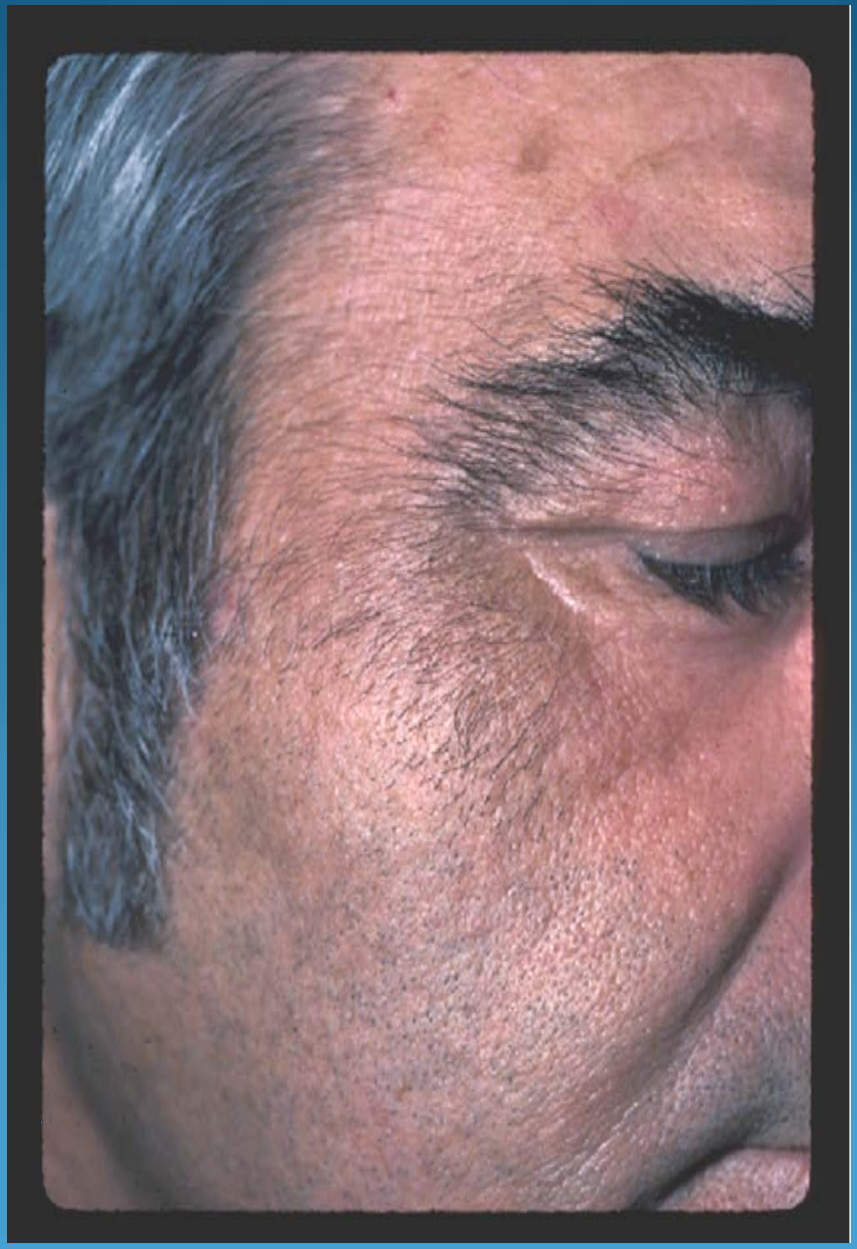
Porphyria Cutanea Tarda

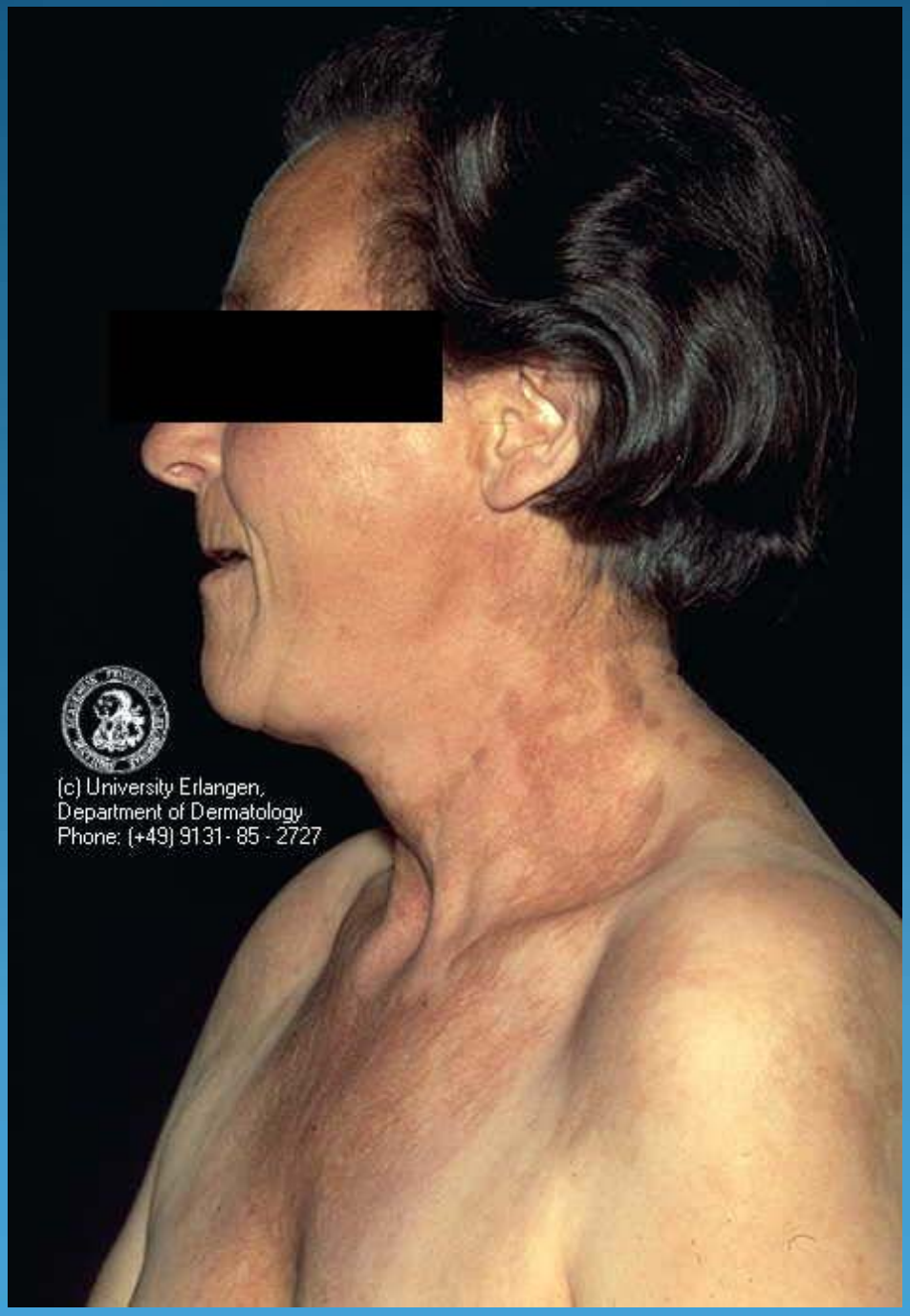
- Presents in 3rd – 4th decade
- Familial cases may present earlier
- Uroporphyrins in skin lead to photosensitization after absorbing light energy in the **Soret Band (400-410 nm)**

PCT: Clinical Features

- Delayed photosensitivity with bullae, erosions, fragility
- Facial hypertrichosis, hyperpigmentation
- Scars, milia, sclerodermoid plaques
- Subcutaneous calcification
- Alopecia
- Liver hemosiderosis
- Diabetes mellitus



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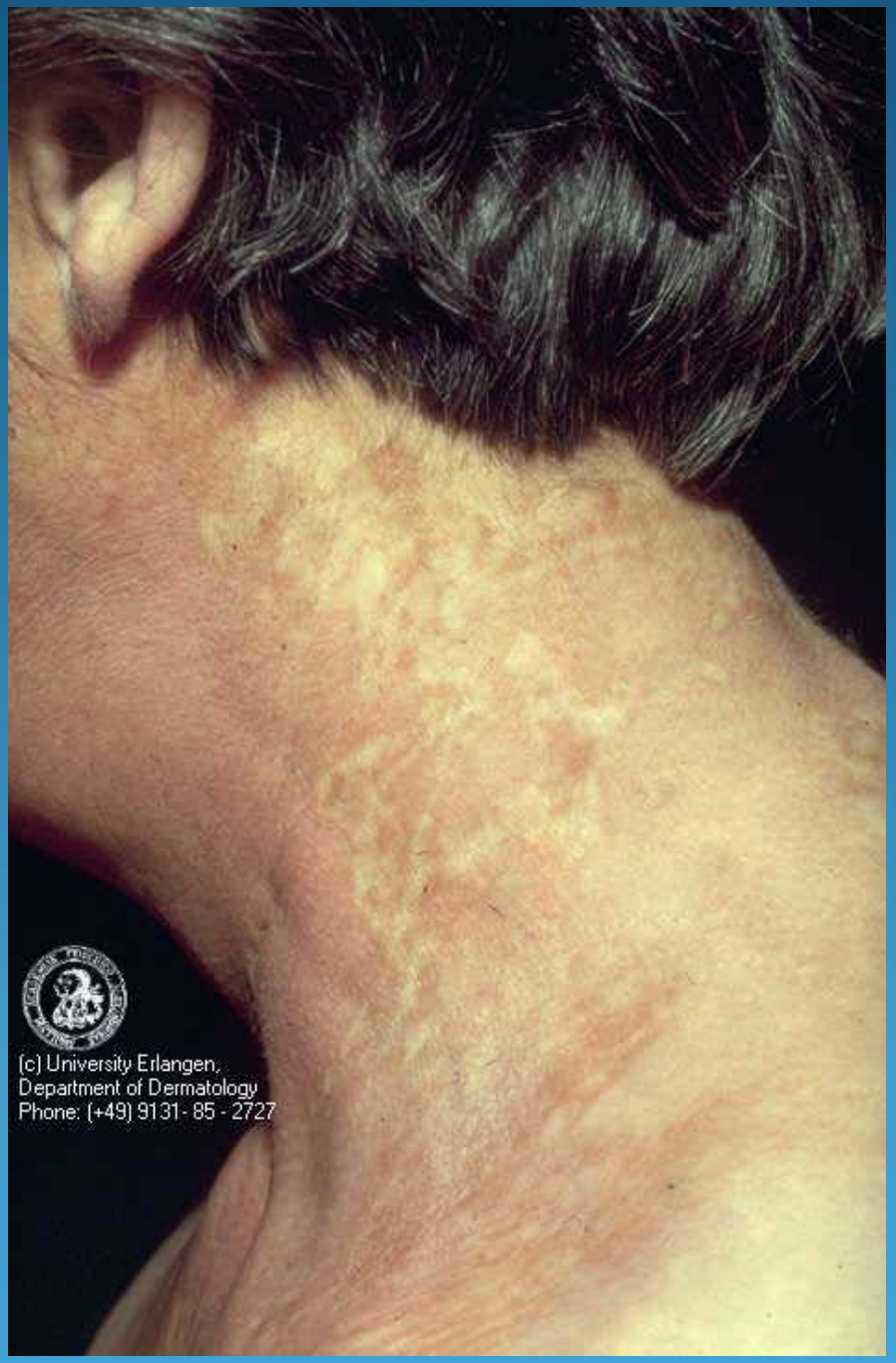
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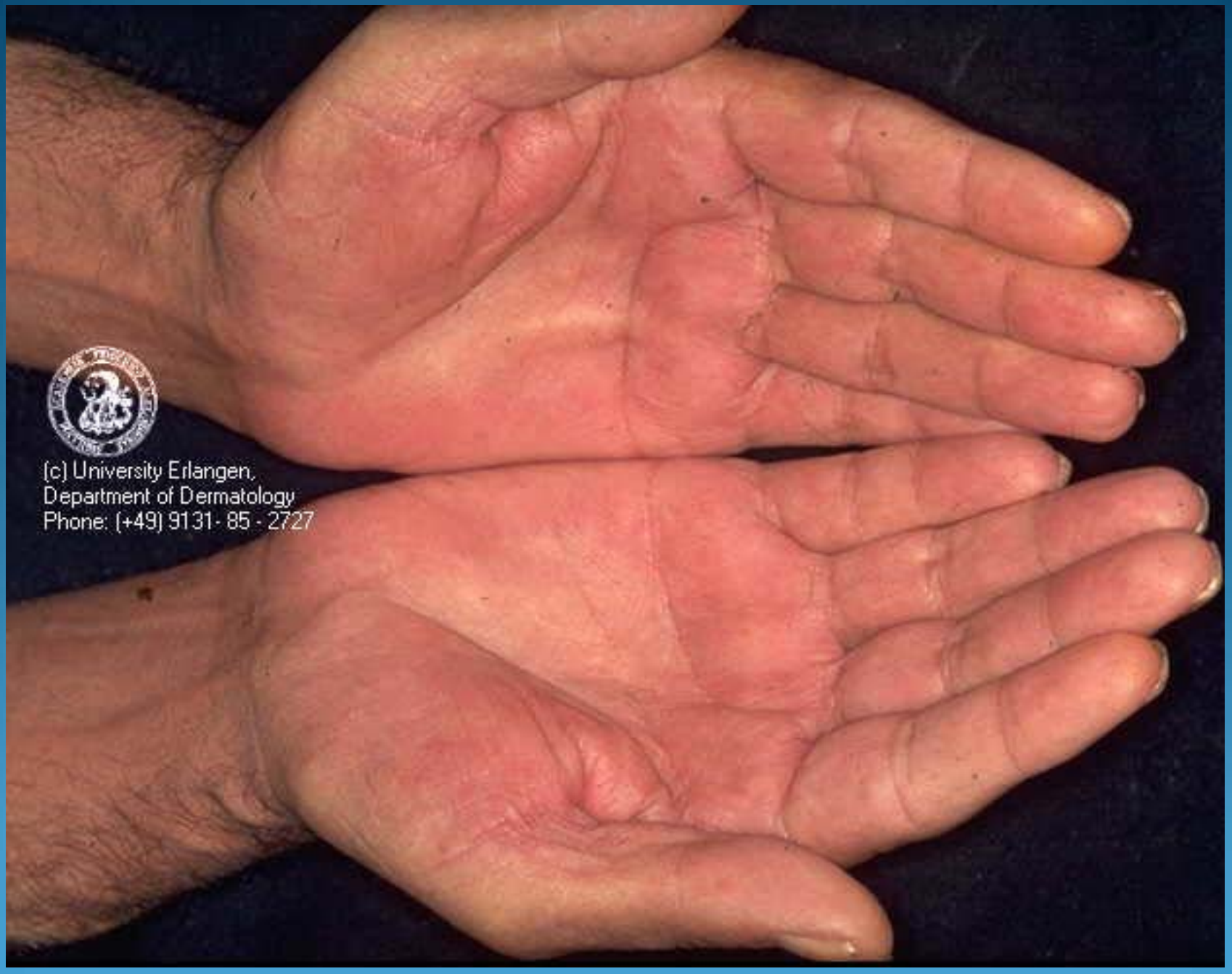
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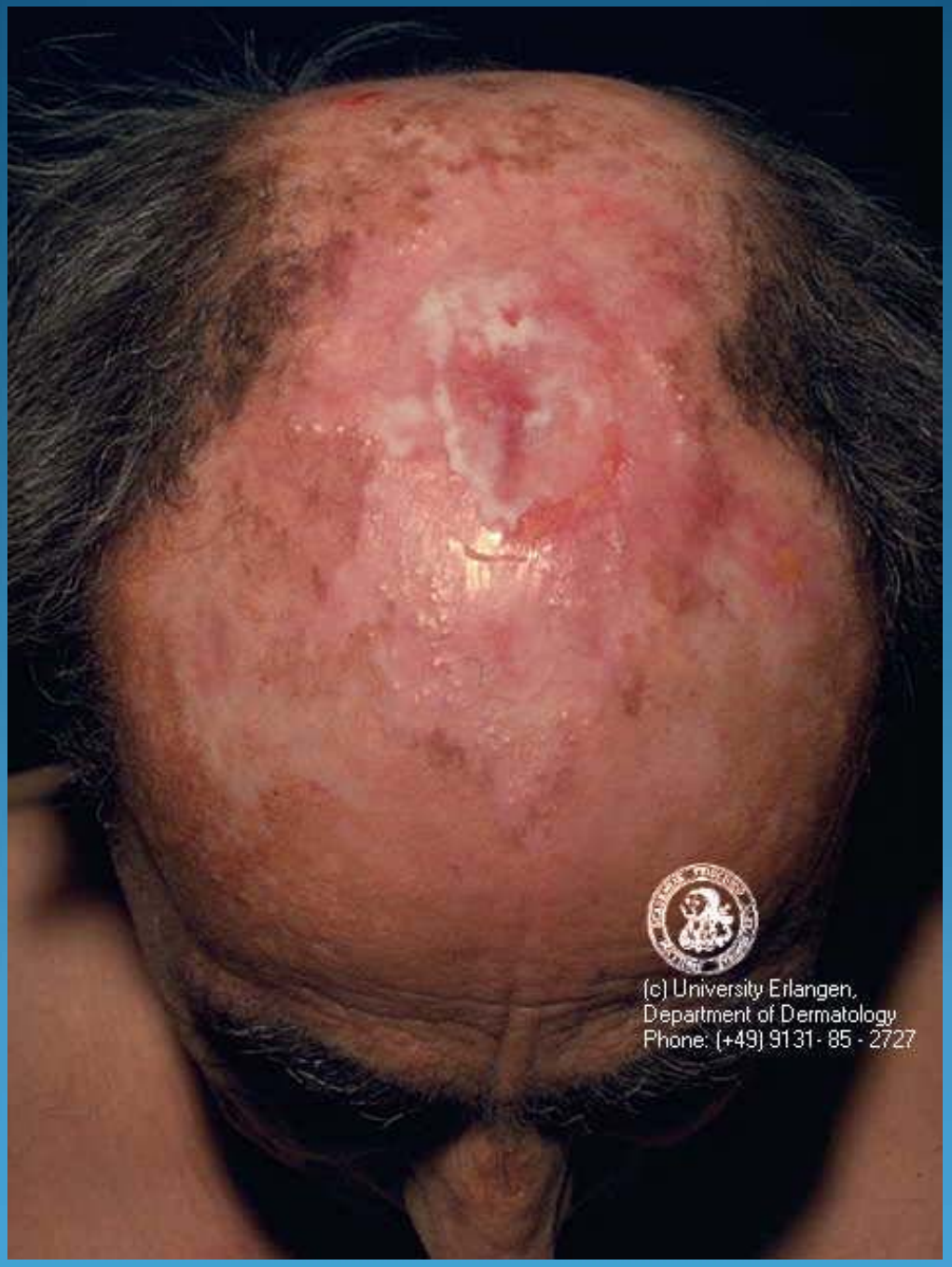
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PCT Labs

- Urine: Uro > Copro
- Feces: Isocopro
- RBC: Normal
- Urine porphyrins fluoresce w/ Wood's lamp
- DDx: Variegate Porphyria
  - Compare urine Uro:Copro ratio
  - PCT= 8:1; VP=1:1 or Copro > Uro

PCT: Management

- Identify the etiology
- Photoprotection
- Phlebotomy: 500ml BIW to Hbg 11/ Hct 35
  - Clinical response lags behind biochemical response
- Plaquenil 100-200mg BIW
  - Rx until urine uroporphyrin < 100micrograms/24hr
- Chloroquine-solubilizes porphyrins for excretion
- Lifestyle modification

Pseudoporphyria

- Mimics PCT (clinical and histo), except:
  - No hypertrichosis or hyperpigmentation
  - No sclerodermoid changes
  - No porphyrin abnormality
- Triggers:
  - Hemodialysis
  - Drugs (naprosyn, furosemide, HCTZ, TCN, nalidixic acid, dapsone, pyridoxine)
  - UVA (tanning beds)

Pseudoporphyria Treatment

- Discontinue offending drugs
- Photoprotection
- Hemodialysis- associated cases:
  - difficult to treat
  - monitor over time for true PCT

Acute Attack Porphyrias

VP; AIP; HCP

Variegate Porphyria

- Autosomal Dominant
- South Africans of Dutch ancestry
- Protoporphyrinogen Oxidase
- **Skin identical to PCT**
- Onset of symptoms after puberty
- Neurovisceral attacks as adults

Acute Neurovisceral Attacks

- Induced by exposure to environmental stressors
  - Drugs (barbiturates, estrogen, griseo, sulfa)
  - Starvation / hypoglycemia
  - Hormonal fluctuations (menses, pregnancy)
  - Infections / fever
- Mechanism:
  - Deranged heme metabolism leads to neural dysfunction
  - Heme precursors ALA, PBG toxic to neural tissues

Acute Neurovisceral Attacks

- GI:
  - Colicky abdominal pain, n/v, constipation
- CNS:
  - peripheral neuropathy w/ pain/weakness/paralysis
  - seizures, psychosis, coma
- CVS:
  - tachycardia, hypertension
- Death

Variegate Porphyria: Labs

- Plasma porphyrin fluorescence spectrum: **627 nm** is diagnostic:
- Increased urinary ALA, PBG during attacks
- Urine: Copro ≥ Uro (**opposite of PCT**)
- Feces: Proto > Copro

Management of Attacks

- Glucose loading
- Hematin infusions (neg. feedback to ALA)
- Analgesia
- Supportive Care
- Avoid triggers
- Prognosis: neuro damage/death from attacks

Acute Intermittent Porphyria

- Autosomal Dominant
- **Porphobilinogen deaminase**
- No skin findings
- Presents after puberty with attacks
- *Enzyme defect alone is insufficient for phenotypic expression: triggers are necessary*

Acute Intermittent Porphyria

- Diagnosis is a challenge
  - Multiple doctors, multiple exploratory laps
- Elevated urinary ALA, PBG during and between attacks
- RBC enzyme assay can confirm (false negs)
- Hyponatremia 2nd to ADH secretion
- **Urine is port-wine colored**

AIP: Port-wine urine

Acute Intermittent Porphyria

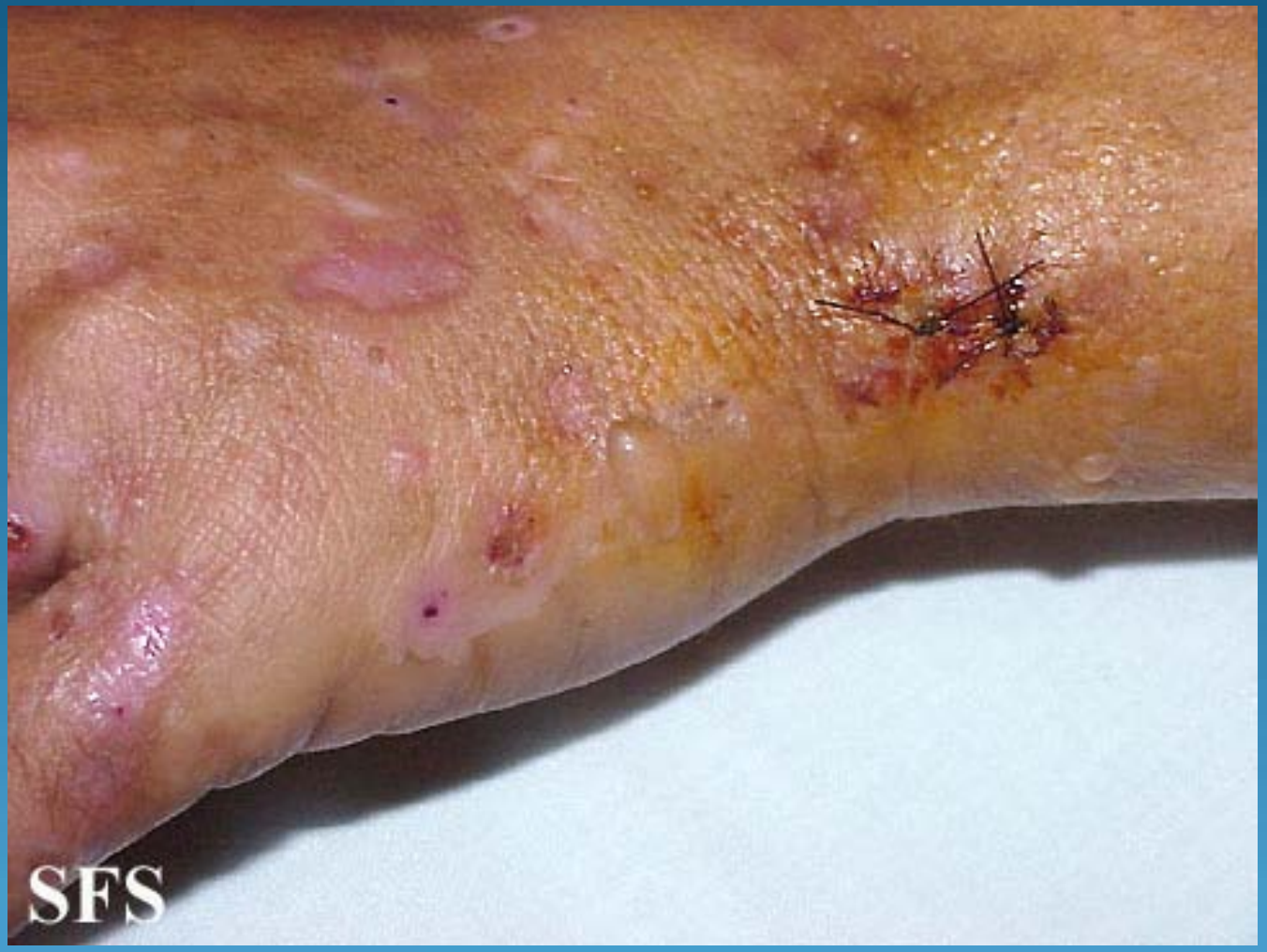
- Prognosis:
  - Permanent neurologic damage can occur
  - Excellent prognosis with early diagnosis, avoidance of triggers

Hereditary Coproporphyria

- Autosomal Dominant
- **Coproporphyrinogen oxidase**
- Presents in 3rd-4th decade
- Acute attacks mimic AIP and VP
  - same triggers
- Skin (30%): similar to PCT, VP
- Neurologic sx more common than skin

Hereditary Coproporphyria

- Elevated urinary ALA, PBG during attacks
- Stool, urine: Copro
  - vs. AIP: "*Ain't in Poop*"



PCT-like skin plus acute attacks: think HCP, VP

Summary: Acute Attack Porphyrias

- AIP: no skin findings
- VP and HCP: skin mimics PCT
  - Differentiate with porphyrin profiles
  - Stool:
    - VP= Proto
    - HCP= Copro
  - Urine:
    - AIP=ALA, PBG during and between attacks
    - VP, HCP=Copro, ALA, PBG during attacks only
    - Pink-red: VP, HCP during attacks
    - Port-wine: AIP during and between attacks

Erythrohepatic Porphyrias

- Hepatoerythropoietic Porphyria
- Erythropoietic Protoporphyria

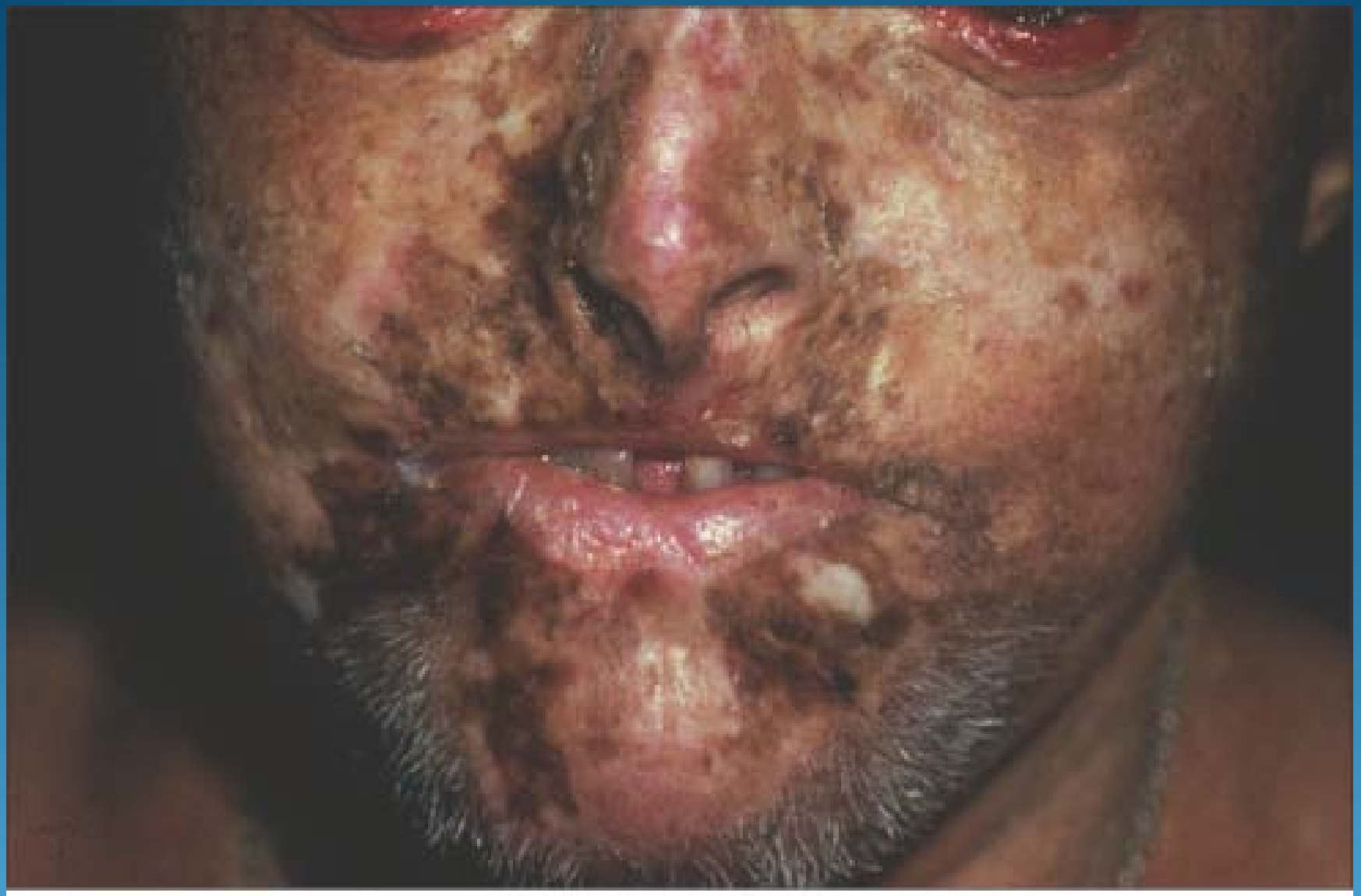
Hepatoerythropoietic Porphyria

- **Uroporphyrinogen Decarboxylase**
  - Autosomal Recessive
  - Homozygous defect (2 mutant copies)
  - PCT: 1 mutant copy

- **Presents in infancy (by age 2)**
  - Similar to mild Gunther's (CEP)
  - Severe photosensitivity, bullae and erosions
  - Dark urine at birth
  - Photosensitivity diminishes with age

Hepatoerythropoietic Porphyria

- **Late clinical findings:**
  - Sclerodermoid plaques and hypertrichosis
  - Mutilating scars in acral areas
  - Acral osteolysis (short digits)
  - Scarring alopecia, ectropion
  - **Erythrodontia**
- **Hemolytic Anemia**
- **Splenomegaly**



HEP: Labs

- **Urine**: Uroporphyrin
- **Feces**: Coprophyrin
- **RBC**: Protoporphyrin
  - vs. CEP: Uro
- Hemolytic Anemia

HEP: Management

- Avoidance, avoidance, avoidance
- **DO NOT** phlebotomize (anemic!)

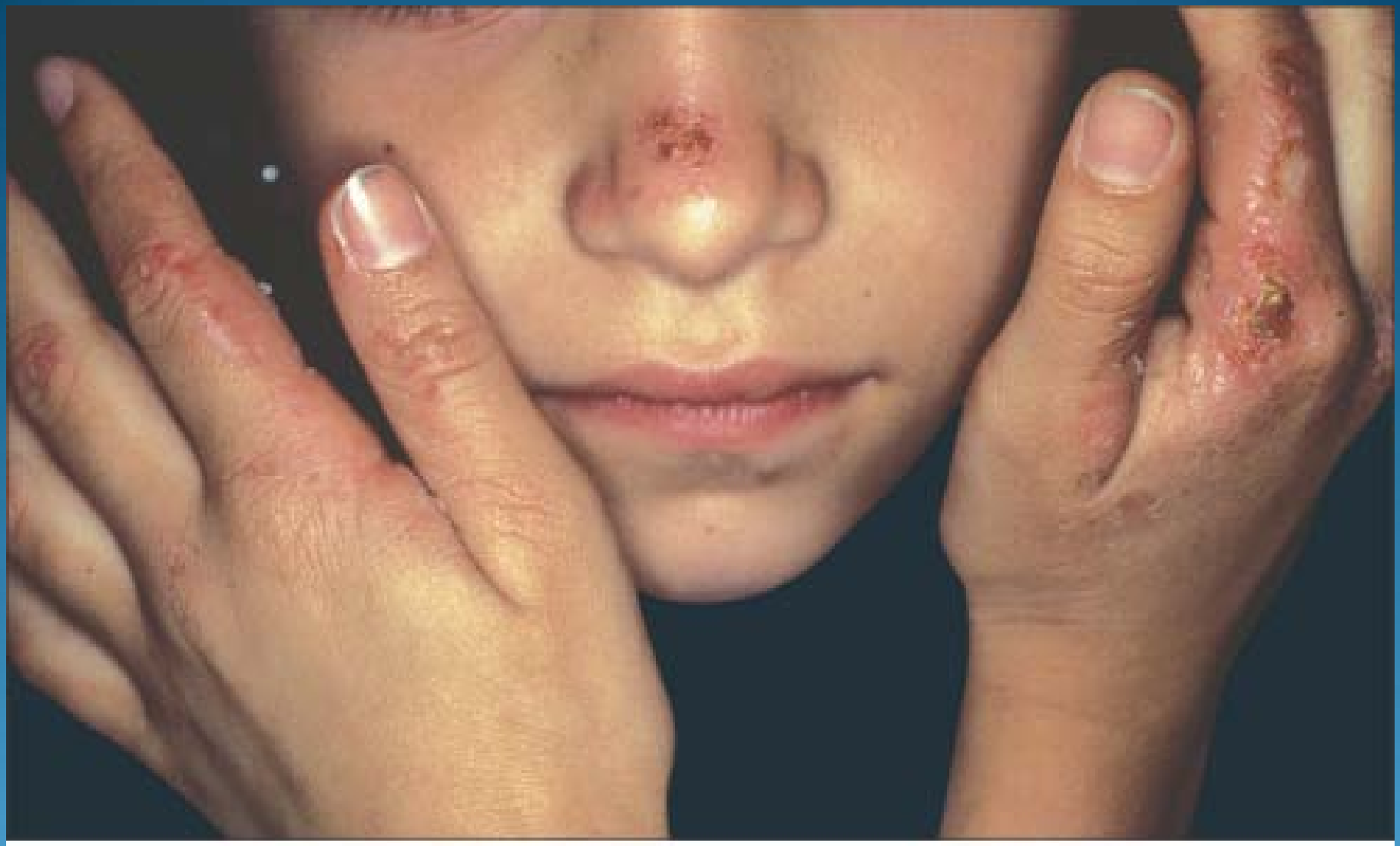
Erythropoietic Protoporphyria

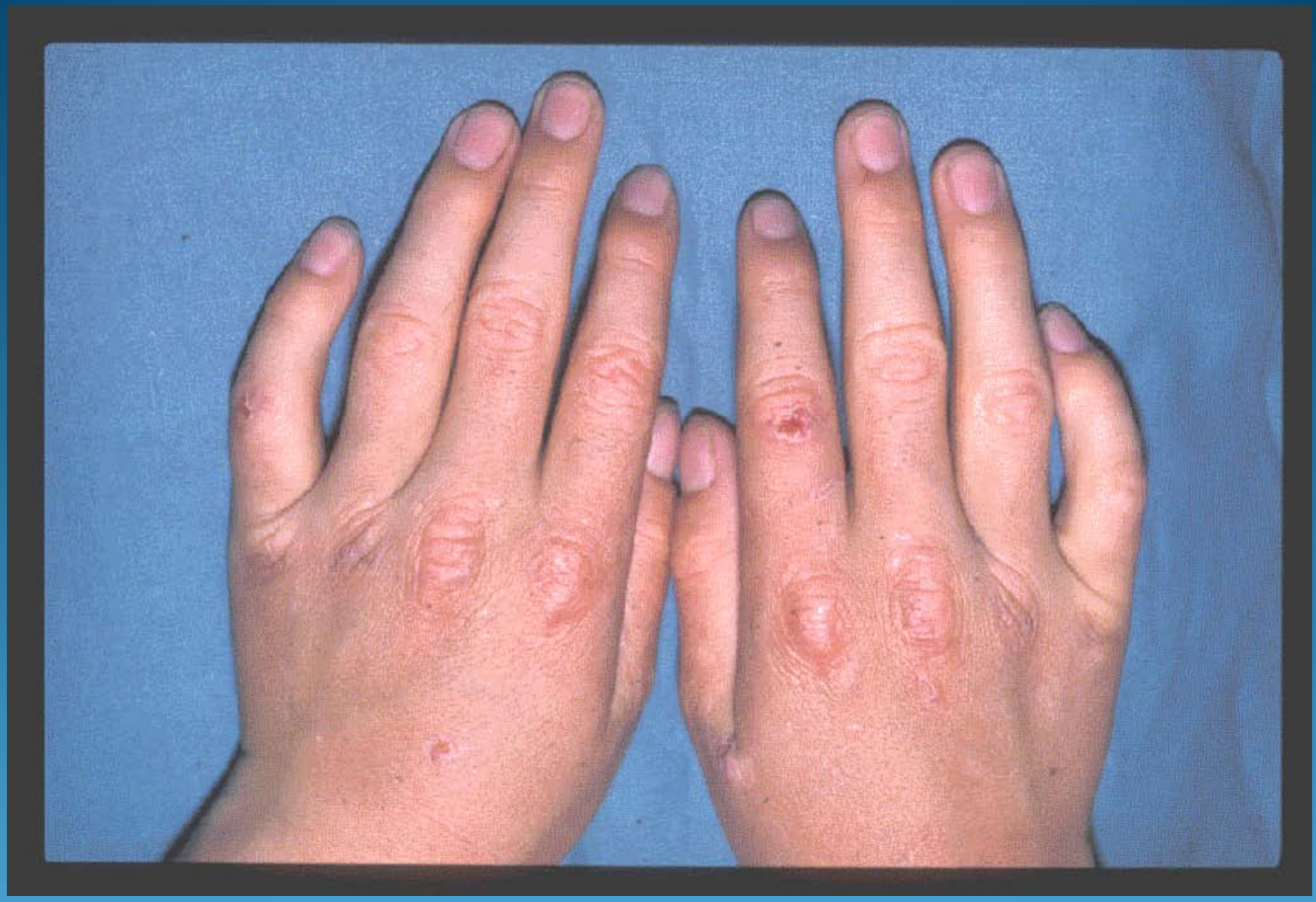
- Autosomal Dominant
- **Ferrochelatase**

- Presents in early childhood (avg. is 4)
- Immediate photosensitivity with burning, erythema and edema (*rare vesicles)*
  - "I don't want to go out"

Erythropoietic Protoporphyria

- **Late**:
  - waxy thickened scars over nose, face, hands creates **pebbling** of the skin
  - elliptical scars on face, perioral area





Easily Produces Pebbly Fingers

Erythropoietic Protoporphyria

- Mild anemia
- Protoporphyrin Cholelithiasis
- Mild liver disease: jaundice
  - Rarely leads to cirrhosis, hepatic failure

- DDx:
  - hydroa vacciniforme, PMLE, solar urticaria, other mild porphyrias

Erythropoietic Protoporphyria

- RBC, plasma, feces: Protoporphyrin
- **NOT** in urine
  - Protoporphyrin are insoluble in water
  - *ain't in pee pee*

EPP: Management

- Photoprotection/Avoidance
- Beta-carotene: 80mg bid- radical scavenger
- Transfusions
- Hematin
- Cholecystectomy
- Liver transplant

Porphyria Pearls

- Congenital Erythropoietic Porphyria
  - Carrot Eating Prevent Usual Terrible Complications
    - Uroporphyrinogen III Cosythetase
- Porphyria Cutanea Tarda
  - People Can Tell U Drink Constantly
    - Uroporphyrinogen Decarboxylase
- Variegate Porphyria
  - Veld People aPpear Pretty Odd
    - Protoporphyrinogen Oxidase

Porphyria Pearls

- Acute Intermittent Porphyria
  - An Insane Prussian Peed Blue Dye
    - PBG Deaminase
- Hereditary Coproporphyria
  - Hairy Crazy People Can Pee Orange
    - Coproporphyrin oxidase
- Hepatoerythropoietic Porphyria
  - His Early Presentation gives U Da Clue
    - Uroporphyrinogen Decarboxylase

Porphyria Pearls

- Erythropoietic Protoporphyria
  - Easily Produces Pebbly Fingers
    - Ferrochelatase