Cutaneous Deposition Diseases

Cutaneous Deposition Disorders

- Group of unrelated conditions characterized by the presence of endogenous or exogenous substances within the dermis or subcutis
- Our focus: endogenous depositions

Endogenous Cutaneous Deposition Disorders

- **Lipoid Proteinosis**
- **Porphyrias**
- Amyloidosis
- Colloid Milium

Lipoid Proteinosis

Hyalinosis Cutis et Mucosae

Urbach-Wiethe Disease

Lipoid Proteinosis

- 1929: Urbach (derm) and Wiethe (ENT)
- Autosomal recessive deposition disorder
- Hyaline-like material deposited in skin, mucous membranes, brain, and viscera

Lipoid Proteinosis: Pathogenesis

- Hyaline-like material is deposited in the walls of blood vessels and free in the papillary dermis

- The deposits consist of 2 substances:
  - True hyaline of fibroblast origin
  - Reduplicated basement membranes produced by multiple cells

Lipoid Proteinosis: Pathogenesis

- Pathogenesis is unknown
- Theories:
  - Structural changes represent a secondary attempt at repair rather than a primary degenerative process
  - Vascular fragility or release of a toxic substance from vessel walls and sweat glands
  - Hypersensitivity to physiologic trauma, thermal damage, or lysosomal fragility

Lipoid Proteinosis: Clinical Features

- **Weak cry in 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
  - Pustules, bullae and hemorrhagic crusts of the skin, mouth and throat
  - Skin lesions resolve with ice-pick acneiform scars on face and distal extremities

Lipoid Proteinosis: Clinical Features

- **Stage 2: Infiltrative**
  - Deposits increase in the dermis
  - Skin becomes thick, yellow, and waxy
  - Papules/plaques/nodules on face, axillae, scrotum. Coalesce into generalized infiltration
  - Verrucous lesions occur on extensor surfaces (elbows) and hands after frictional trauma
  - Generalized hyperkeratosis may occur

Lipoid Proteinosis: Clinical Features

- Eyes:
  - **Moniliform blepharosis (beaded papules)** on the palpebral margins
- Lips:
  - Pebbling of lip mucosa
  - Induration in childhood and granular lesions with pitting later

Lipoid Proteinosis: Clinical Features

- Tongue:
  - Infiltration of posterior aspect and frenulum
  - Fixed to the floor of the mouth
  - Firm and woody

- All oropharyngeal surfaces, vocal cords, and respiratory tract may be involved

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
- Extracellular cholesterolosis

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

- 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: Histology

- Deposits may surround hair follicles, sebaceous glands, and arrector pili muscles
- The perineurium of upper dermal nerves is hyalinized in advanced cases
- Decreased collagen and elastic fibers within the hyaline masses
- The subcutaneous fat is normal

Lipoid Proteinosis: Staining Pattern

- The hyaline is PAS positive, diastase resistant:
  - indicating neutral mucopolysaccharides
- Alcian Blue and Hyaluronidase:
  - reveal hyaluronic acid
- Sudan Stain and Oil Red O:
  - stain fat if present

Lipoid Proteinosis: Histologic Differential

- Erythropoietic Protoporphyria
  - Hyalinization is milder and more focal
- Amyloidosis
  - Amyloid stains are usually negative
- Diabetic microangiopathy
  - Identical histology
- Colloid milium
  - Devoid of striking perivascular distribution

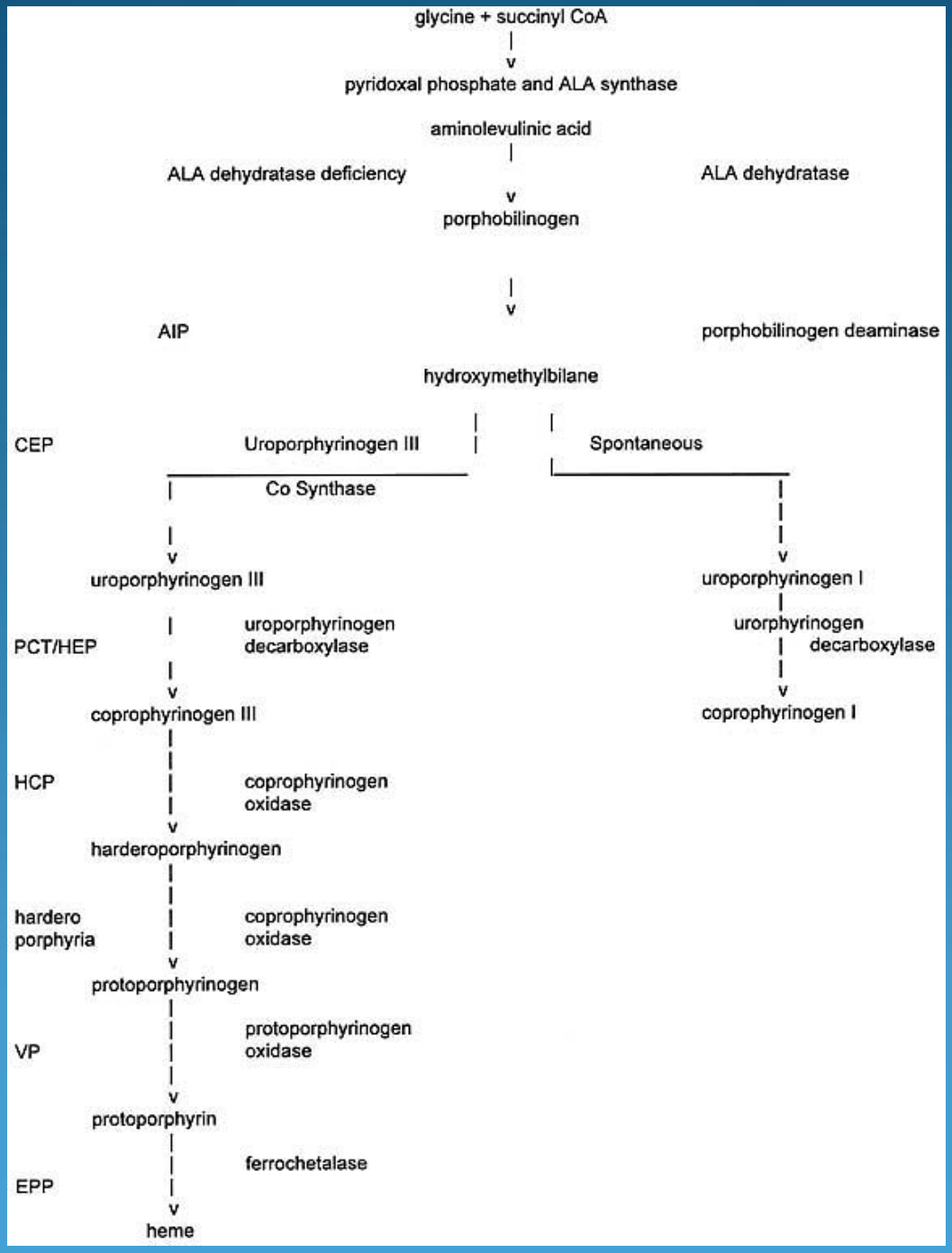
Lipoid Proteinosis: Treatment

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

Porphyrias

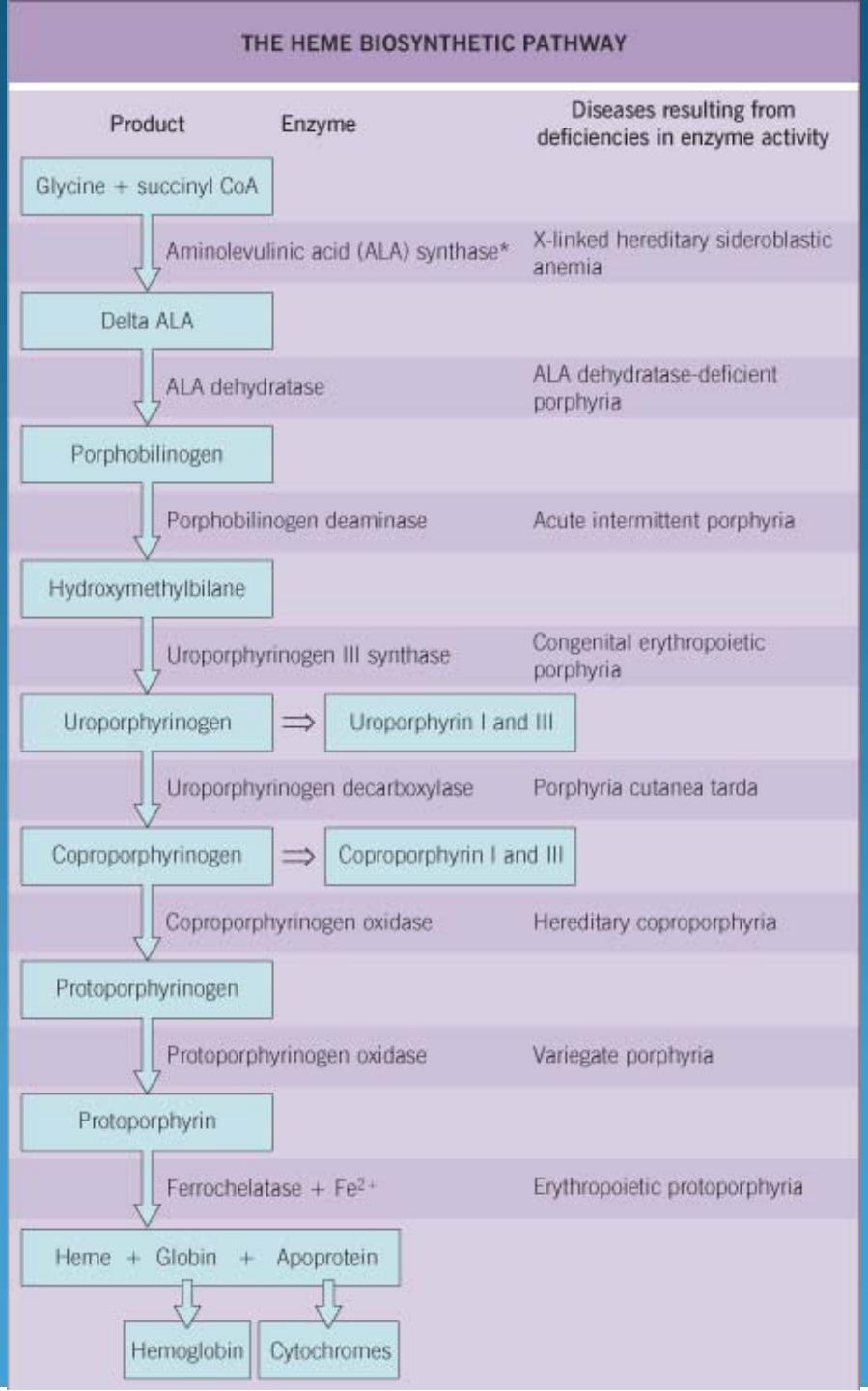
The Porphyrias

- 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


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

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)


THE HEME BIOSYNTHETIC PATHWAY
Product
Enzyme
Diseases resulting from deficiencies in enzyme activity
Glycine + succinyl CoA
Aminolevulinic acid (ALA) synthase*
X-linked hereditary sideroblastic anemia
Delta ALA
ALA dehydratase
ALA dehydratase-deficient porphyria
Porphobilinogen
Porphobilinogen deaminase
Acute intermittent porphyria
Hydroxymethylbilane
Uroporphyrinogen III synthase
Congenital erythropoietic porphyria
Uroporphyrinogen
Uroporphyrin I and III
Uroporphyrinogen decarboxylase
Porphyria cutanea tarda
Coproporphyrinogen
Coproporphyrin I and III
Coproporphyrinogen oxidase
Hereditary coproporphyria
Protoporphyrinogen
Protoporphyrinogen oxidase
Variegate porphyria
Protoporphyrin
Ferrochelatase + Fe2+
Erythropoietic protoporphyria
Heme + Globin + Apoprotein
Hemoglobin
Cytochromes

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

- Porphyrins become excited/unstable
- Energy is transferred to oxygen, creating **reactive oxygen species**
  - singlet O_2, H_2O_2, superoxide radicals
- Oxygen radicals transfer energy to cells and DNA, causing tissue damage in the skin, liver, and erythrocytes

Erythropoietic Porphyrias

Congenital Erythropoietic Porphyria

Gunther's Disease

Congenital Erythropoietic Porphyria

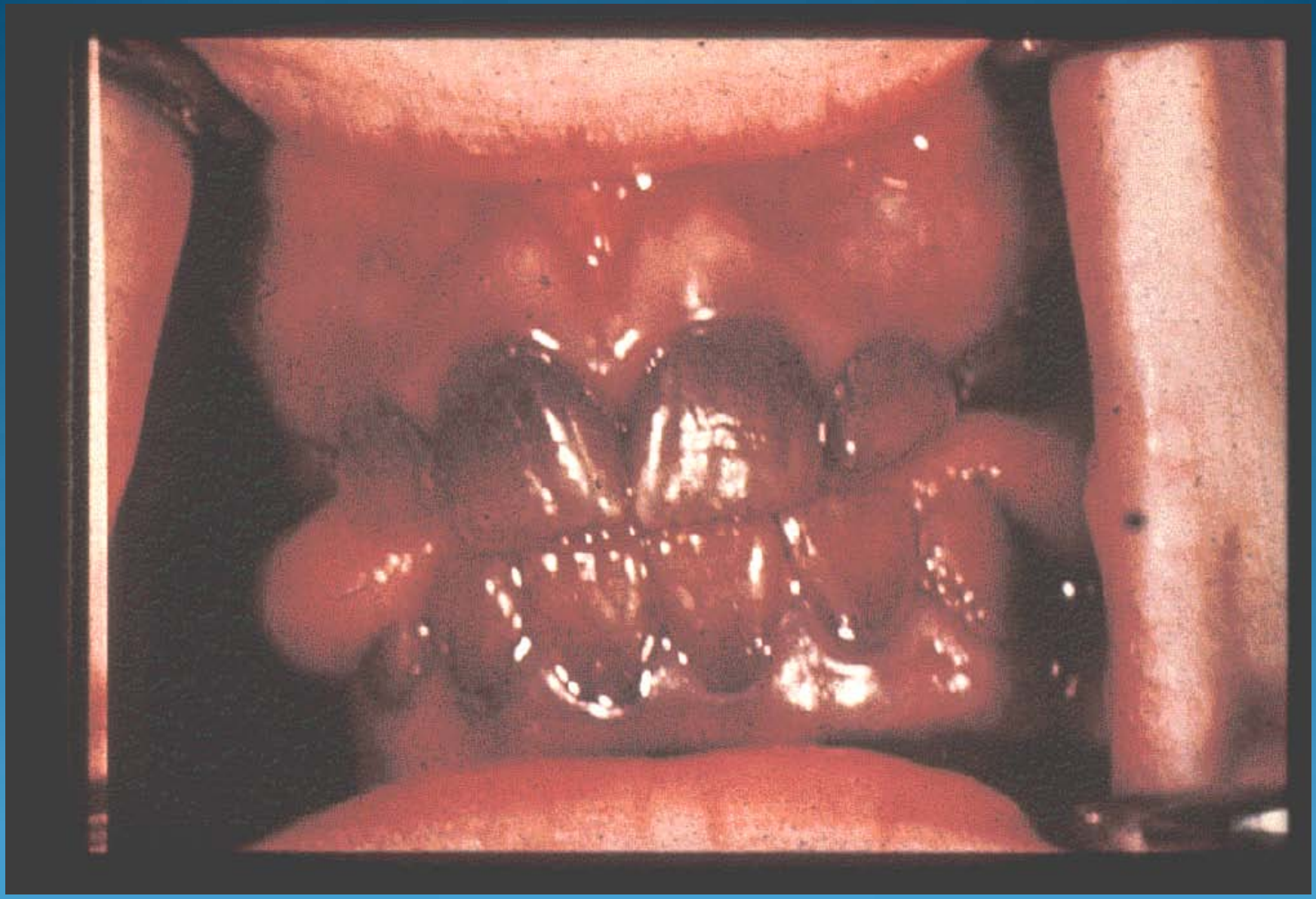
- Autosomal Recessive
- Presents between birth and 5 years
- **Uroporphyrinogen III Cosynthetase**

Congenital Erythropoietic Porphyria

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

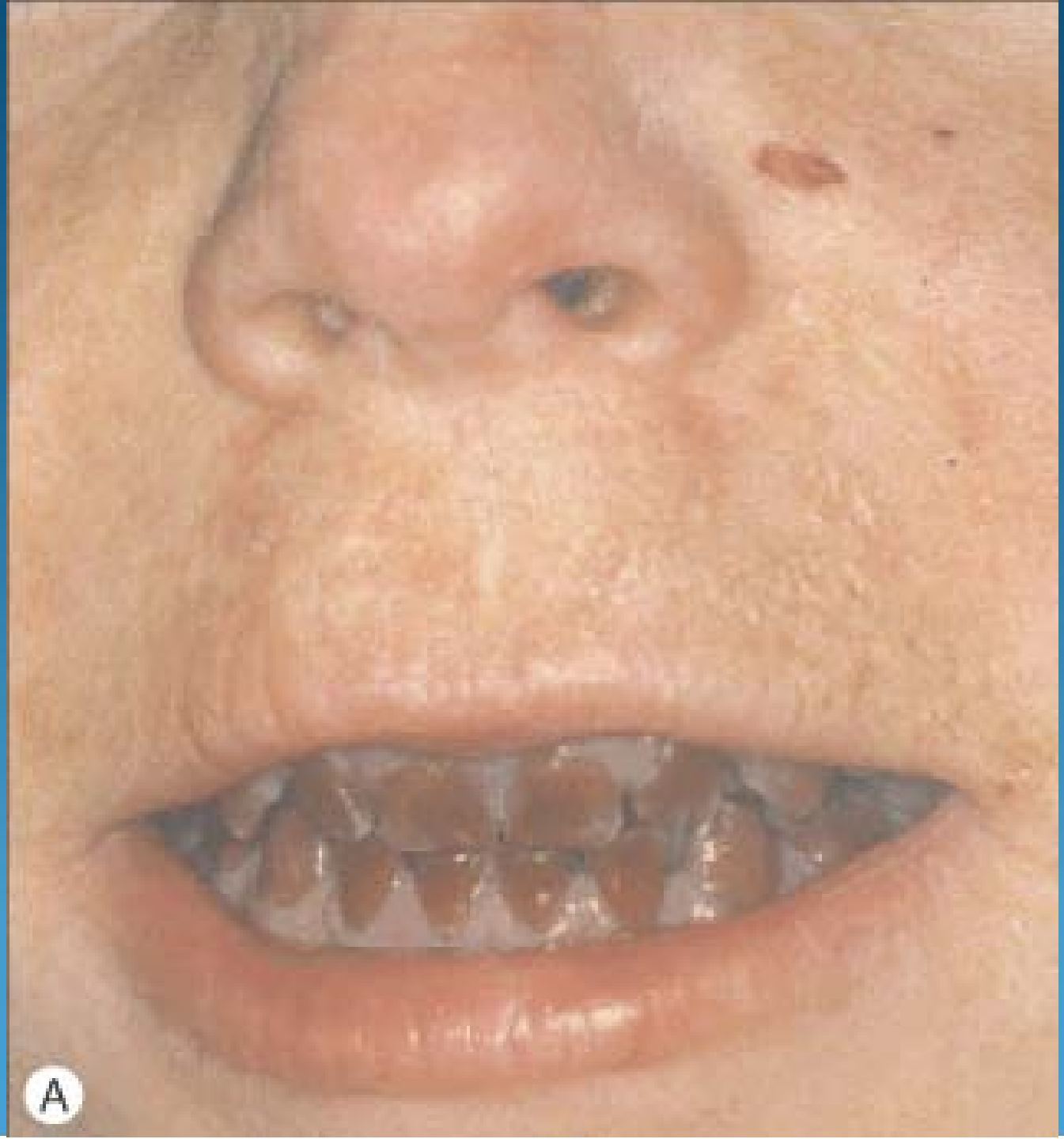
Congenital Erythropoietic Porphyria

- Delayed phototoxicity with erythema, stinging, and blistering after UV exposure
- Ulcers/mutilating scars of nose and ears
- Corneal scarring, blindness
- Erythrodontia
- Hemolytic anemia
- HSM



Congenital Erythropoietic Porphyria

- Bone involvement:
  - **Erythrodontia**
  - Fragility
  - Short stature
  - Acral osteolysis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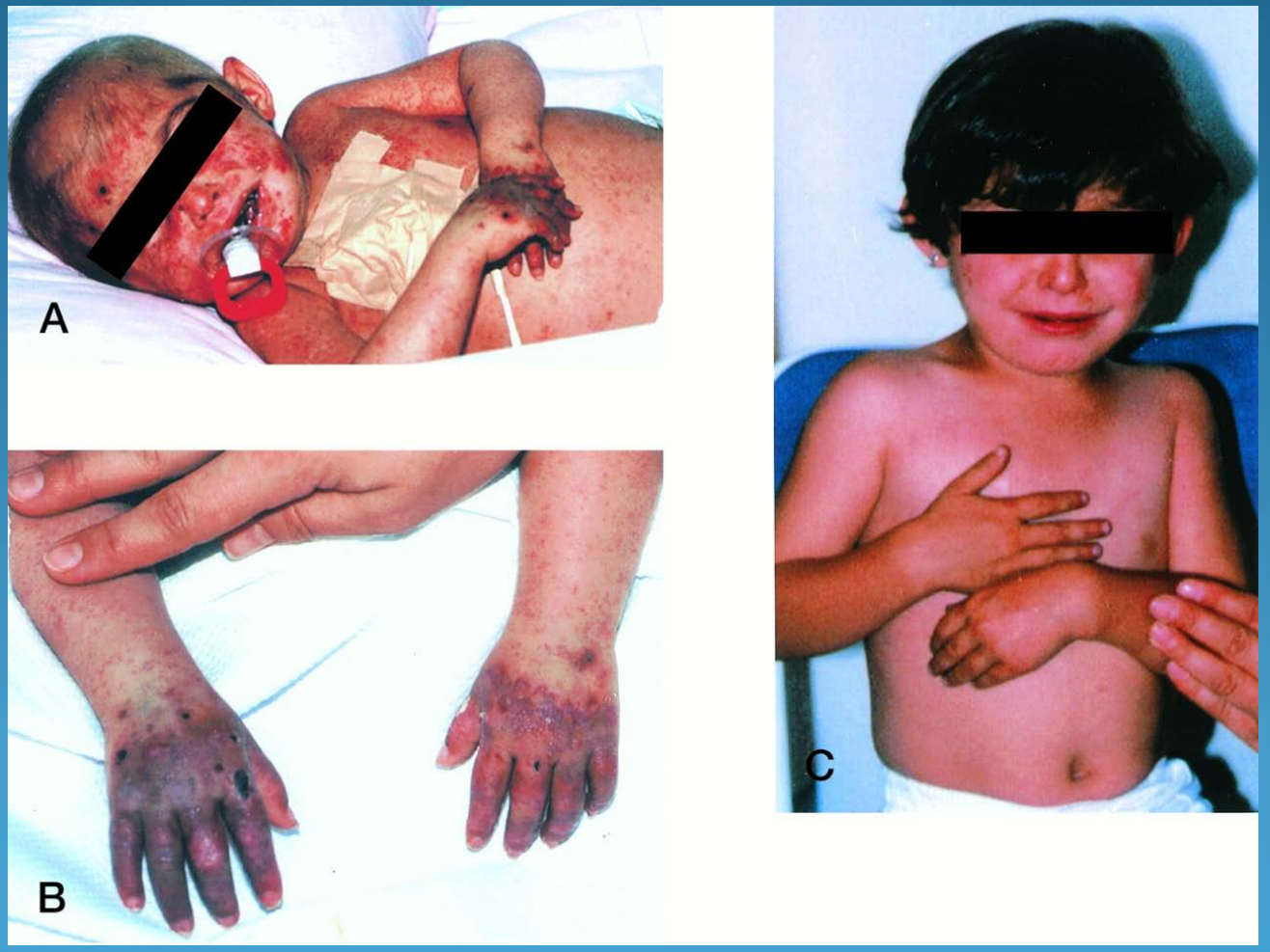
CEP: Labs

- CBC: anemia with schistocytes/hemolysis
- Urine, Feces, Plasma, RBC: Uro, Copro
- RBC: Zinc protoporphyrin

CEP: Management

- Photoprotection (even bili lights!)
- Transfusions
- Splenectomy
- Beta-carotene
- Hydroxyurea: suppress BM heme synthesis
- Bone Marrow Transplant

CEP successfully treated with BMT



Hepatic Porphyrias

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

} Acute Attack Porphyrias

Acute Neurovisceral Attacks

- Mechanism:
  - Heme precursors ALA, PBG toxic to neural tissues
  - Deranged heme metabolism leads to neural dysfunction
- Pain: Abdomen, chest, back and limbs
- GI: N/V/D, cramps, distention, and ileus
- GU: retention, renal failure, frequency
- Sympathetic Surge: fever, tachy, HTN, sweating
- Neuro: seizures, paralysis, coma, psychosis
- Death

Acute Attacks

- Exposure to environmental factors / stressors are often required to induce overt phenotypical expression

- Triggers:
  - Drugs (antibiotics, anticonvulsants, griseo)
  - Starvation / hypoglycemia
  - Hormonal fluctuations (menses, pregnancy)
  - Infections

Acute Intermittent Porphyria

- **Porphobilinogen deaminase**
- Autosomal Dominant
- *Gene defect alone does not induce disease unless precipitating factors are present*
- No skin findings

AIP: Labs

- Elevated urinary **ALA** and **PBG** during attacks

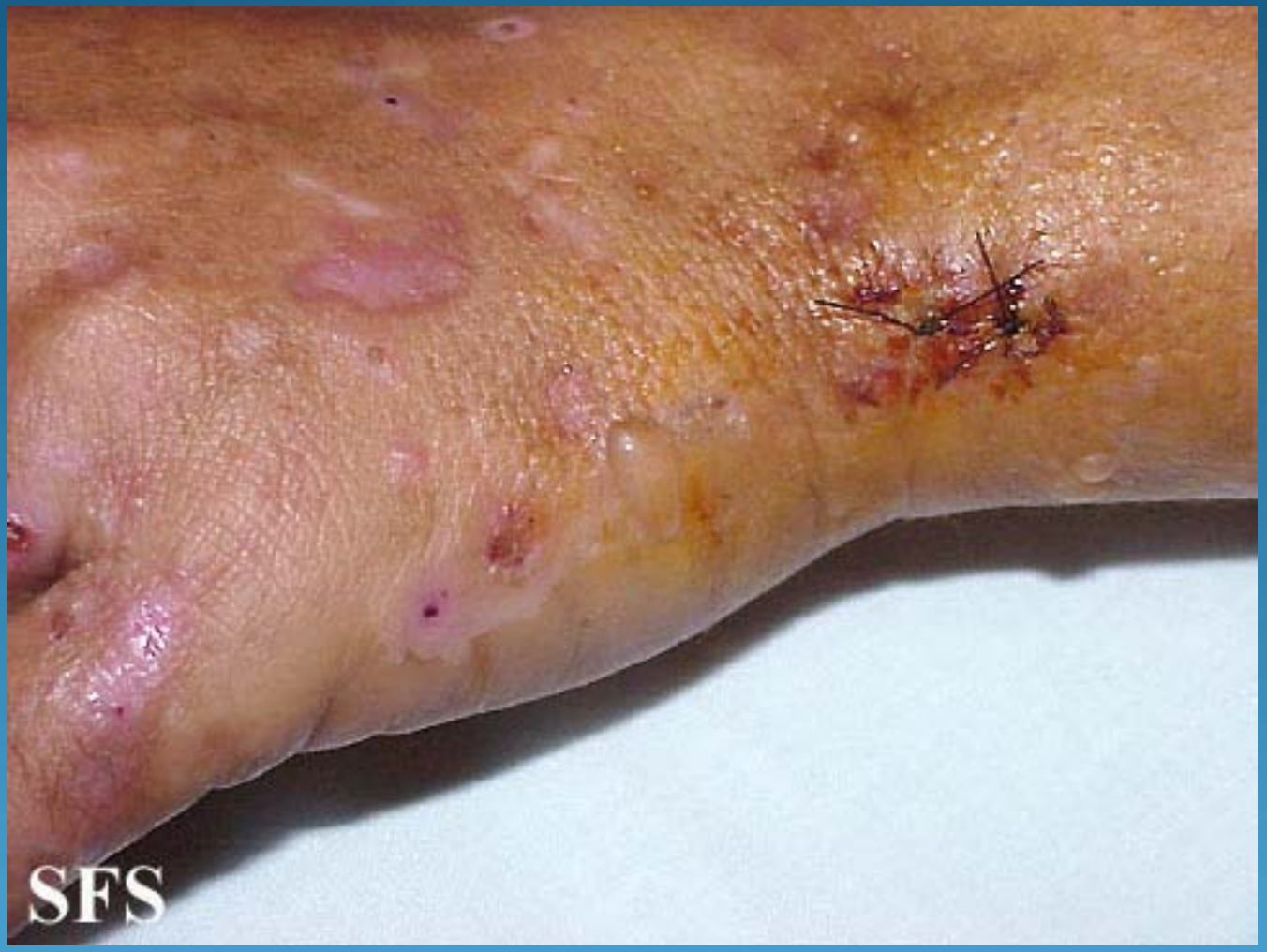
- An Insane Prussian Peed Blue Dye

Acute Attack Porphyrias: **Hereditary Coproporphyria**

- Autosomal Dominant
- **Coproporphyrinogen oxidase**
- Acute attacks mimic AIP, skin mimics PCT

Hereditary Coproporphyria

- Urinary copro, ALA, and PBG during attacks
- Fecal Copro (vs. AIP: *Ain't in Poop*)
- Copro always elevated in feces
- Harry Crazy People Can Pee Orange



PCT-like skin plus acute attacks: think HCP

Variegate Porphyria

- Autosomal Dominant
- South Africans of Dutch ancestry
- Onset of symptoms after puberty
- Skin identical to PCT, but earlier (20's)
- Neurovisceral attacks as adults

Variegate Porphyria

- **Protoporphyrinogen Oxidase**
- Increased urinary ALA, PBG, uro, and copro during attacks
- Urine: Copro > Uro (**opposite of PCT**)
- Feces: Proto, Copro
- Specific fluorescence of plasma porphyrins at **627nm** peak

Management of Attacks (AIP, HCP, VP)

- Identify/remove inducers
- Glucose infusions
- Analgesia
- Hematin infusions (neg. feedback to ALA)
- Supportive Care

Porphyria Cutanea Tarda

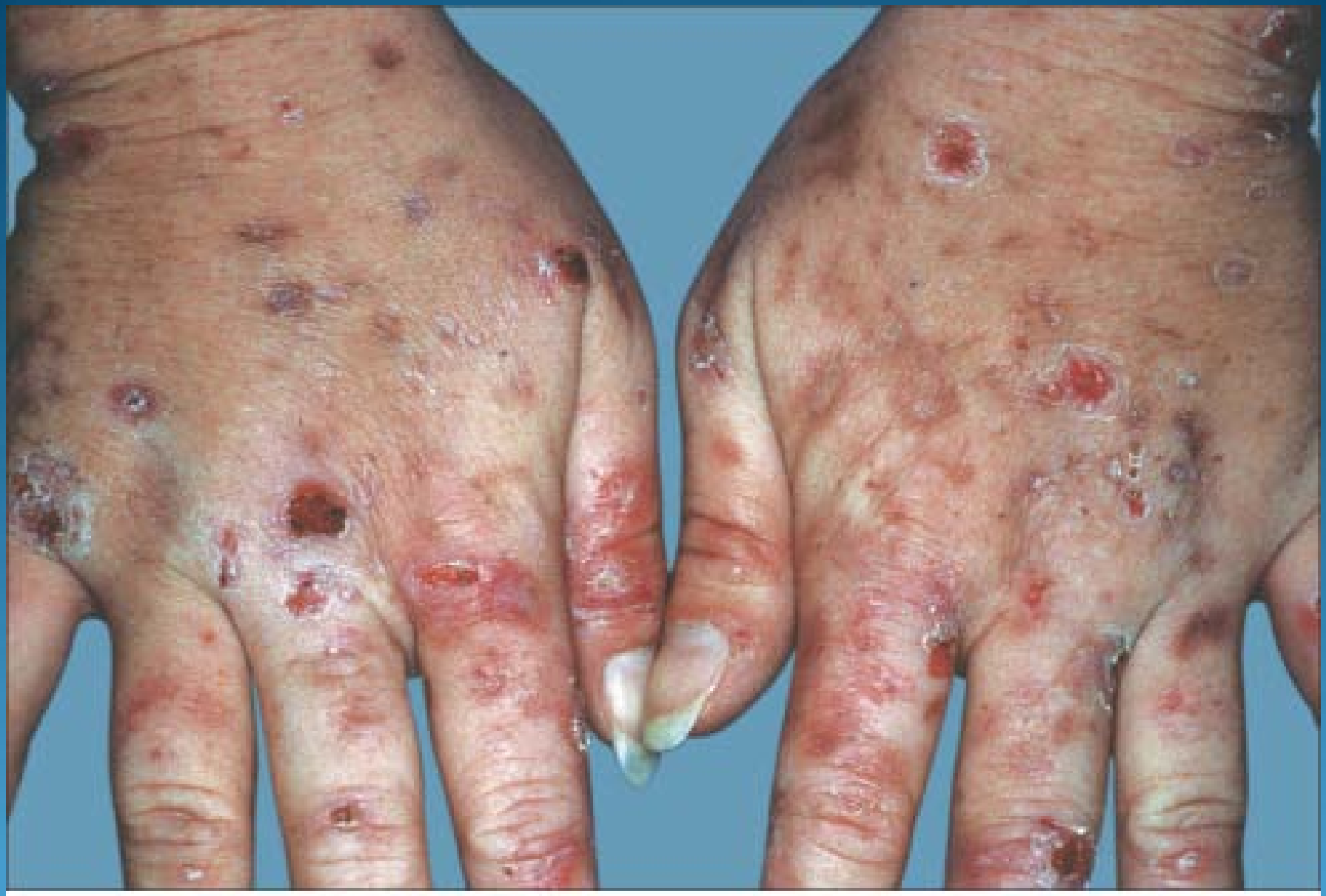
- Most common form in N.America, Europe
- Autosomal Dominant or Acquired
- **Uroporphyrinogen decarboxylase**

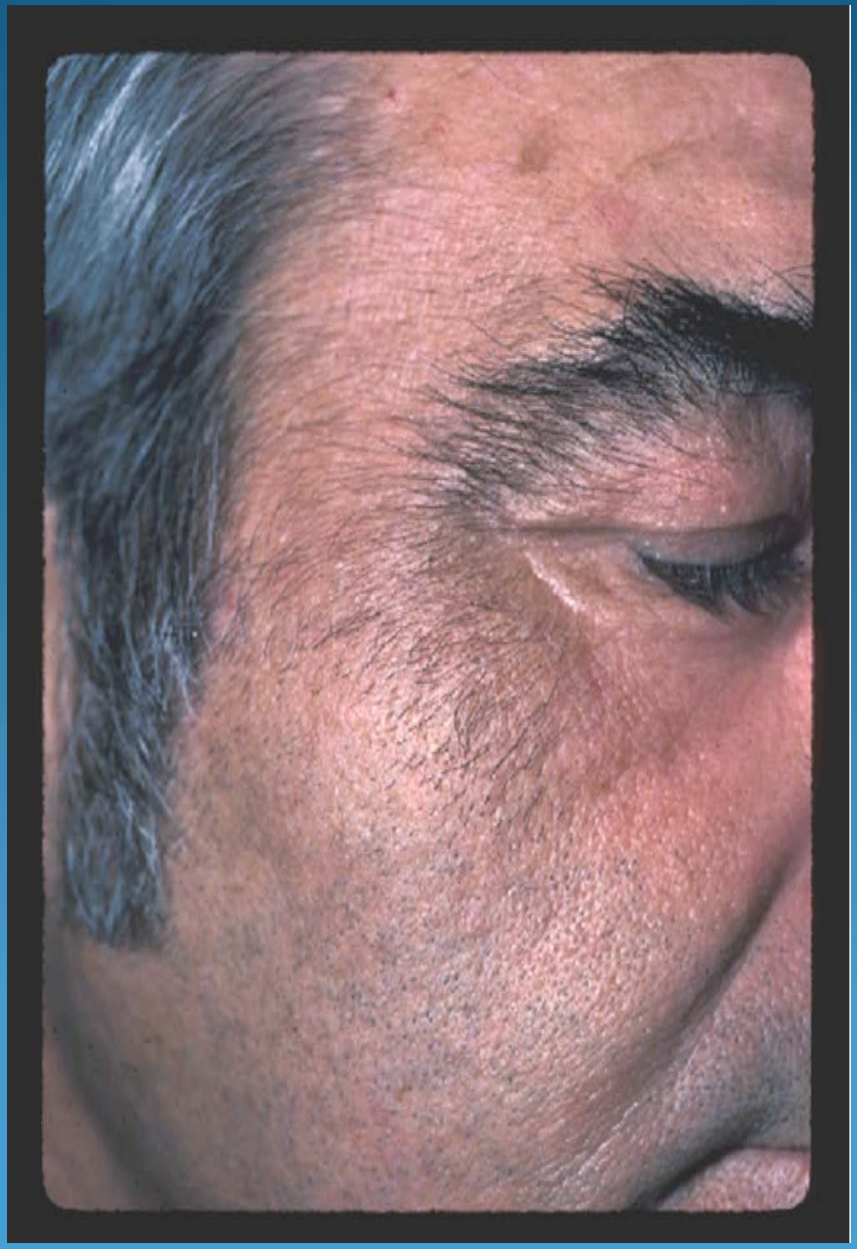
Porphyria Cutanea Tarda

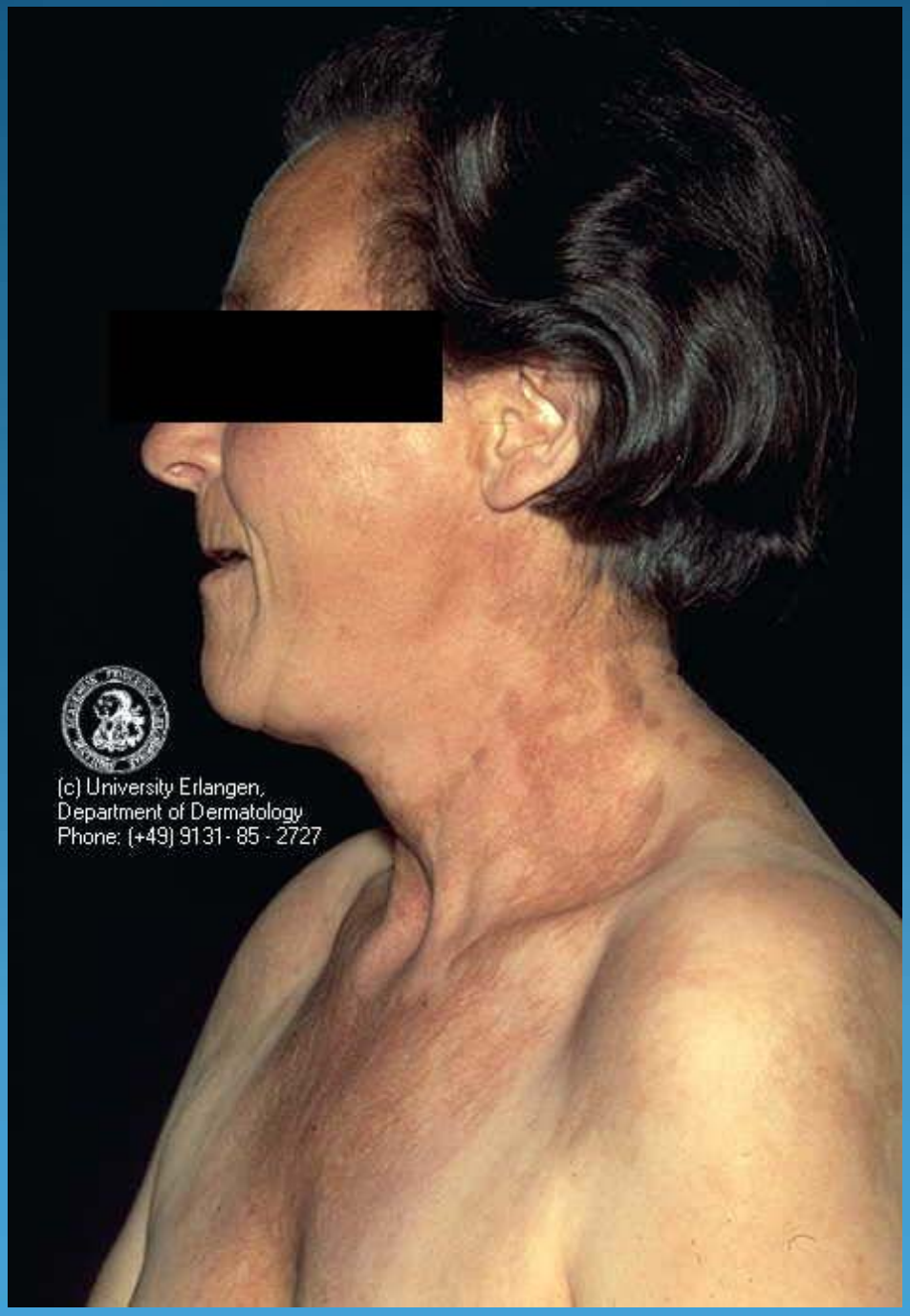
- **Acquired Form**:
  - Sporadic or induced by toxins or drugs
  - Sporadic: only the *hepatic* enzyme is deficient
  - Inducers:
    - Alcohol, iron, hemodialysis, HCV, HBV, HIV, estrogens, hepatic neoplasms, polychlorinated hydrocarbons
- **Homozygous inherited form**:
  - Hepatoerythropoietic Porphyria (HEP)
  - erythrocyte *and* hepatic enzymes are deficient

Porphyria Cutanea Tarda

- Defect in **C282Y** gene predisposes to hemochromatosis and PCT



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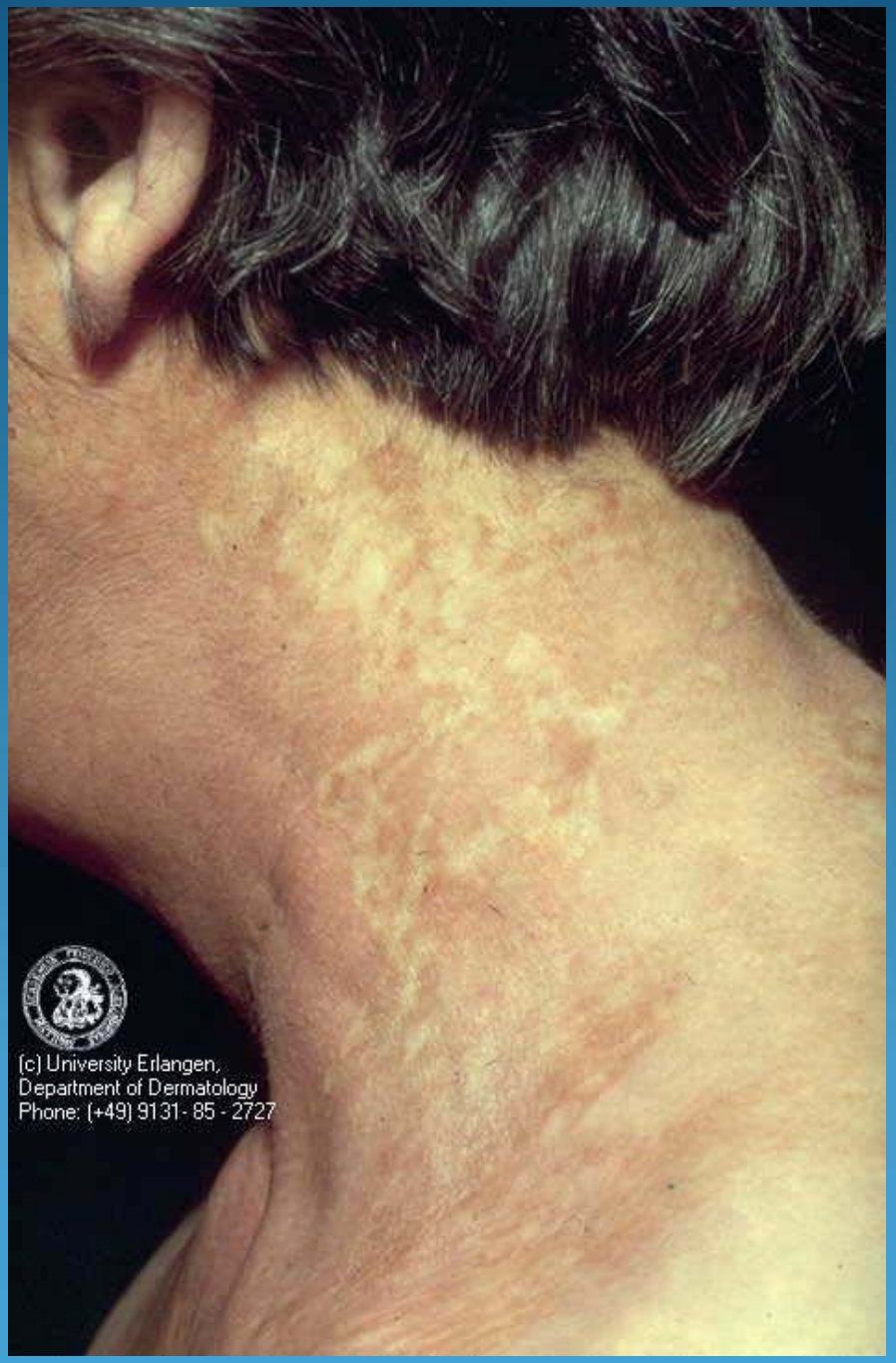
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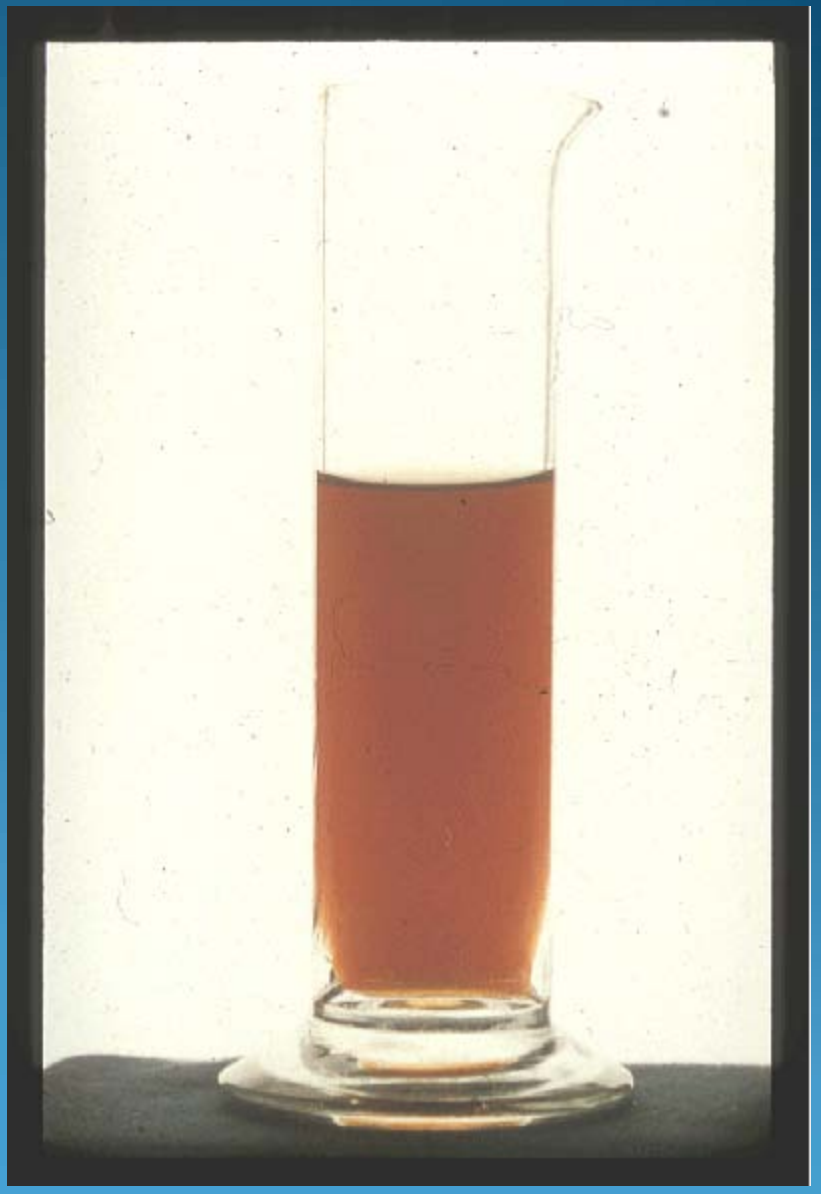
PCT Labs

- Urine: Uro > Coproporphyrins
- Feces: Isocoproporphyrins
- RBC: Normal
- Urine porphyrins fluoresce under Wood's lamp

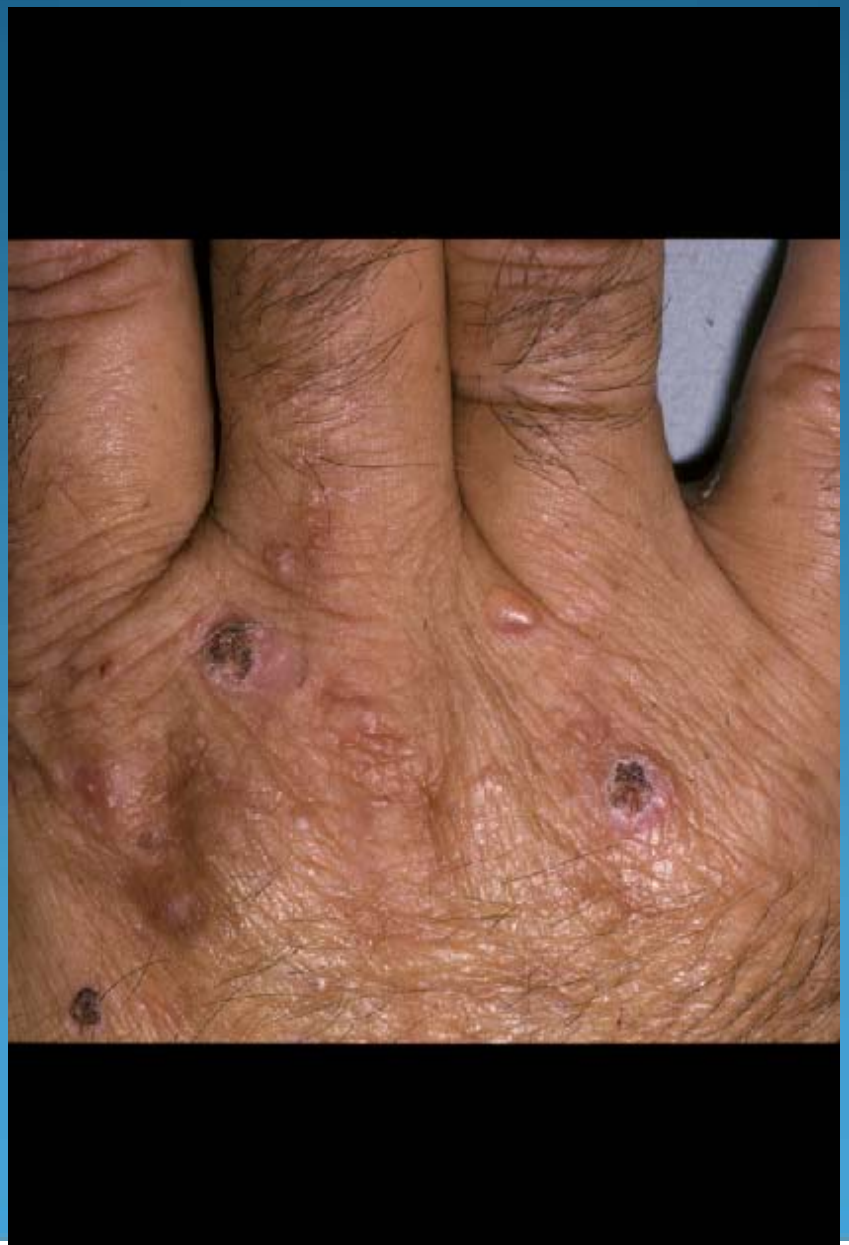

Corbis.com



PCT: Management

- Identify the etiology!!!
- Photoprotection
- Phlebotomy: 500ml BIW to Hbg 10-11
- Plaquenil 100-200mg BIW
  - Rx until urine uroporphyrin < 100microgram/24hours
- Chloroquine-solubilizes porphyrins for excretion
- Enteric absorbents (cholestyramine)
- Lifestyle modification

PCT: People Can Tell U Drink Constantly



Pseudoporphyria

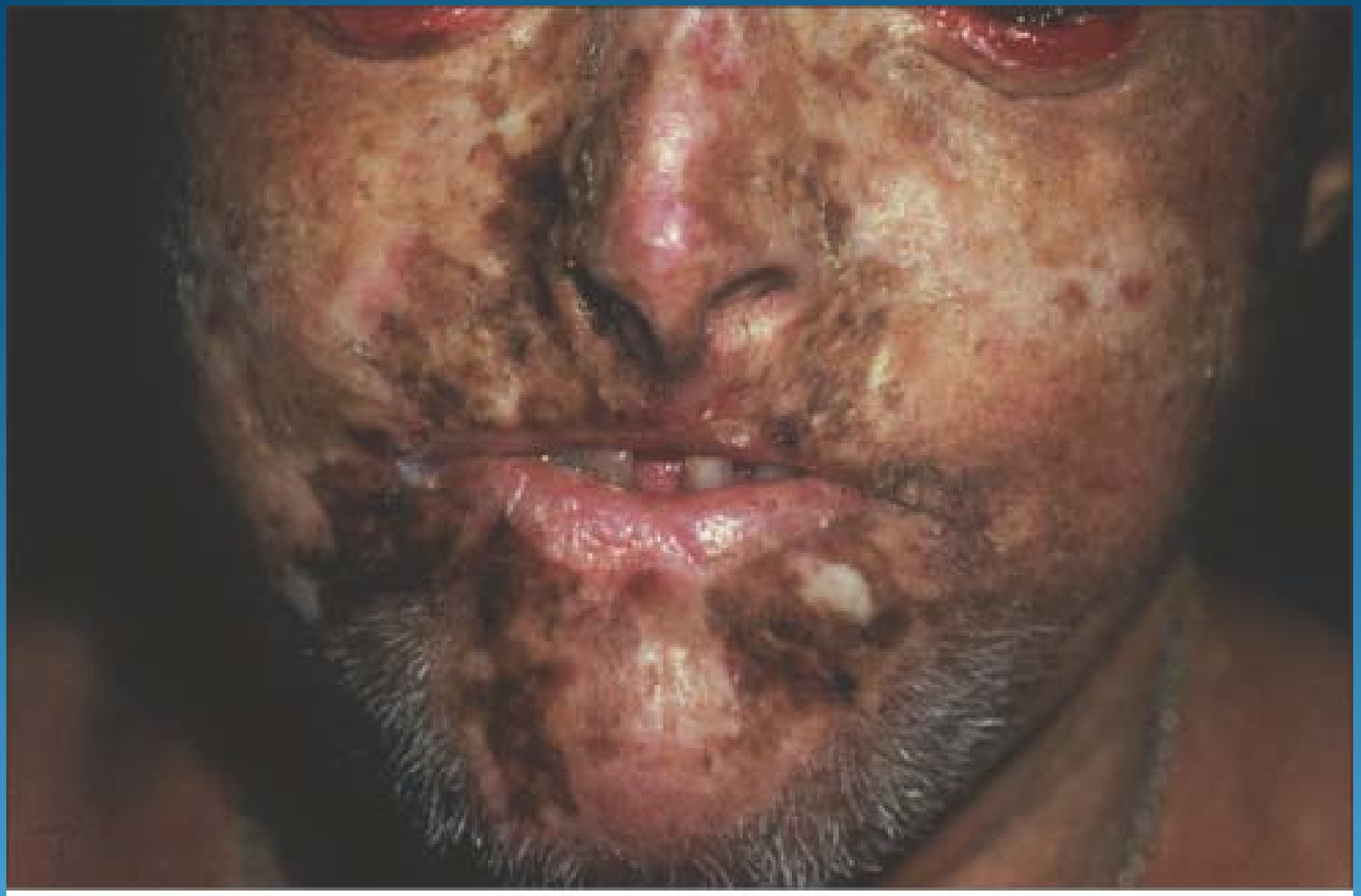
- Mimics PCT (clinical and histo), except:
  - No hypertrichosis or hyperpigmentation
  - No sclerodermoid changes
  - No porphyrin abnormality
- Triggers:
  - Hemodialysis
  - Drugs (naprosyn, furosemide, HCTZ, TCN, nalidixic acid, dapsone, pyridoxine)
  - UVA (tanning beds)

Pseudoporphyria Treatment

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

Hepatoerythropoietic Porphyria

- **Presents in infancy:**
  - photosensitivity, bullae and erosions
- **Late clinical findings:**
  - Sclerodermoid plaques and hypertrichosis
  - Mutilating scars in acral areas
  - Acral osteolysis (short digits)
  - Scarring alopecia, ectropion
  - **Erythrodontia**
- **Anemia, HSM**

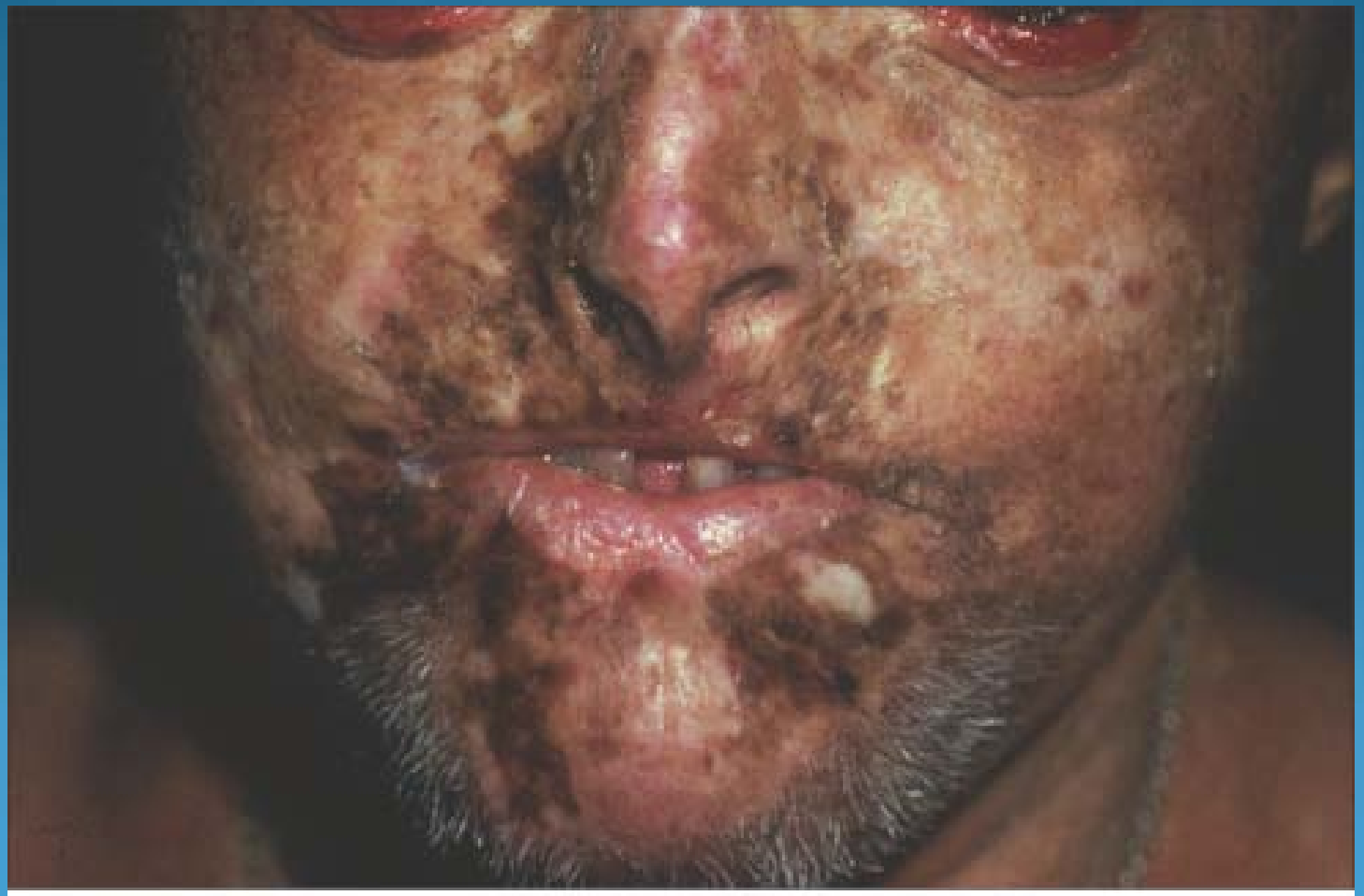


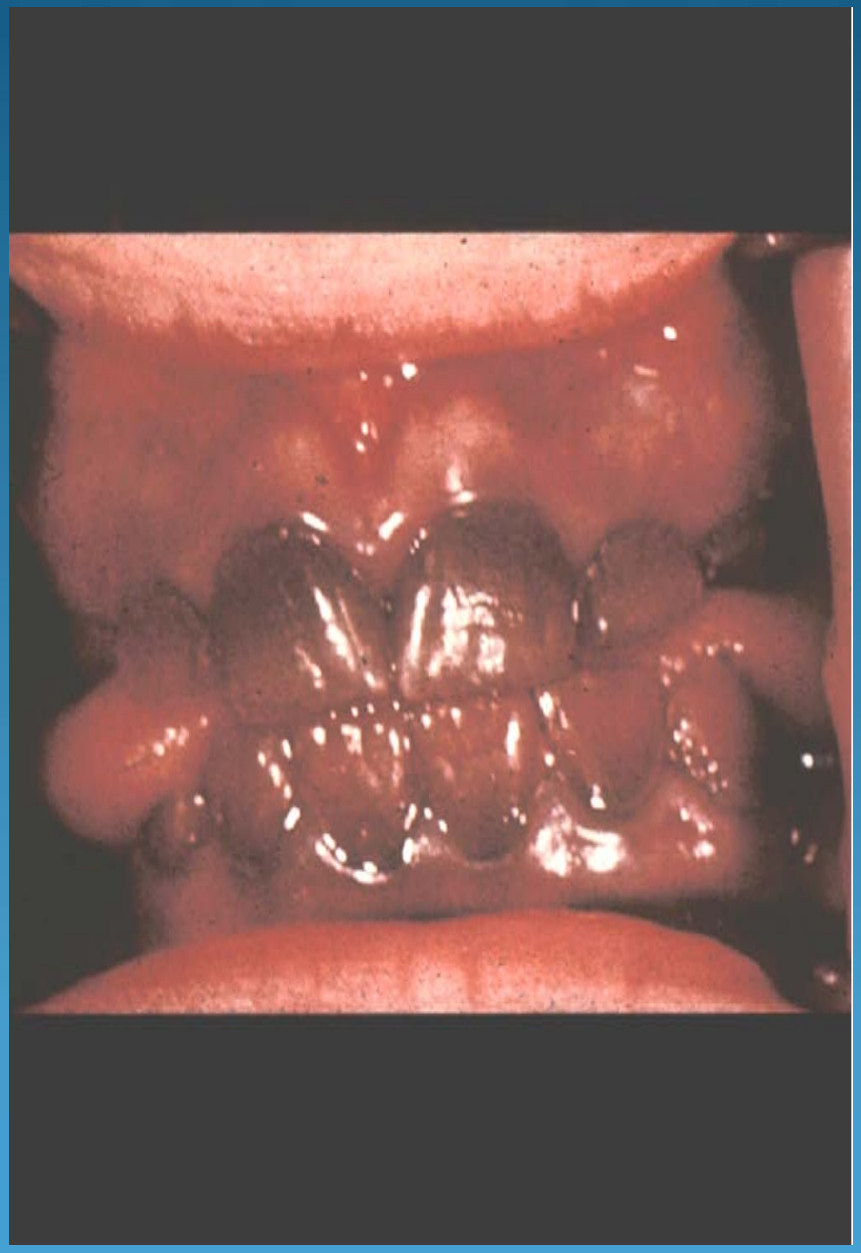
Hepatoerythropoietic Porphyria

- Autosomal recessive, homozygous form of PCT

- **Uroporphyrinogen Decarboxylase**
  - HEP: 2 mutant copies
  - PCT: 1 mutant copy

His Early Presentation gives U Da Clue





HEP: Labs

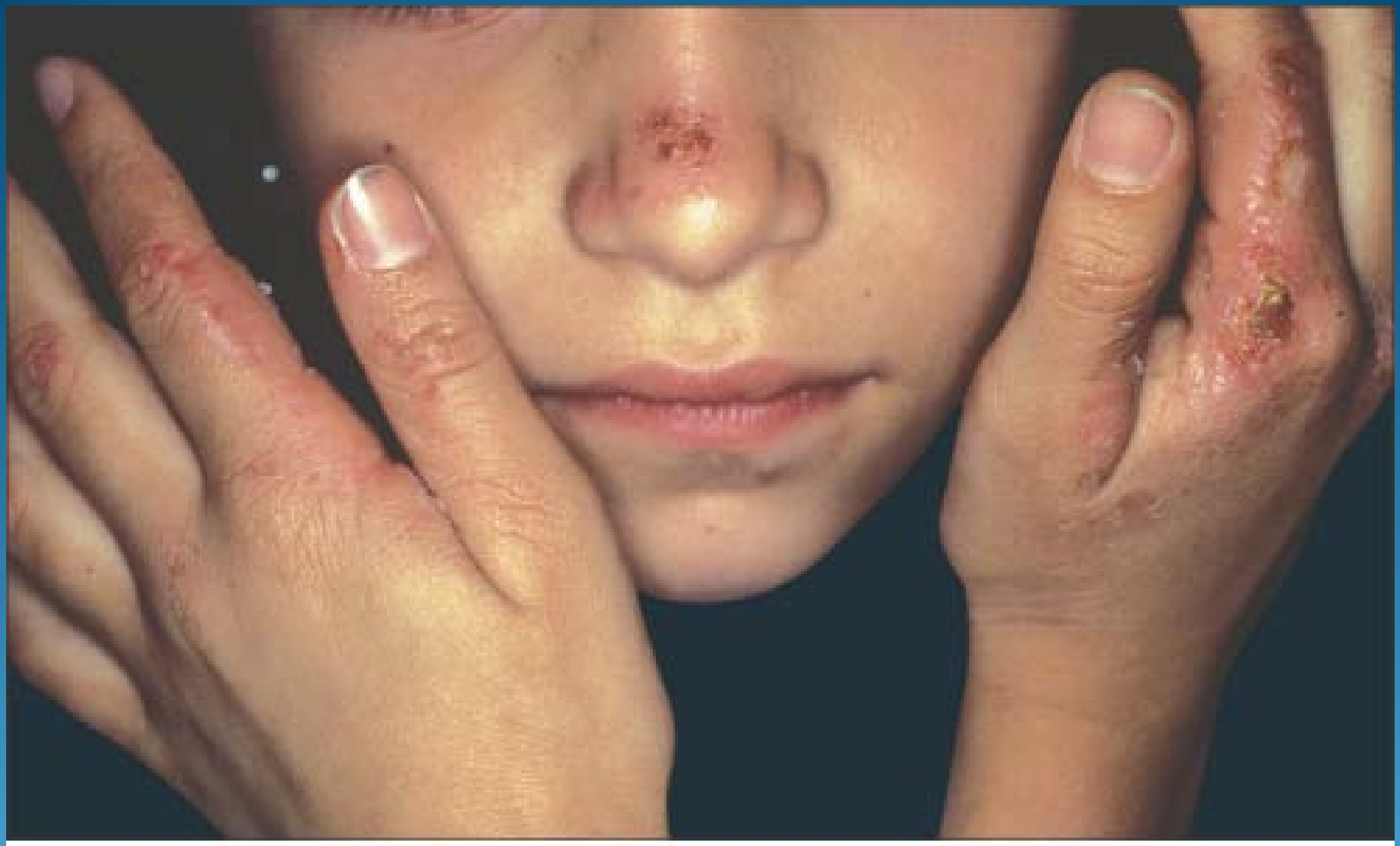
- **Urine**: Uroporphyrin I-III
- **Feces**: Uro, Iso, coprophyrin
- **RBC**: Zinc-Protoporphyrin
- Anemia, with normal iron levels

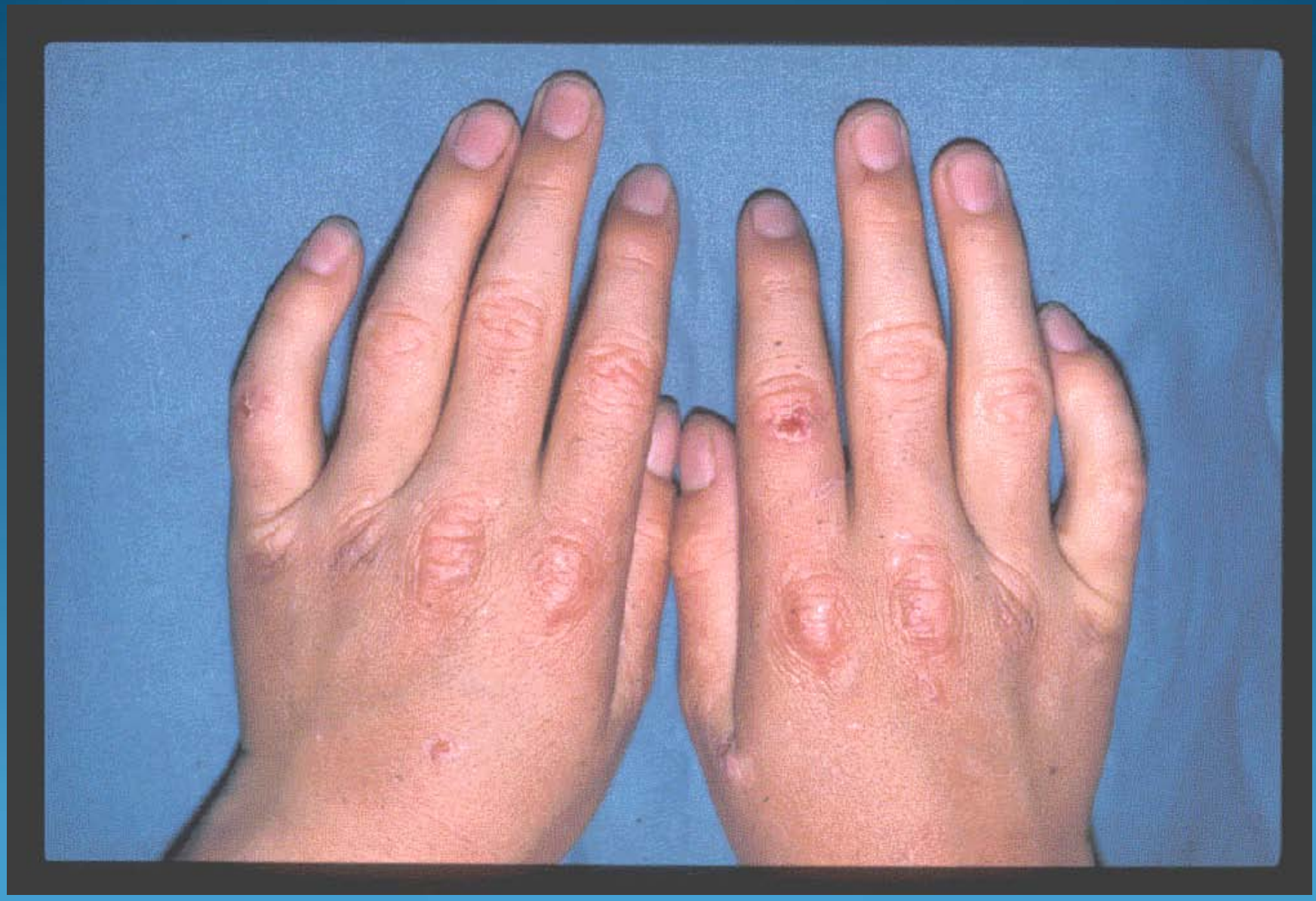
HEP: Management

- Sun avoidance
- **DO NOT** phlebotomize (anemic!)

Erythropoietic Protoporphyria

- Autosomal Dominant
- Presents in early childhood
- Immediate photosensitivity with pain, erythema and edema
- Linear crusted lesions on face/hands
- Heals with elliptical scars
- Waxy thickening of the nose and hands creates **pebbling** of skin





Erythropoietic Protoporphyria

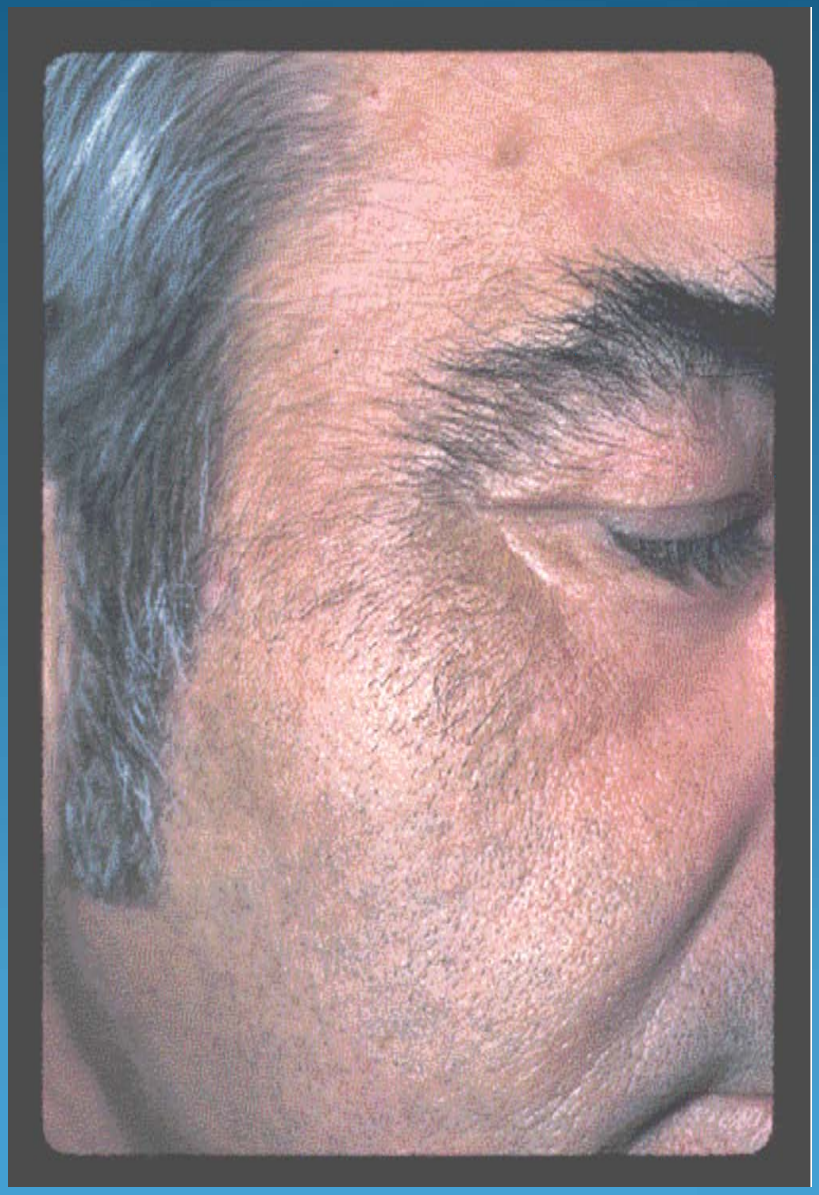
- 10% have anemia
- Protoporphyrin cholelithiasis
- Mild liver disease
  - 5% develop hepatic failure

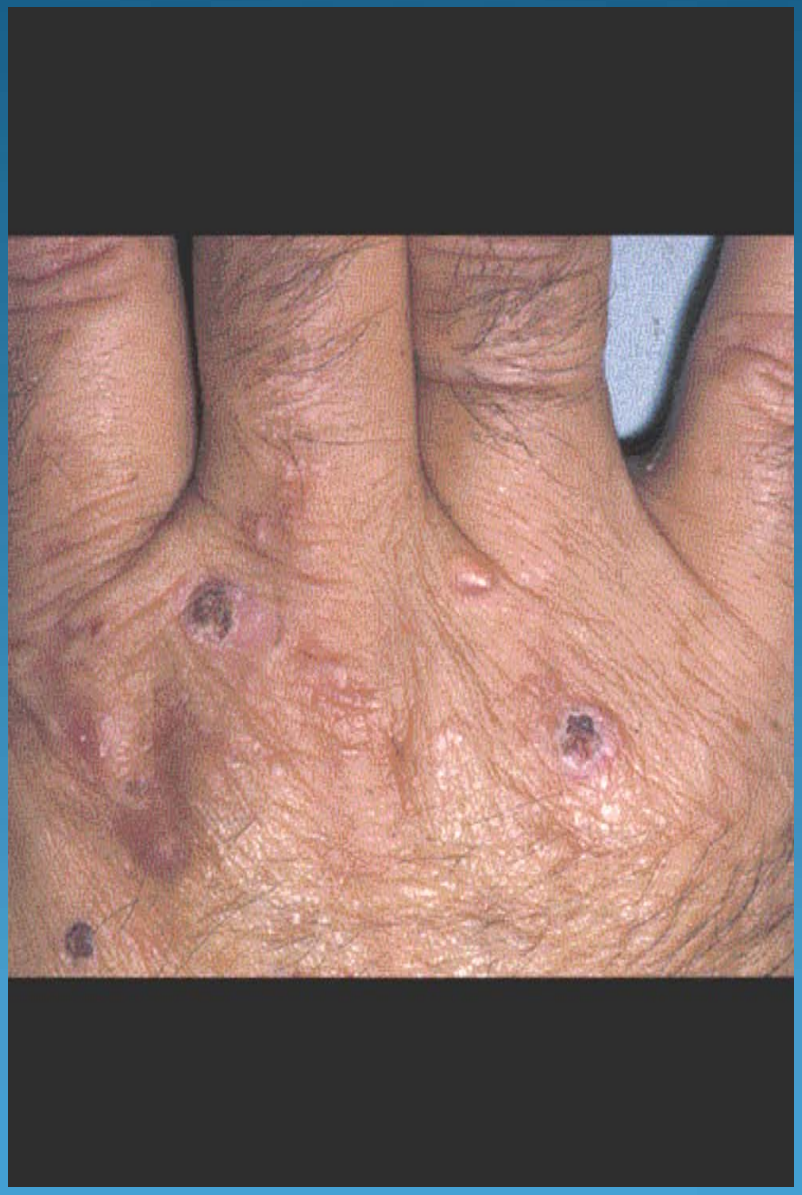
Erythropoietic Protoporphyria

- **Ferrochelatase**
- Protoporphyrin IX in RBC, plasma, feces
- **NOT** in urine (*ain't in pee pee*)
- Protoporphyrin is excreted by hepatic system in feces (not water soluble)
- *Easily Produces Pebbly Fingers*

EPP: Management

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





Porphyria Pearls

- PCT: People Can Tell U Drink Constantly
- HEP: His Early presentation gives U Da Clue
- CEP: Carrot Eating Prevents Usual Terrible Complications
- HCP: Harry Crazy People Can Pee Orange
- AIP: An Insane Prussian Peed Blue Dye
- EPP: Easily Produces Pebbly Fingers

Porphyria Pearls

- Congenital Erythropoietic Porphyria
  - Carrot Eating Prevent Usual Terrible Complications
    - Uroporphyrinogen III Cosythetase
- Erythropoietic Protoporphyria
  - Easily Produces Pebbly Fingers
    - Ferrochelatase

Porphyria Pearls

- Porphyria Cutanea Tarda
  - People Can Tell U Drink Constantly
    - Uroporphyrinogen Decarboxylase
- Variegate Porphyria
  - Veld People aPpear Pretty Odd
    - Protoporphyrinogen Oxidase
- Hereditary Coproporphyria
  - Hairy Crazy People Can Pee Orange
    - Coproporphyrin oxidase
- Acute Intermittent Porphyria
  - An Insane Prussian Peed Blue Dye
    - PBG Deaminase