ESIM Winter School
Saas Fee January 2011

Porphyrias at a glance: diagnosis and treatment.

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The Porphyrias

“Porphyrias” include a wide spectrum of hereditary disorders due to abnormal heme biosynthesis

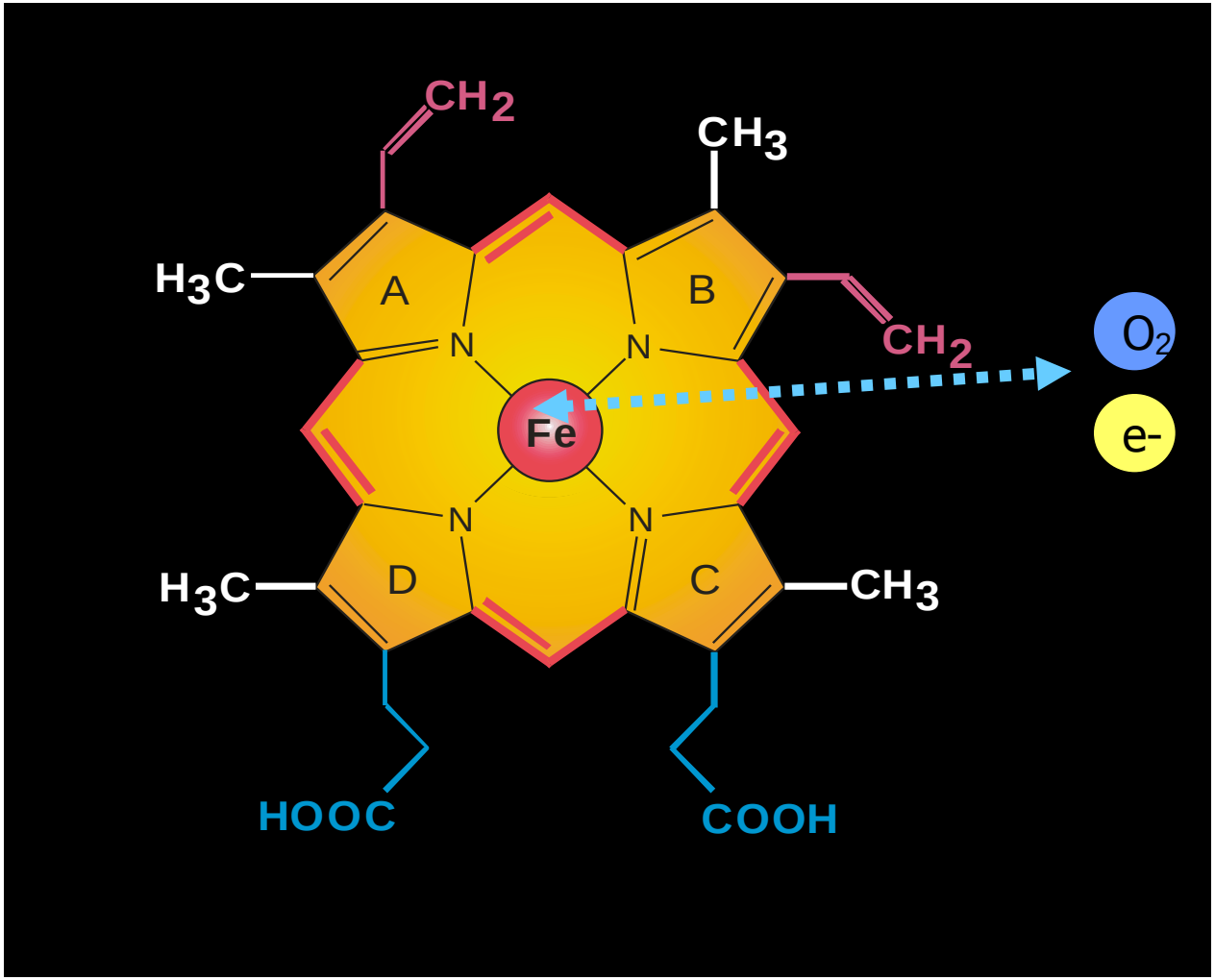
In relation to the enzyme defect along the heme biosynthetic pathway, each type of porphyria is characterized by a specific pattern of overproduction, accumulation and excretion of different heme precursors.

Agenda

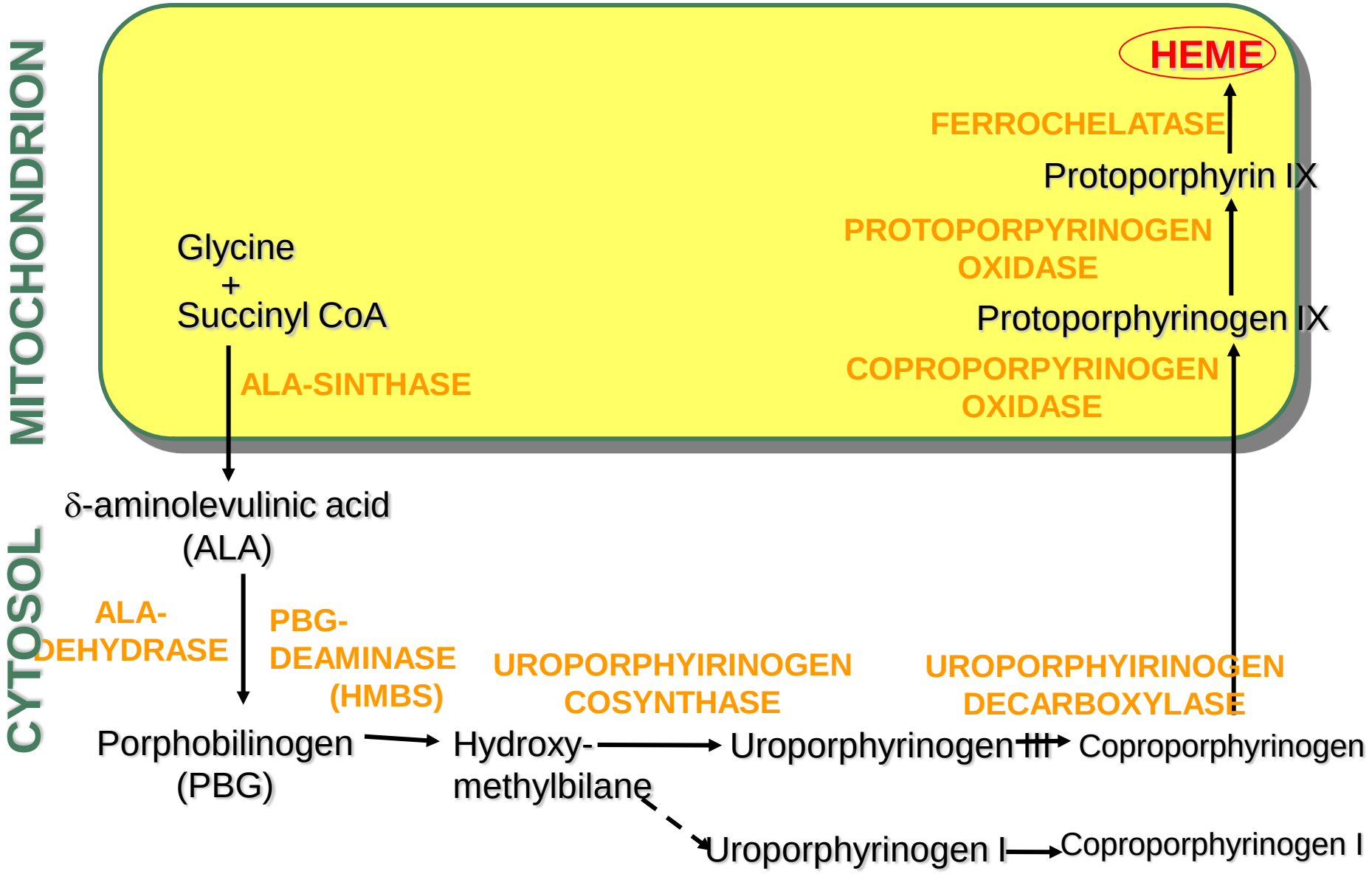
- Physiophatology
- Diagnosis
- Therapy

Heme

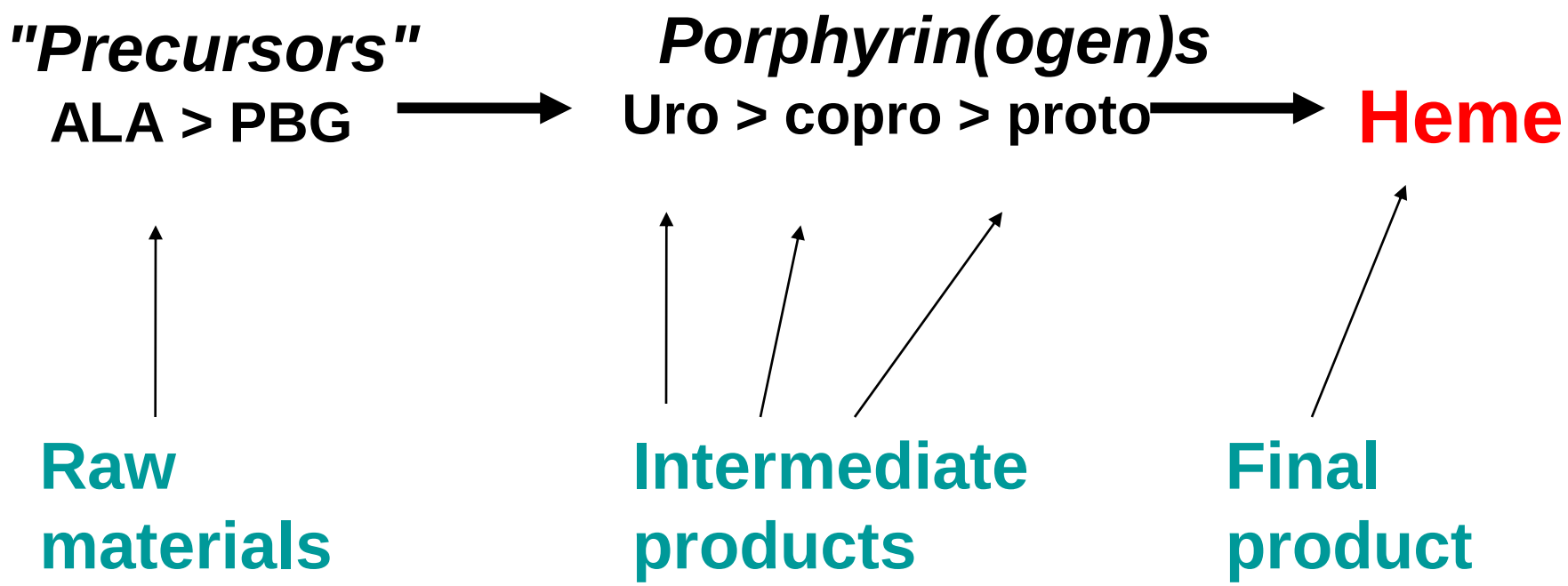
Protoporphyrine IX + Fe^{2+}



The heme biosynthetic pathway



Heme Biosynthesis



ALA : δ Aminolevulinic acid, PBG : Porphobilinogen

Hemoproteins

- $O2_2$ transport and storage **Hemoglobin / Myoglobin**
- Cellular respiratory chain **Cytochromes**
- Hepatic detoxification **Cytochromes P450**
- $H2O2_2$ metabolism **Catalase / peroxydase**
- Fe reduction **Dcytb (duodenal cytochrome b)**
- Tryptophan catabolism **Tryptophan 2,3 dioxigenase**
- Prostaglandins synthesis **Cyclooxigenase**
- ...

Major Heme Functions

- **85%:** **Oxygen transport**
  Hb 98% (Bone Marrow), MyoG 2%
- **15%:** **Oxidation (Liver + all cells)**

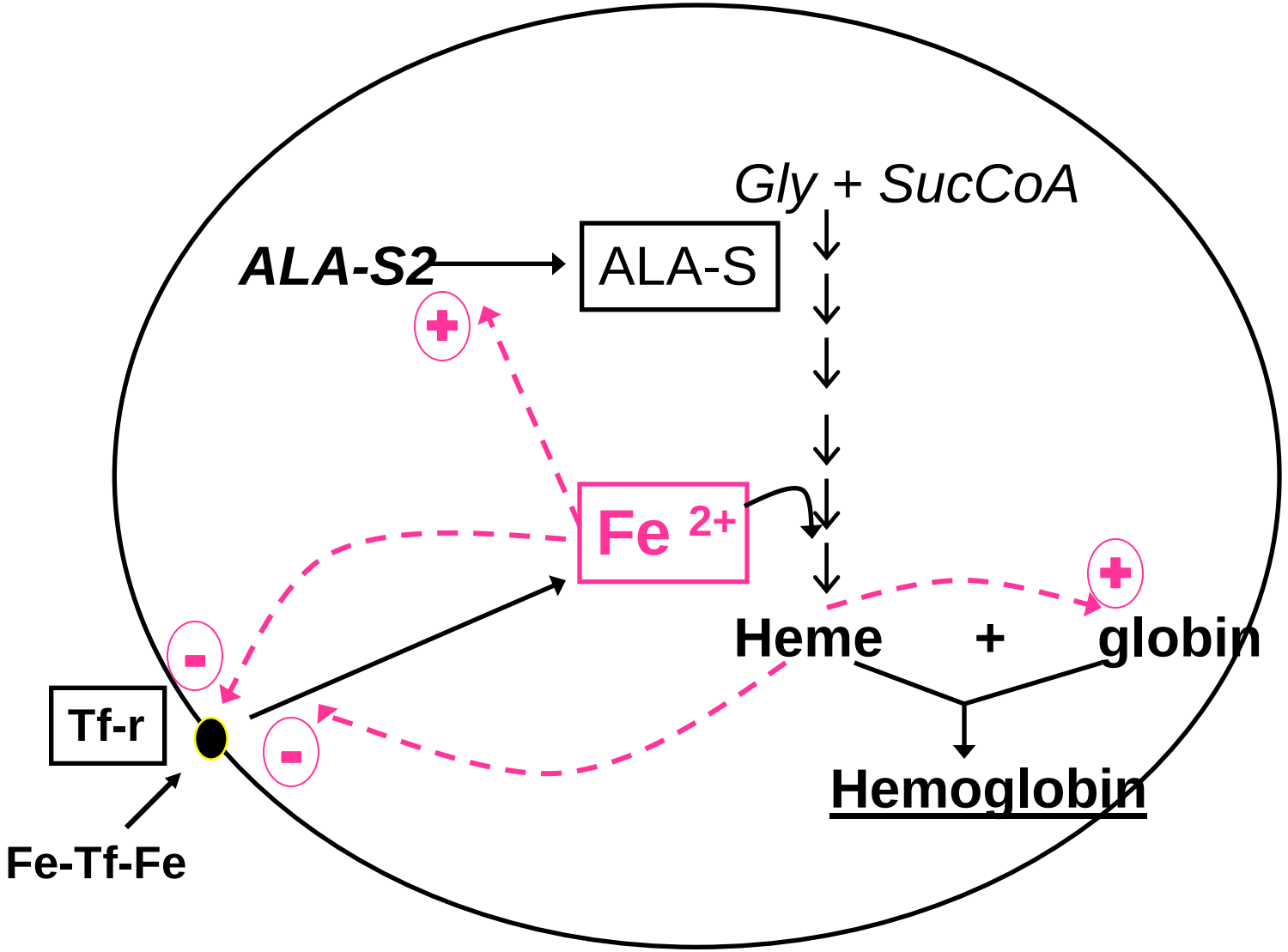
  Non-inducible (Mito cyto & cytosolic b5, 15%)
  Inducible (P450, 65%)

A single biosynthetic pathway that needs two tissue-specific regulations :

BM : continuous massive erythroid production
Liver : rapid, according to local needs

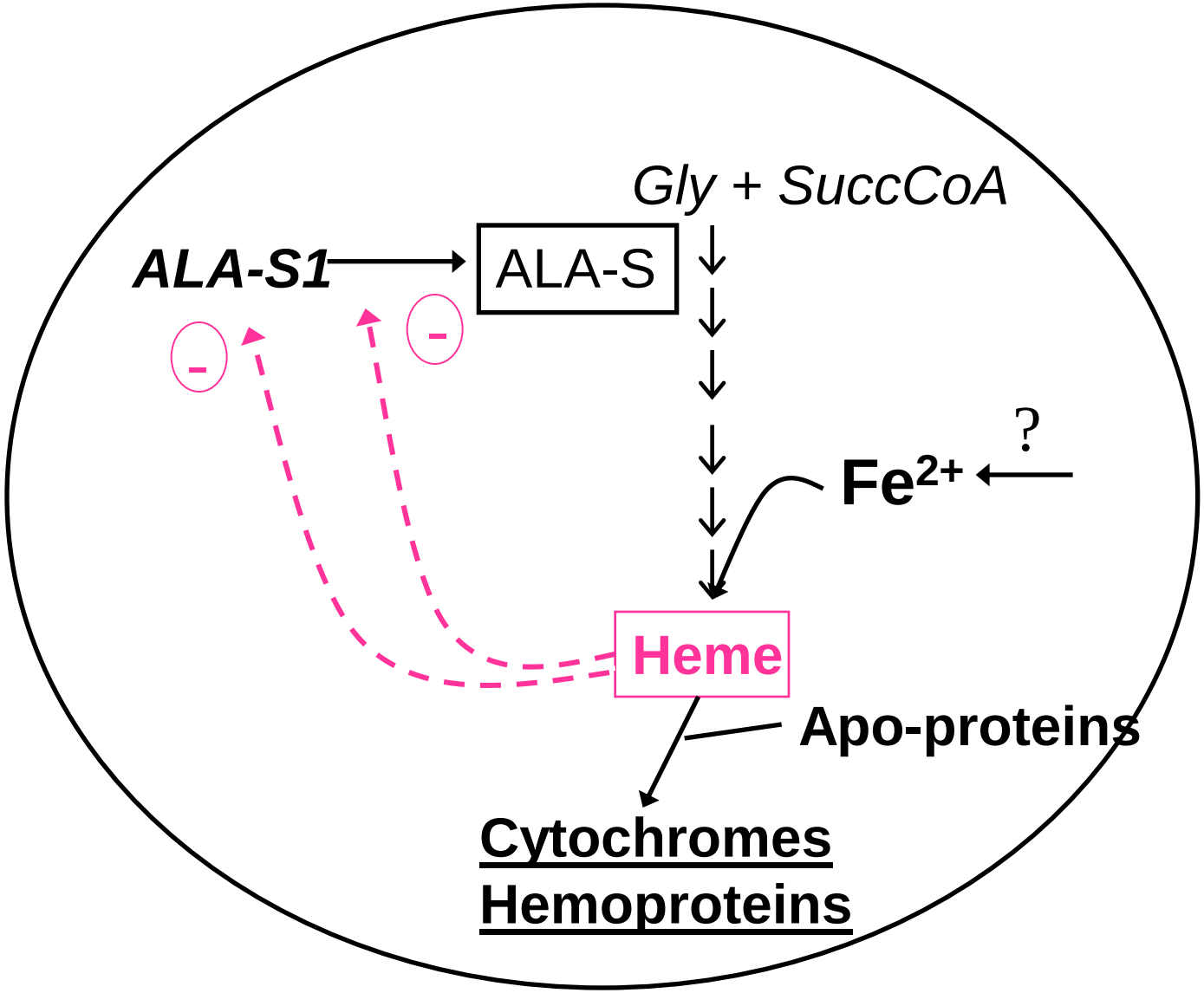
Erythroid Heme Synthesis Regulation

B.Marrow : 85% of body heme production



Hepatic Heme Synthesis Regulation

Liver : 15% of body heme production



Elisa, 26 yrs famale.

• During the last 3 yrs she had several episodes of abdominal pain associated to nausea and vomiting. Tachycardia.
• Five admissions to ER for those symptoms usually controlled by antispastic and analgesic drugs
• One admission to ward: abdominal ultrasound, EGDS, colonscopy, abdominal CT: negatives

Elisa, 26 yrs.

- **Physical Exam:** pt very anxious and painful during the pain crisis. BP 140/90 HR.90-100r. Heart: normal auscultatory findings. No liver or spleen enlargment
- **Physical Exam: :** completely normal out of pain crisis
- **Lab:** hypercholesteremia for which a diet poor of fats and sugar was suggested. Therapy with simvastatin was also suggested

Elisa, 26 yrs.

Physical Exam: pt very anxious and painful during the pain crisis. BP 140/90 HR.90-100r. Heart: normal auscultatory findings. No liver or spleen enlargment

Physical Exam: : completely normal out of pain crisis

Lab: hypercholesteremia for which a diet poor of fats and sugar was suggested. Therapy with simvastatin was also suggested

Francesca, 32 yrs Female

- For 2 yrs repeated episodes of abdominal pain with nausea and vomiting

- 3 admissions at ER for those symptoms usually controlled by antispastic and analgesic drugs

Elisa, 26 yrs.

Physical Exam: pt very anxious and painful during the pain crisis. BP 140/90 HR.90-100r. Heart: normal auscultatory findings. No liver or spleen enlargment

Physical Exam: : completely normal out of pain crisis

Lab: hypercholesteremia for which a diet poor of fats and sugar was suggested. Therapy with simvastatin was also suggested

Francesca, 32 yrs

- **Physical Exam**: Pt painful, anxious and aggressive Murphy: positive
- **Abdominal ultrasound**: micro-galstones . No liver and spleen enlargement

Elisa, 26 yrs.

• **Conclusions**:no organic disease; pt under stress

It was suggested to consult a psychiatricien

Francesca, 32 yrs

• **Conclusions:** Galstones. Colecystectomy is advisable

Elisa, 26 yrs.

•May 2010 : she started therapy with diazepam.

• End of july:abdominal pain, confusion, respiratory insufficiency. Urgent admission to ER

Francesca, 32 yrs

• March 2010 : colecystectomy

• At the end of surgery: acute respiratory insufficiency
• Urgent admission to ER

Accadde qualcosa,qualcosa che si sarebbe potuto evitare, e Paula subì un grave danno cerebrale. Non servirebbe a nulla adesso andare a verificare come successe o attribuire colpe, è sufficiente dire che, con un po' di fortuna, oggi mia figlia sarebbe viva……

da.: Per Paula lettere dal mondo

Isabelle Allende

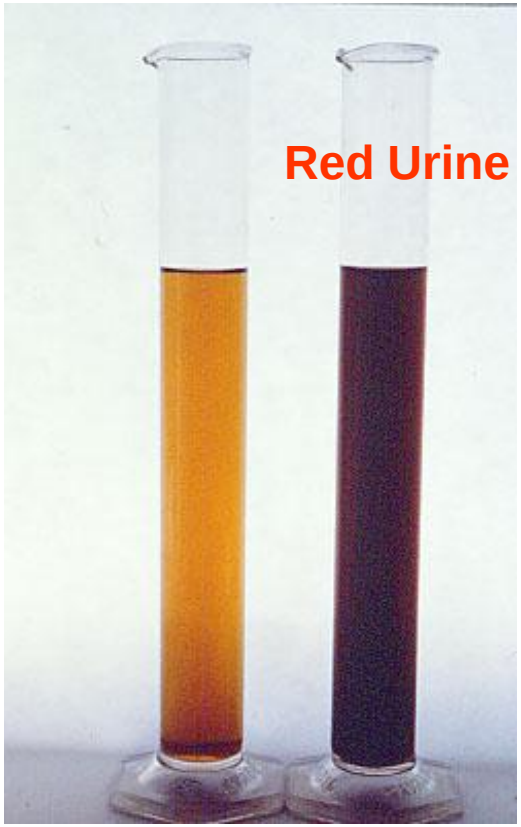
Human Porphyrias

“Obscure diseases with confusing names considered only when the need for a diagnosis is desperate”

(Antony McDonagh, 1997)

What to do?

- Think of possible Porphyria attacks
- Collect accurate informations
- Look at the urines



Acute Intermittent Porphyria

- Ala: 44 mg/L (0-2)
- PBG: 138 mg/l (0-2)

- Total Urine Porphyrines :
  2864 mcg/L (<150)
(uro56%;copro 27%)

- PBGD: 74.80 (72.8-179.6);

- Molecular defect
c.913-1 G>C in HMBS

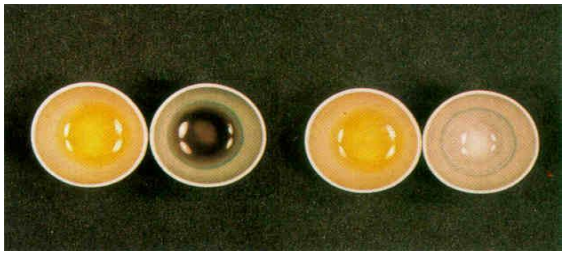
Acute Intermittent Porphyria

- Ala 23.1 mg/L (0-2)
- PBG 44.4 mg/l (0-2)

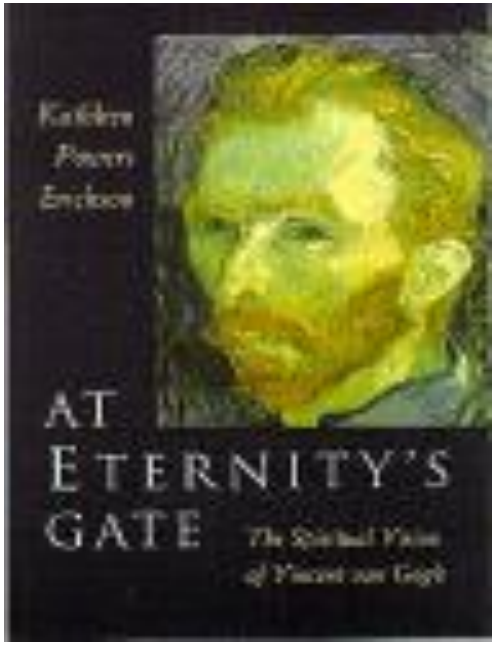
- Total urine Porphyrines:
 488 (v.n. <150)
(uro 49%;copro 47%)

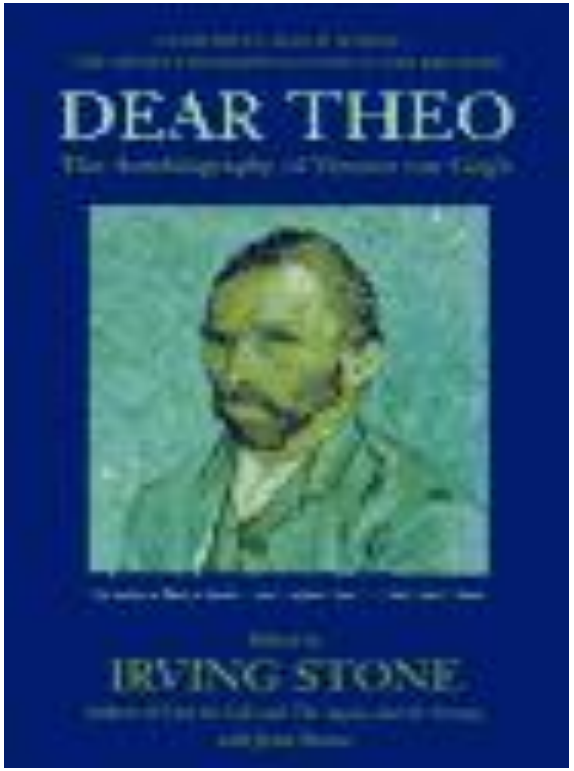
- PBGD 57.3 (72.8-179.6);

- Molecular defect
c.499-?_1086+?del exons10-15 in HMBS

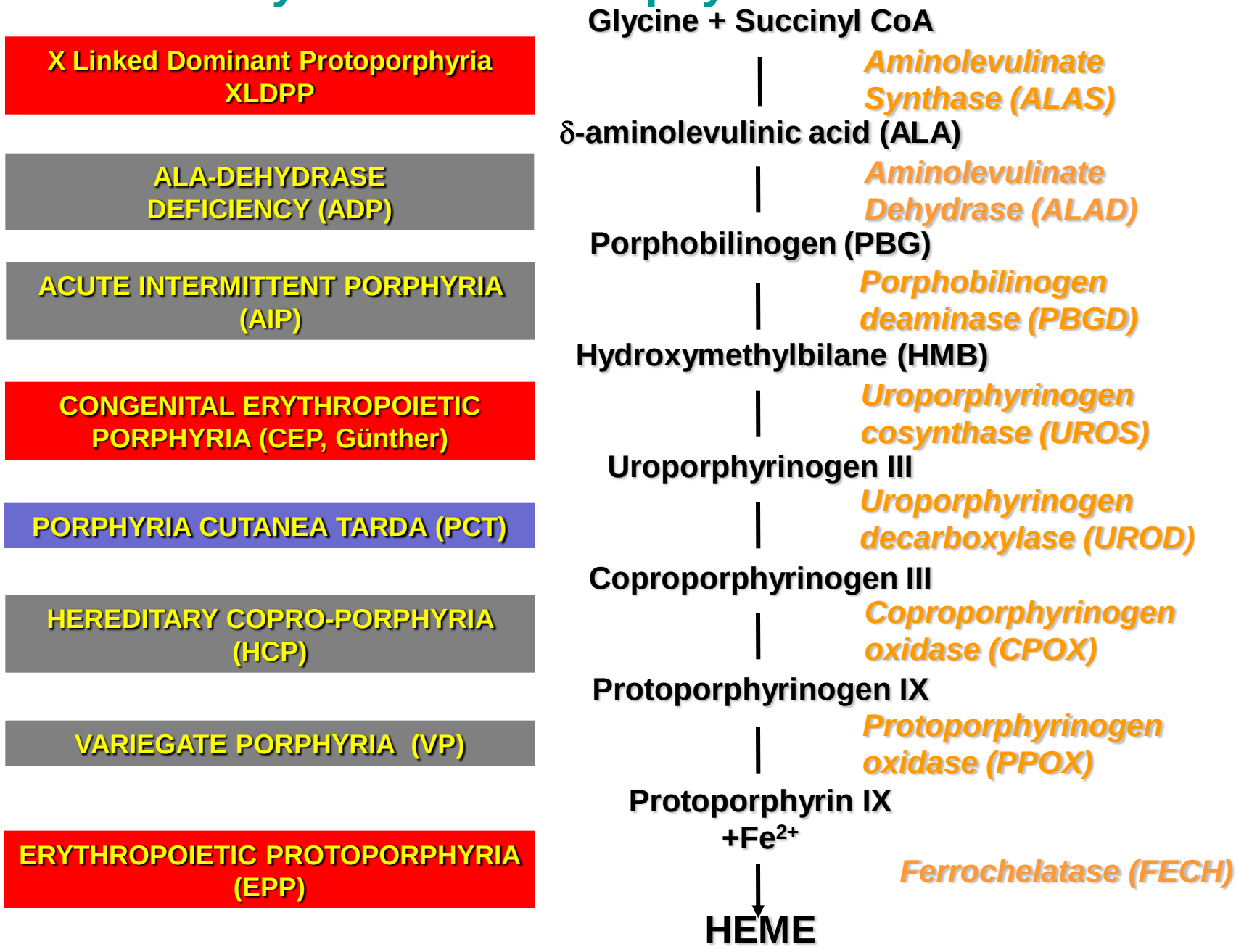


Sir George Backer,
18th October 1788





Heme biosynthesis and Porphyrias



Human Porphyrias:

…from greek « porphyros » : red pigment

- **7 rare genetic diseases (~1/75 000) Due to a partial deficiency in one of the enzymes of the heme biosynthetic pathway caused by specific gene mutations**
- **+ 1 "EPP like" (XLDPP) due to gain of function mutations in ALAS2 gene**
- **Abnormal accumulation and excretion of porphyrins and precursors (urine, faeces, blood, organs…)**
- **Acute neurovisceral attacks and/or skin lesions**
- **Pathophysiology largely unknown +++ *: "Why patients are patients ?"***

THE PORPHYRIAS

- The porphyrias are classified in acute or chronic on the basis of clinical manifestations or in erythropoietic or hepatic depending on the site of expression of the enzyme defect.

Classification

- ***Hepatic* porphyrias (AD, adult)**
  - **Acute Intermittent Porphyria, AIP**
  - **Hereditary Coproporphyria, HC**
  - **Variegate Porphyria, VP**
  - **Porphyria cutanea, PCT**

Acute

- ***Erythropoietic* porphyrias (AR, child)**
  - **Congenital Erythropoietic Porphyria, CEP**
  - **Erythropoietic Protoporphyria, EPP**
  - **X linked Erythropoietic protoporphyria, XLDPP**

Acute Hepatic Porphyrias

Acute Porphyric Attack :
Incidence of Symptoms

- **Abdominal and back pain** **99 %**
- **Muscle weakness** **90**
- **Vomiting, constipation** **72**
- **Tachycardia** **62**
- **Insomnia, anxiety, agitation** **60**
- **Hypertension** **45**
- **Convulsions** **15**
- **Paralysis** **10**
- ***Colored/red urines*** ***90***

Acute Neurovisceral Attack :

General Clinical Features

- **Women (80 %), men (20 %)**
- **Mean age 20-45, rare before puberty**
- **Severe abdominal pain +++**
- **Risk of neuropathy (paralysis)**
- **Precipitating factors (hormones, fasting, infection, drugs, alcohol, stress...)**

Neuropathy in acute attacks

Autonomic

Abdominal pain

Constipation

Vomiting

Hypertension

Tachycardia

Peripheral

Motor neuropathy

Extremity pain

CNS

Anxiety

Hallucinations

Agitation

Epilepsy

Acute porphyrias: neurological manifestations

- The abdominal and cardiovascular symptoms have been ascribed to an autonomic neuropathy

- A severe attack may progress to peripheral neuropathy which may resemble a Guillain-Barré syndrome

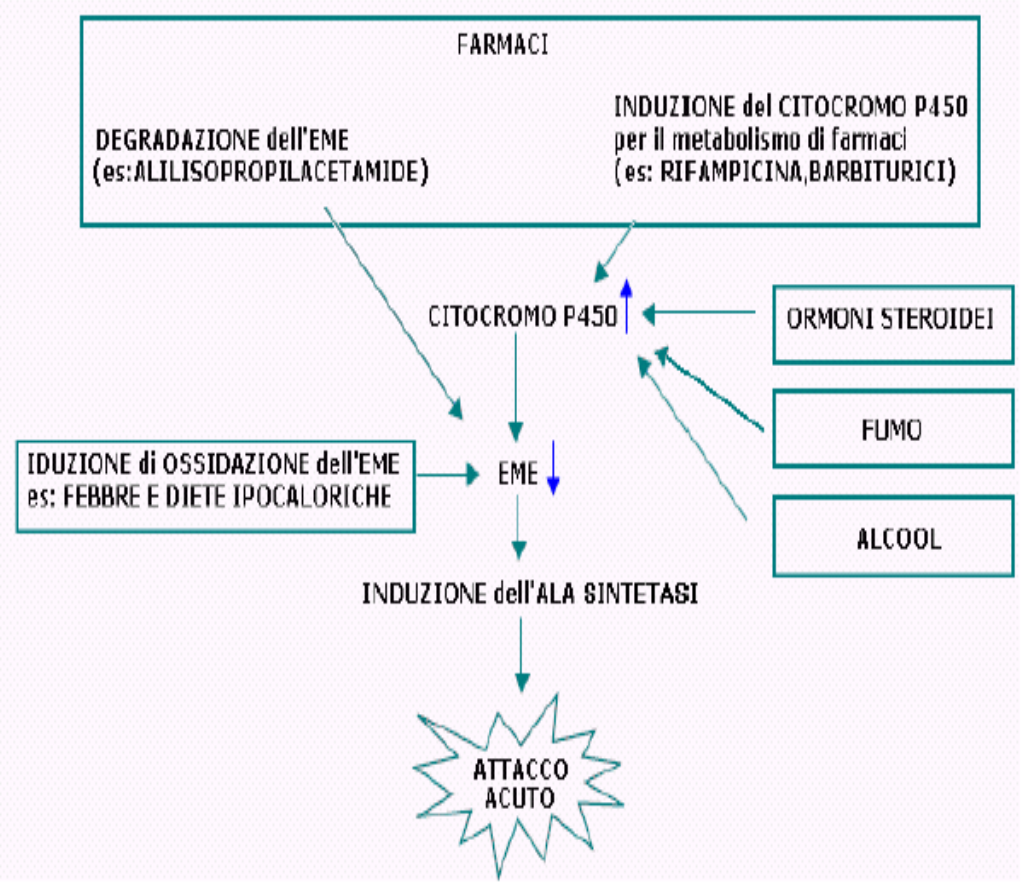
- The neuropathy is predominantly motor

Hypotheses of the pathogenesis of nervous system dysfunction in acute porphyrias

1. ALA, PBG or porphyrins overproduced and accumulating in liver or nervous system are neurotoxic
2. A relative heme deficiency in the liver and/or nervous system leads to decreased hemeprotein function in neural tissues
3. Abnormal products derived from ALA or PBG are neurotoxic (free radicals, hydroxyhemopyrroline, porphobilin)
4. Depletion of essential substrates or cofactors resulting from the disturbance of heme synthesis cause the symptoms (depletion of pyridoxal phosphate, zinc or glycine)

Trigger factors in acute porphyrias

- Drugs
- Estrogens
- Oral contraceptives
- Pregnancy
- Menses
- Alchol
- Smoke (?)
- Infections
- Stress
- Hypocaloric intake



Biological diagnosis

Symptomatic Patient

- ALA, ***PBG*** in urine : 10 to 50 X N

  → **Acute attack of hepatic porphyria**

  Sensibility and specificity: 100%

- ALA, PBG & porphyrins in urine, faeces and plasma

  → **Type of acute hepatic porphyria**

  → **orientation for enzymatic diagnosis**

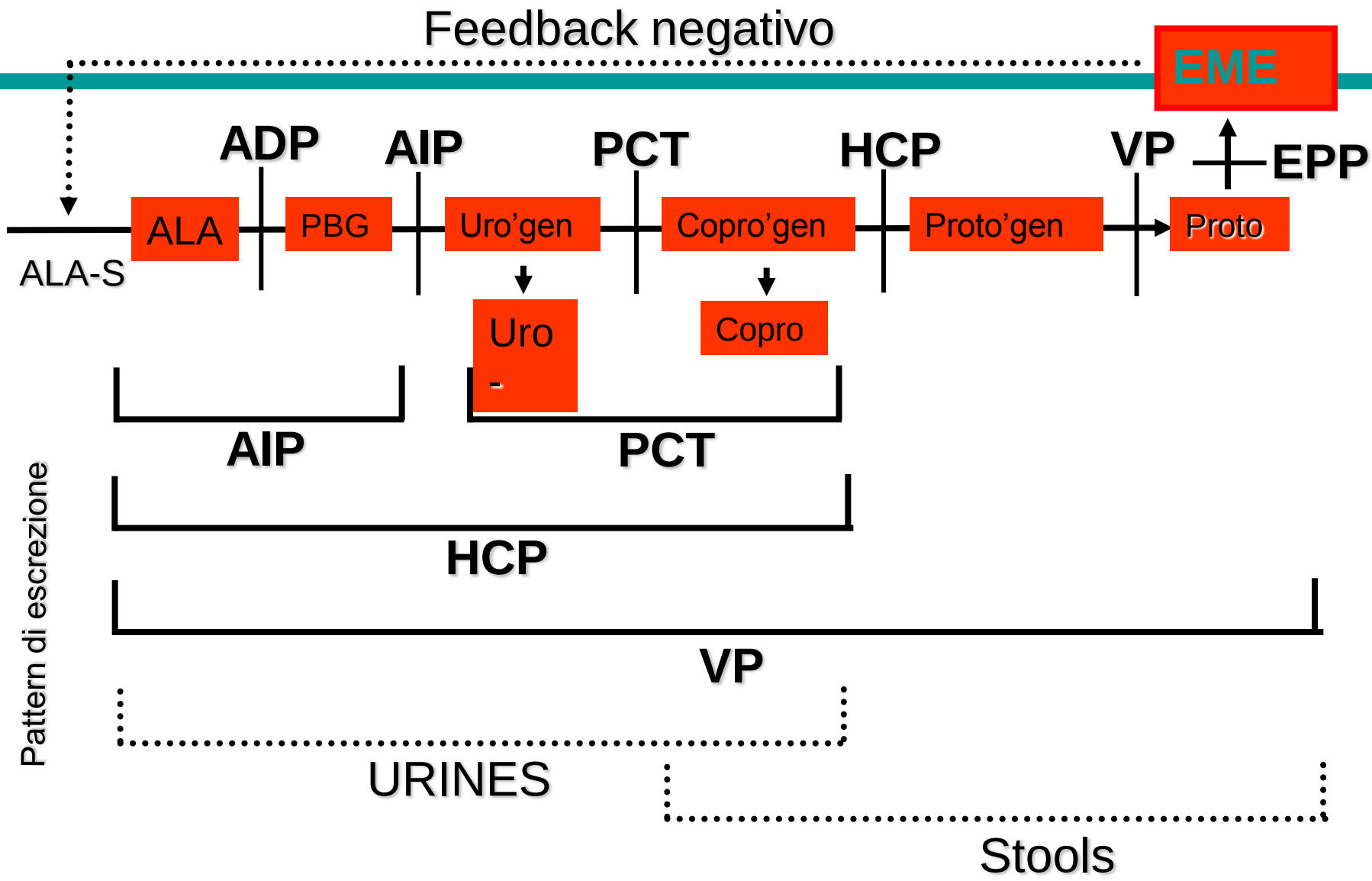
Specific Biochemical Condition in Acute Porphyric Attacks

- **Markedly increased activity of ALA synthase In the liver**

- **Increased production, accumulation and excretion of ALA and PBG**

- **Specific porphyrin excretion profile depending on the location of the enzymatic defect**

Pattern of precursors excretion



Diagnosis : Clinical and Biochemical

Tipo di Malattia	Manifestaz. Cutanee	ALA / PBG Urine	Porfirine Urinarie	Porfirine Fecali	Altro
Porfiria Acuta Intermittente	Assenti	↑↑ (PBG>ALA) (valori più alti dur. gli attacchi)	↑↑ (uro e copro) (overt AIP)	Normali	
Coproporfiria Ereditaria	Les. bollose dur. attacco acuto – fragilità cute (30% pts)	↑↑ (PBG>ALA) (valori più alti dur. gli attacchi)	↑↑ (uro e copro)	↑↑ (copro >> proto)	
Porfiria Variegata	Les. bollose dur. attacco acuto (20-30% pts.)	↑↑ (PBG>ALA) (solo dur. attacco)	↑↑ (prev. copro)	↑↑ (proto > copro)	Fluorescenza plasma (626-628 nm)
Porfiria da def. di Ala-D (Doss' Porphyria)	Assenti	↑↑ solo ALA	↑↑ (copro)	Normali	
Plumboporfiria (Intossicazione da Piombo)	Assenti	↑↑ solo ALA	↑↑ (copro)	Normali	Esposiz. Piombo (incidentale, professionale) Anemia ↑↑Piombemia e piomburia

Genetics and epidemiology of Acute Hepatic Porphyrias

- **Autosomal dominant**
- **Low penetrance (1-5%)**
- **Prevalence : 1/100 000 ?**
- **Mutated gene (AIP) : 1/1600**
- **Molecular defect : wide allelic heterogeneity**
- **Low rate of *de novo* mutation (3%)**
- **No phenotype – genotype relationship**
- ***Incidence (EU countries, EPNET 2010) :***

0.12 new case/10^6/year

Molecolar Diagnosis

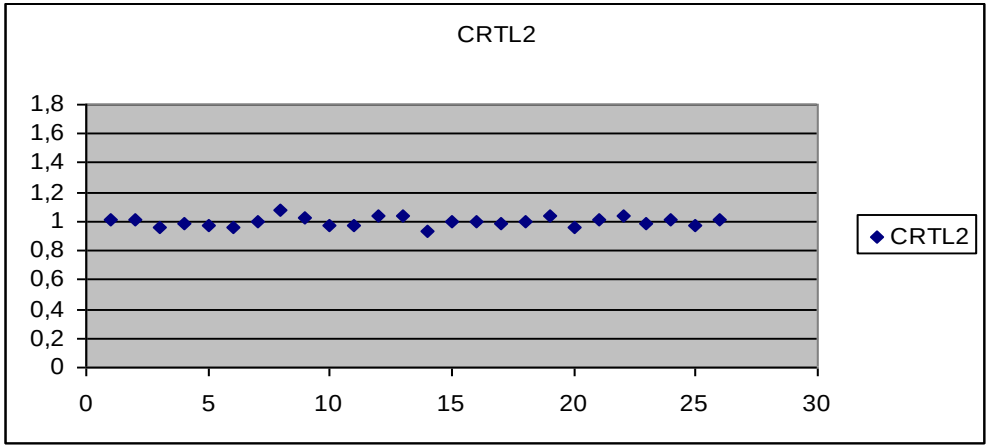
Single mutations:

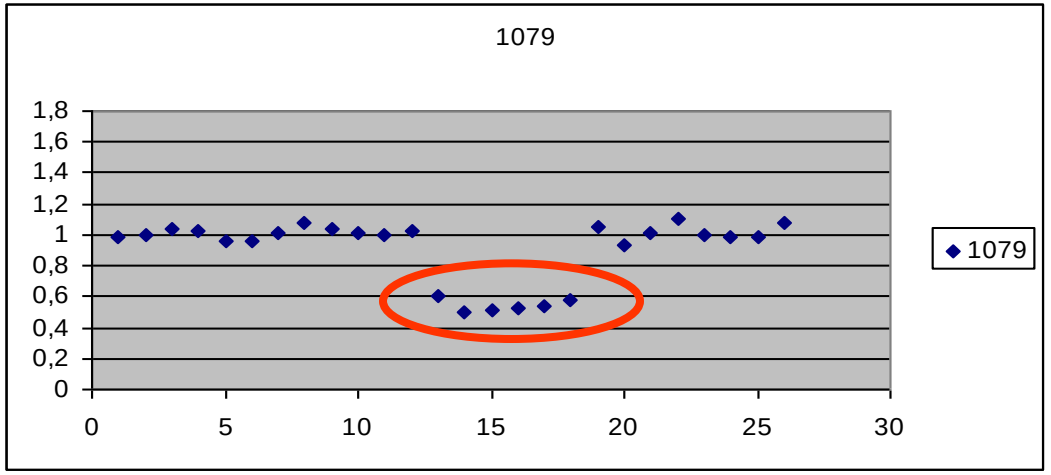
Missense	***RFLP***
Non-sense	***RFLP***
Splicing	***RFLP, RNA***
RNA regulatory sites	***RFLP***
Functional analysis	***(EMSA, transfection…)***

Small Insertions/Deletions: ***PAGE***

Long Insertions/Deletions **: MLPA**

MLPA (multiplex ligation-dependent probe amplification)





Management of an acute porphyric attack

- Admission to hospital
- Withdrawal of all common precipitants (drugs, alcohol, fasting, infection...)
- Opiates and chlorpromazine
- Carbohydrates (200-300 g/day)
- Early Normosang® (human hemin) infusion (5 mg/kg/24 hours x 4 days)

Normosang® in Acute Attacks

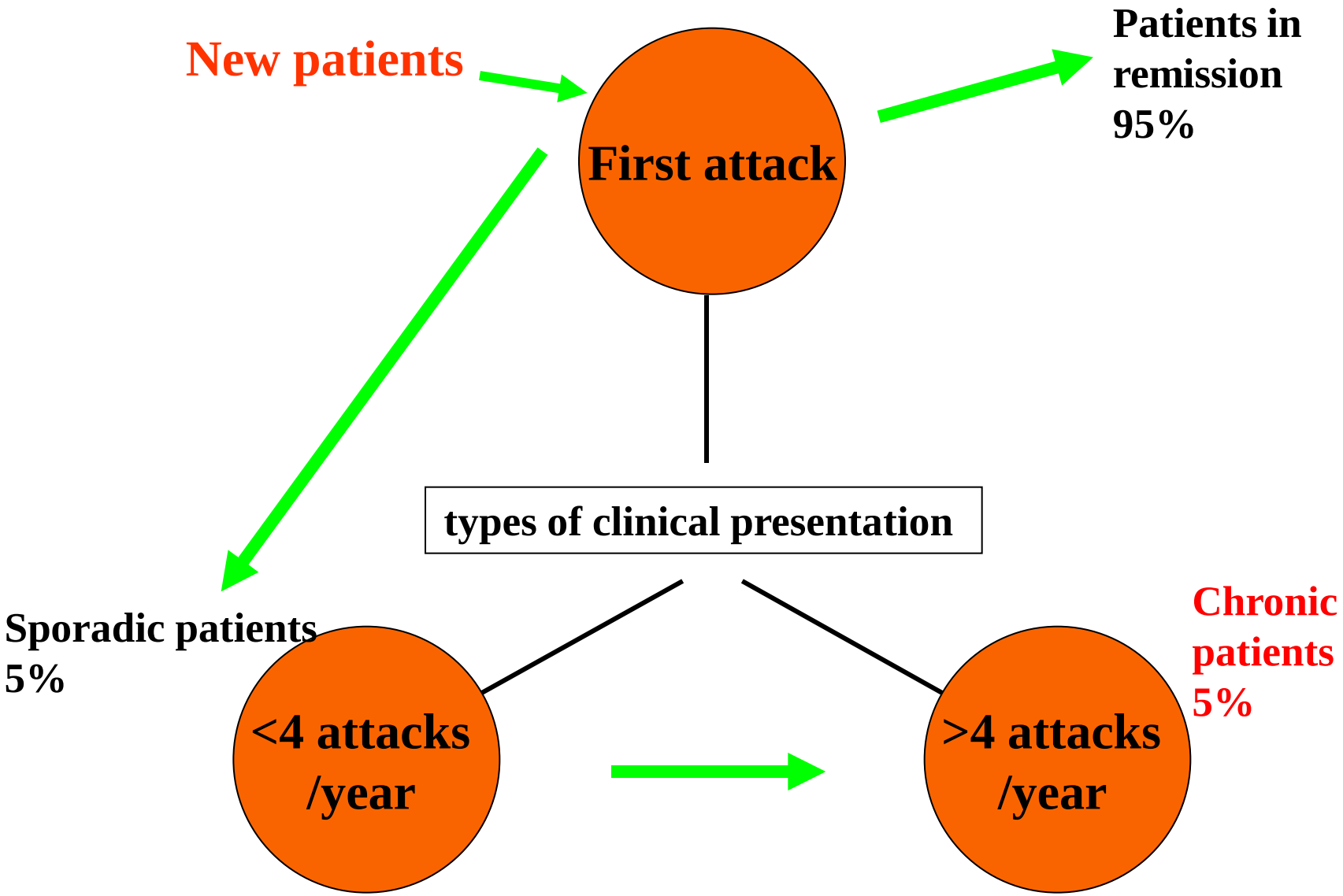
Rapid clinical improvement

- **Mean abdominal pain duration** **2-3 d**
- **Decreased urinary ALA/PBG** **2-3 d**
- **Hospital duration** **< 5 d**
- **No further neurological complications**
- **No major side effects**
- **No known risk during pregnancy**

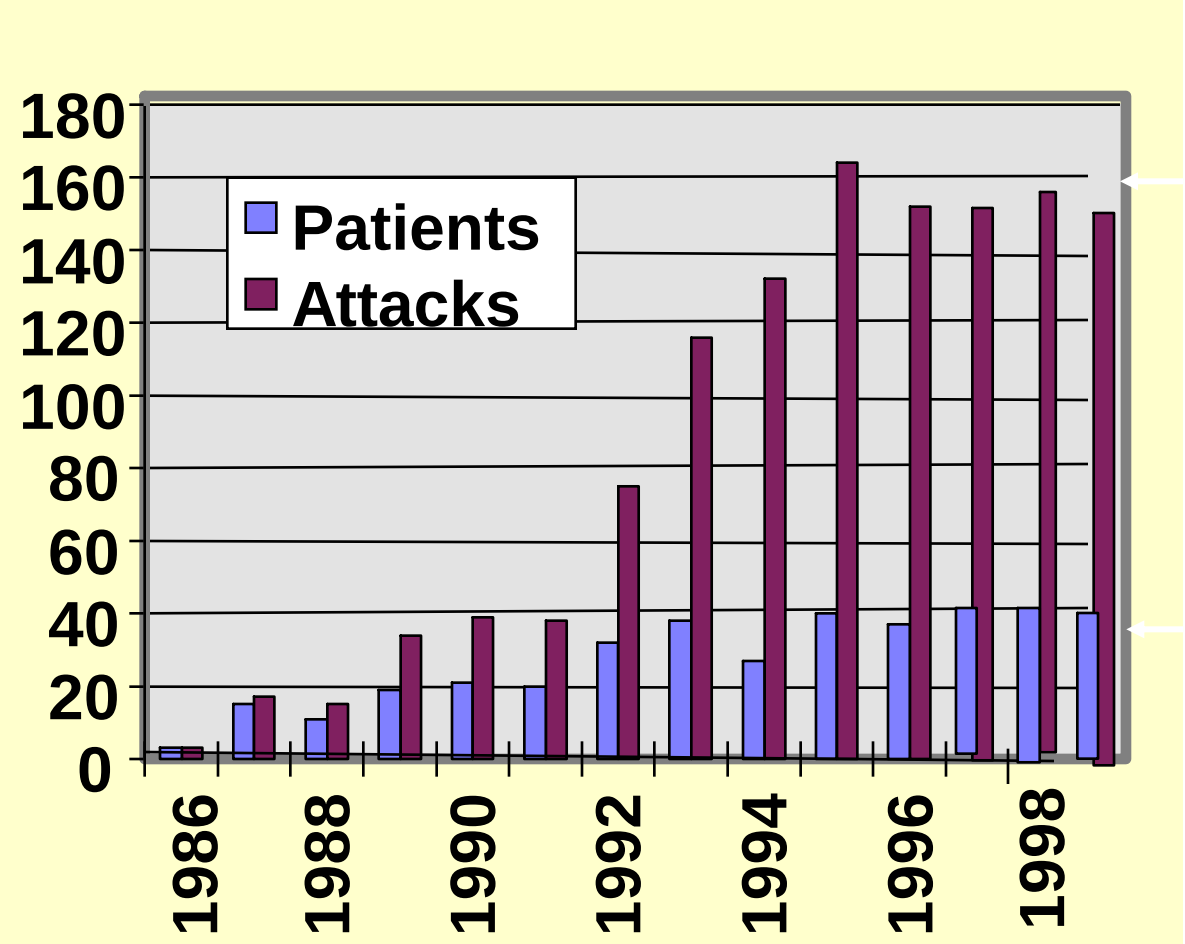
Albumin protocol

- **10 ml *Normosang*® diluted in 100ml of albumin 4% or 20%**
- **Slow 30 minute perfusion**
- **Flush through 4 x 10ml physiological saline using a syringe**
- **Use remaining solution in normal perfusion (85ml)**

Acute Hepatic Porphyria: *natural history*



Recurrent attacks



654 recurrent attacks in only 25 patients *(AIP)*

Courtesy JC Deybach

AIP associated chronic manifestations

- **Reccurent acute attacks (5-8%)**
- **Chronic renal failure (35 %)**

  Progressive tubulo interstitial nephropathy
- **Hepato-Cellular Carcinoma (1%)**

  Risk factor X 36

Biological data from AIP patients with recurrent attacks

- **Different type of PBG-D gene mutations**
- **No viral infection (HIV, HBV, HCV)**
- ***High cumulative dose of iron (up to 25g)***
- **Ferritin > 1000 in some of them**

New therapeutic strategies in AHP

- **Enzyme replacement therapy in AIP:**

  Porphozyme® (human recombinant PBG Deaminase) ➡ clinical trial in France, Denmark, Sweden, Finland and the US (2005-2006)

  negative results ➡ rhPBGD was not targeted to the liver

- **Liver transplantation :**

  10 patients (8 AIP, 2 VP)

  ➡*Pathophysiology* : AHP = metabolic liver diseases ?

Prophylactic Measures

Precipating Factors

- **Specific Gene defect**
  - ➡**Family screening**
- **Endogenous Hormones**
  - ➡**LHRH agonists**
- **Drugs**
  - ➡**Data bank on drug porphyrogenicity**
- **Nutrition**
  - ➡**Glucose effect**
- **Stress**
  - ➡**?**

Family Screening : Presymptomatic Patients detection

to minimize risk of acute attack

- Specific heme synthesis enzyme defect:

  → ***porphyria reference lab***

  → ***probabilistic approach***

  Specificity ~ 90% Sensitivity ~ 80%

- DNA analysis : Molecular diagnosis

  → identification of specific family mutation (wide allelic heterogeneity)

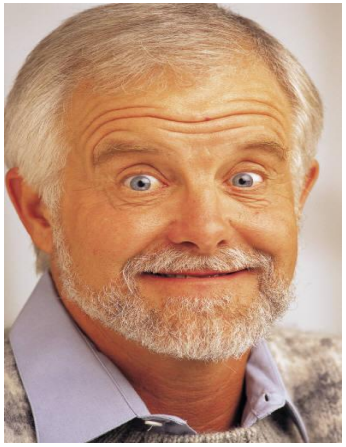
  → identification of presymptomatic carriers in patient family *(certitude)*

Drugs & AIP

- Many drugs and chemicals have the potential to induce Cytochrome P450 enzyme complex which consume haem
- Drugs may also directly induce ALAS
- Both result in acute attacks of AIP
- Both patients and physicians must have lists or access to drug databases :
  - **www.drugs-porphyria.org**

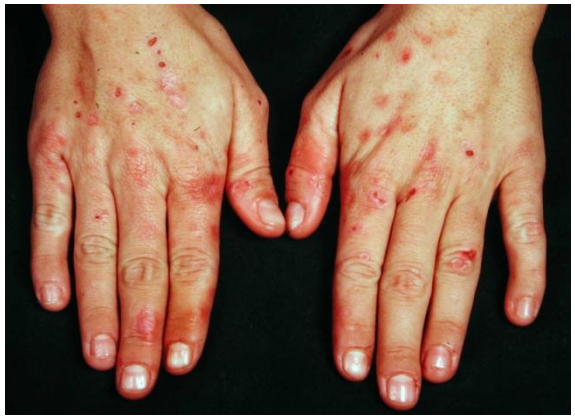
Take home message

- Differential diagnosis in case of abdominal pain “sine materia” in young women
- Collect careful information (anamnesis)
- Look at the urine color
- Do not give drugs without urgent need
- Wait and see before any surgery



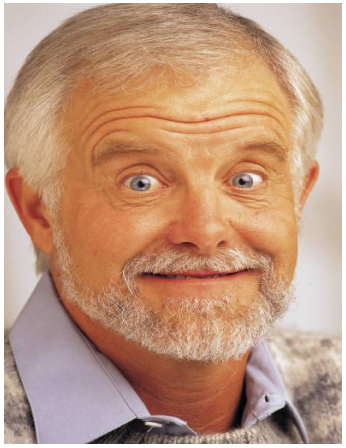
Luigi, 56 yrs, male.

- Car's industry worker
- 3 glasses of wine/d, no diet restriction
- Apparently good health since 1 year back
- Since 1 yr, fatigue, malaise
- Since 2 months apparence of skin lesions



Luigi, 56 yrs.

- **Physical exam:** bollous skin lesions on exposed body areas
- **Liver:** enlarged (2 cm)
- **Lab:** Hb: 13.5g/dl
  ALT 52. AST 76
  GammaGT 65
  FA 182
  HCV : positive
  Ferritin: 850

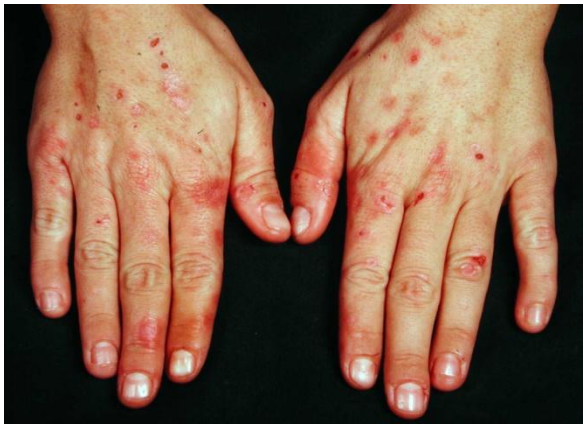


Luigi, 56 yrs.
Physical exam: bollous skin lesions on exposed body areas
Liver: enlarged (2 cm)
No spleen enlargment
Lab: Hb: 13.5g/dl
ALT 52. AST 76
GammaGT 65
AF 182
HCV : positive
Ferritin: 850

Davide, 37 yrs,male.

- Teacher
- Normal life; no abuse
- Since 4 yrs photo-sensitivity after sun exposure (rubor, brusing,pain)

- Since 3 yrs occasional abnormalities of AF and gammaGt;hepatomegaly)



Luigi, 56 yrs.
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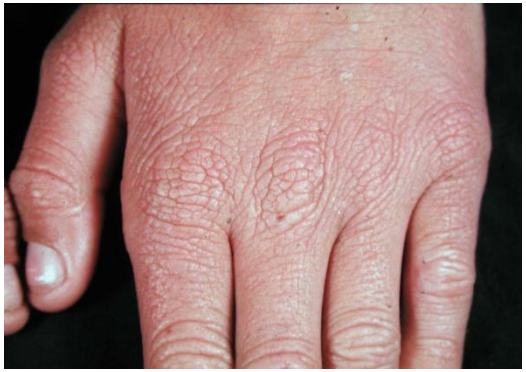
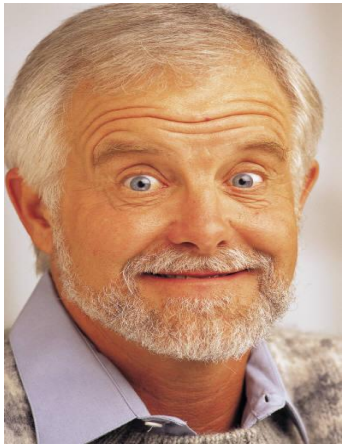


Davide, 37 yrs.

• **Physical Exam**:eritema, edema, rubor
• liver:enlarged (2 cm). No splenomegaly
•**Lab:**Hb: 12.5g/dl
ALT 47 AST 51
GammaGT: 95
AF:325
Ferritin:125ug/L

Porphyria Cutanea Tarda



- Pick: 620 nm positive
- Fluorocytes 0.2%
- Ala: 4.8 mg/L (0-2)
- PBG: 0.6 mg/l (0-2)

- Total urine Porphyrines: **5347mcg/L (<150)** (uro64%;epta28%;copro 2%)
Porfirine fecali totali 299 (<8) (epta 47%; iso-copro 7%)

- Molecular defect: **c.815 T>C in UROD**

Erythropoietic Protoporphyria

- Pick: **632nm positivo**
- Fluorocytes **78.22%**
- ALA 2.2 (v.n. 0-2)
- PBG 2.1 (v.n. 0-2)

- Total urine porphyrines: 71 (v.n. <150) (uro 16%;copro 61%);
Fecal Porphyrines 63 (<8) (proto 73%; copro 7%)

- MOlecular defect **c.215dupT in FECH in trans Aplotype GTC**

Heme biosynthesis and Porphyrias

X Linked Dominant Protoporphyria XLDPP

ALA-DEHYDRASE DEFICIENCY (ADP)

ACUTE INTERMITTENT PORPHYRIA (AIP)

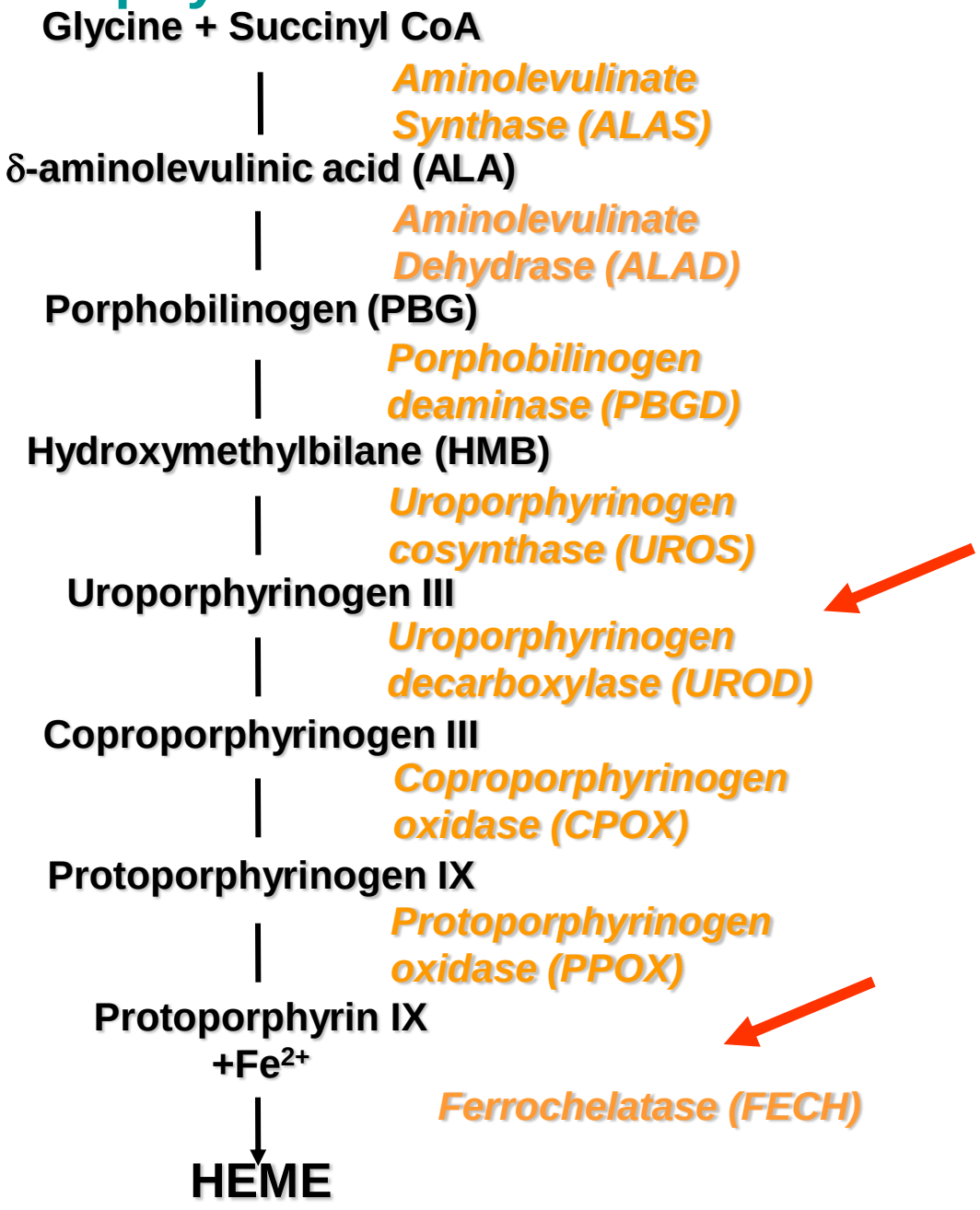
CONGENITAL ERYTHROPOIETIC PORPHYRIA (CEP, Günther)

PORPHYRIA CUTANEA TARDA (PCT)

HEREDITARY COPRO-PORPHYRIA (HCP)

VARIEGATE PORPHYRIA (VP)

ERYTHROPOIETIC PROTOPORPHYRIA (EPP)



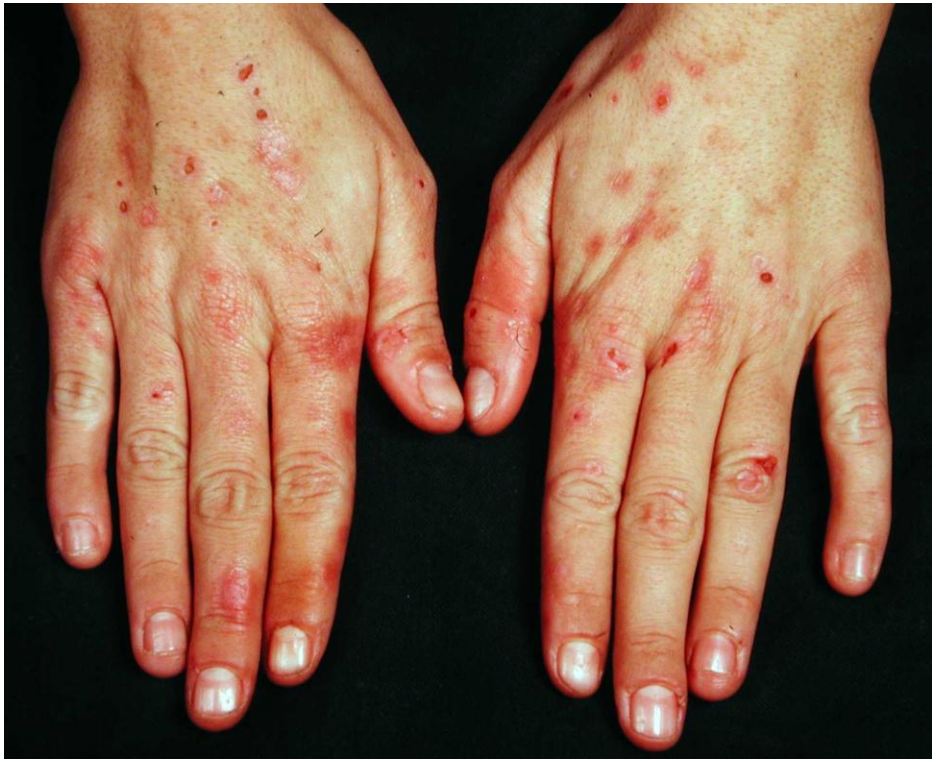
Diagnosis of Chronic Porphyrias

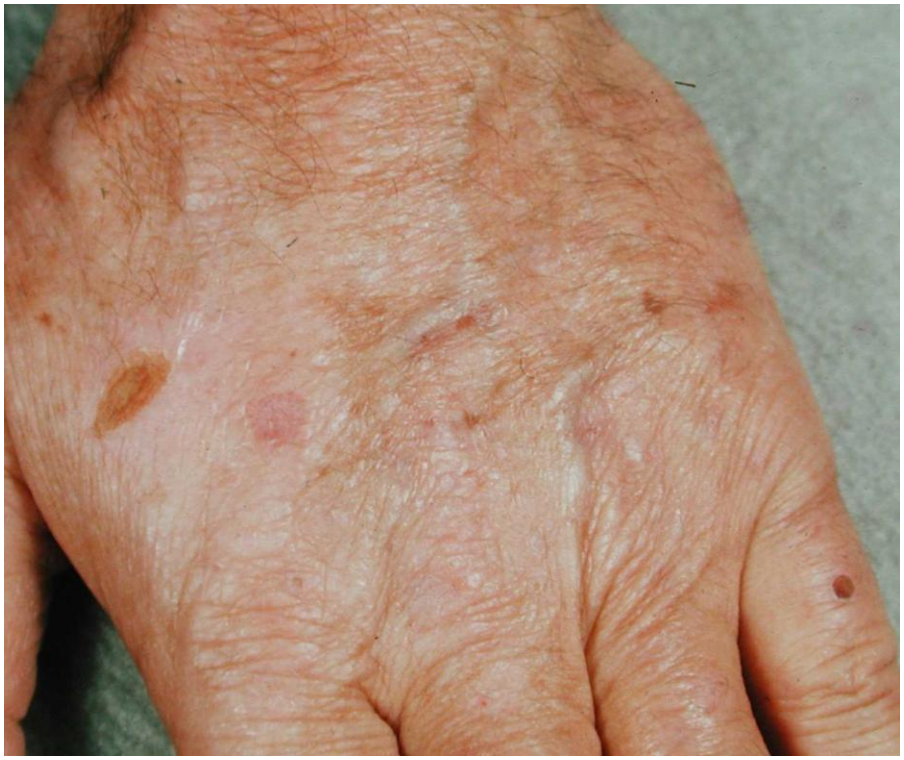
- Examine properly the skin lesions
- Accurate informations
- Measurement ot total urine porphyrines
- Plasma pick at different lenght waives
- Fluorocytes
- Molecular analysis

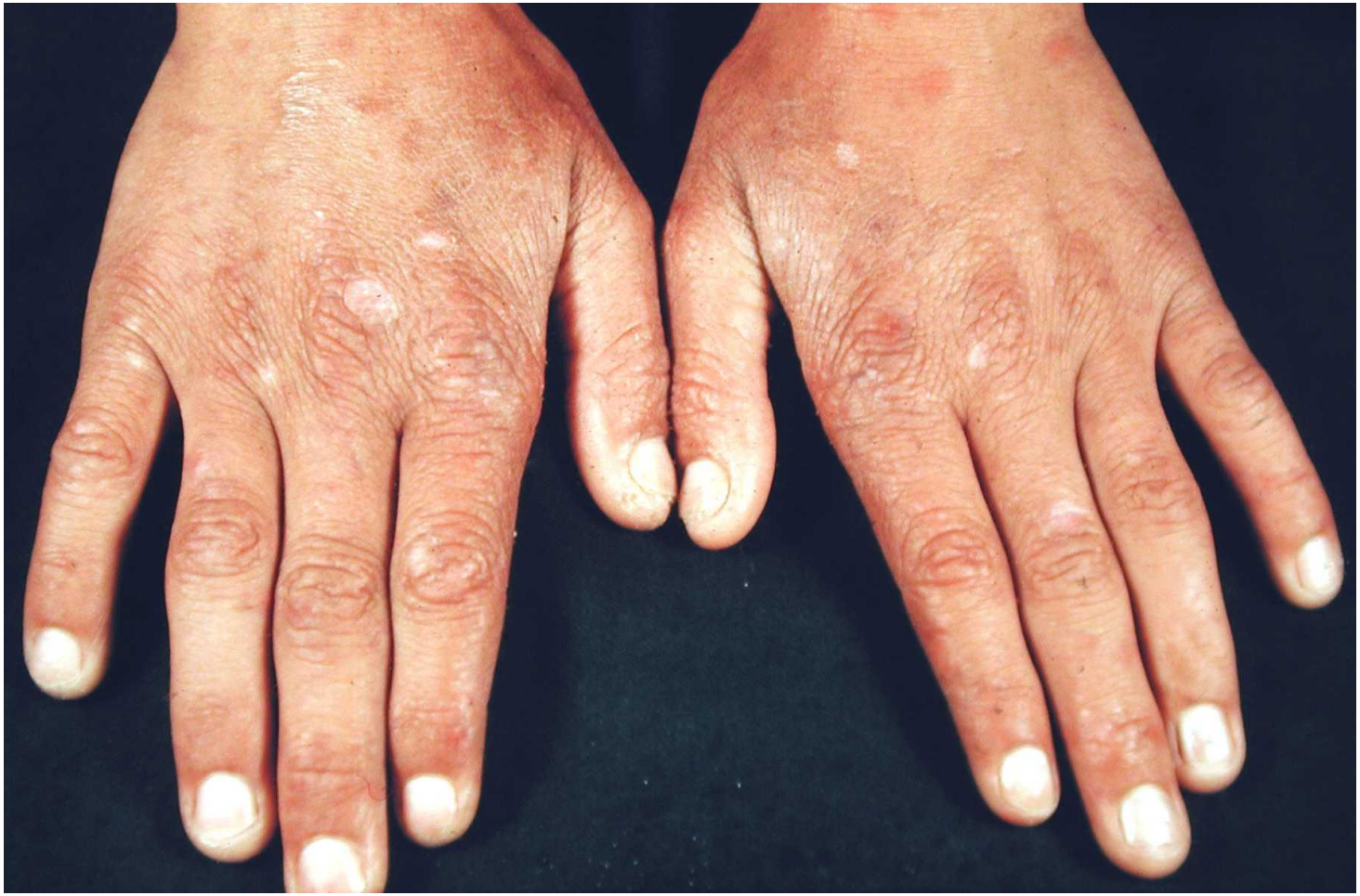
Classification of Porphyria Cutanea Tarda

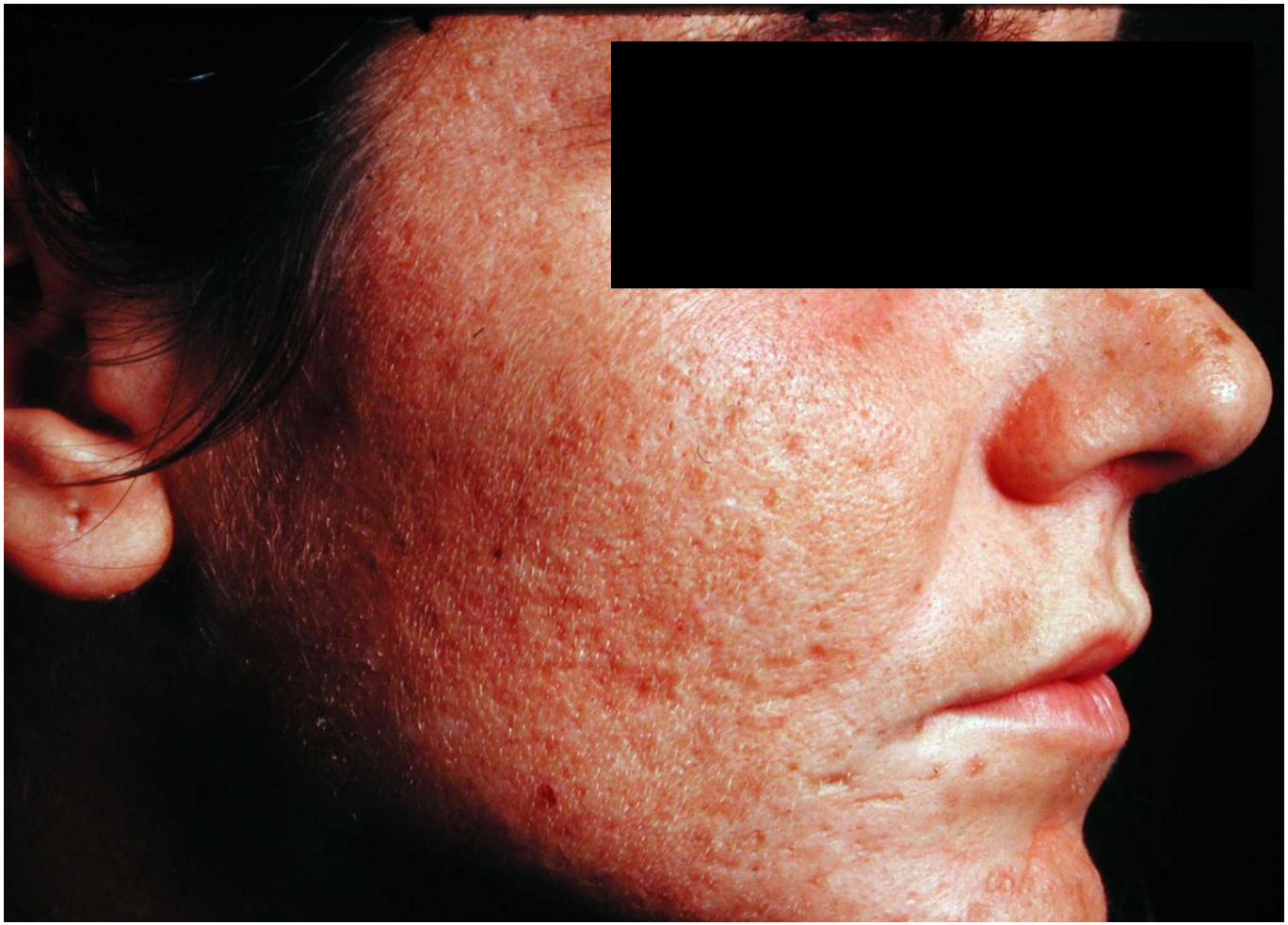
Type	Familial Occurrence	Mode of inheritance	URO-D activity	
			Erythrocytes	Liver
I	**no**	**Not inherited**	**Normal**	**Decreased**
II	**yes**	**Autosomal dominant**	**Decreased**	**Decreased**
III	**yes**	**Autosomal dominant**	**Normal**	**Decreased**

Porphyria Cutanea Tarda



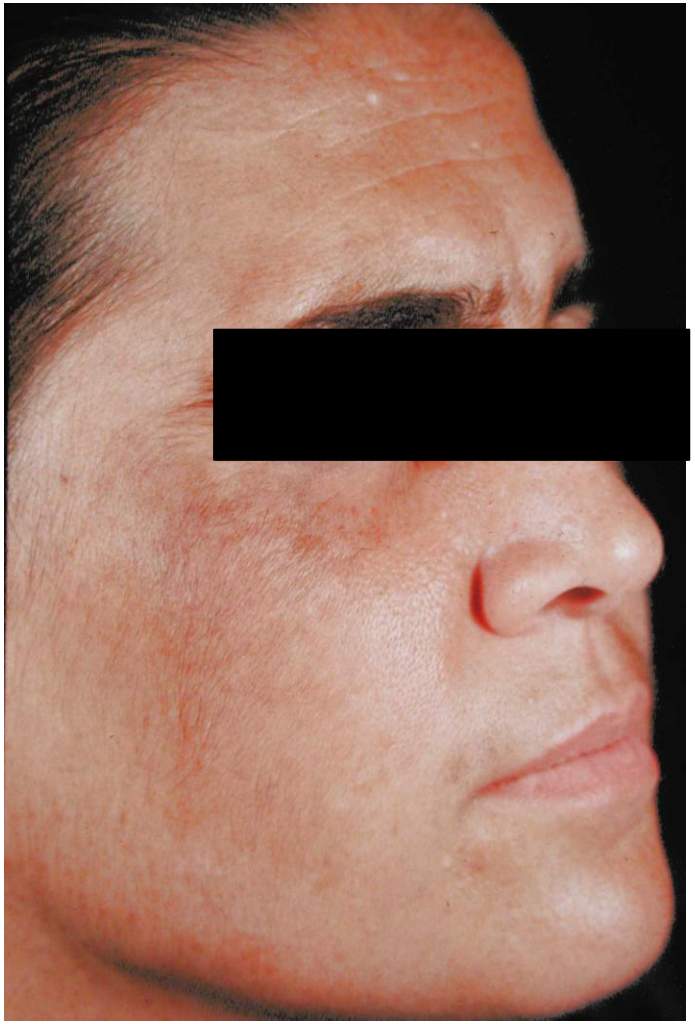






Porphyria Cutanea Tarda

HYPERTRICOSIS



Treatment of PCT

- Avoid trigger factors as alchool, drugs, estrogens
- Life-style
- HCV and HIV, HFE gene contribute to phenotype expression of PCTc
- Phlebotomy (300-500ml every 2 week) is the first choice treatmente particularly in presence of iron overload. Stop when transferrin saturation is< 20% and ferritin 50-100ng/dl and possibly when urinary porphyrines become normal.

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- Low doses of clorochine (100–200 mg twice week)

Heme biosynthesis and Porphyrias

X Linked Dominant Protoporphyria XLDPP

ALA-DEHYDRASE DEFICIENCY (ADP)

ACUTE INTERMITTENT PORPHYRIA (AIP)

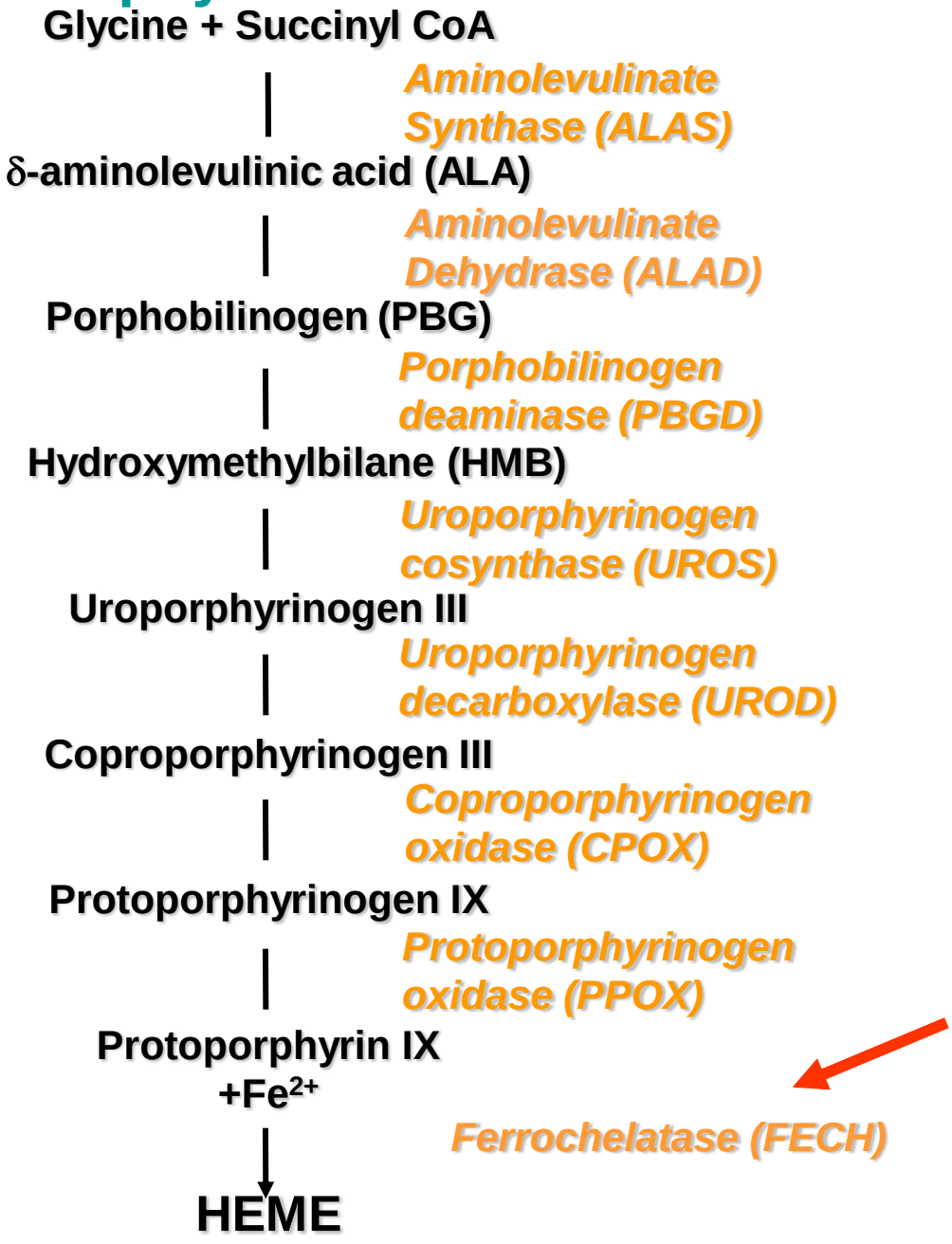
CONGENITAL ERYTHROPOIETIC PORPHYRIA (CEP, Günther)

PORPHYRIA CUTANEA TARDA (PCT)

HEREDITARY COPRO-PORPHYRIA (HCP)

VARIEGATE PORPHYRIA (VP)

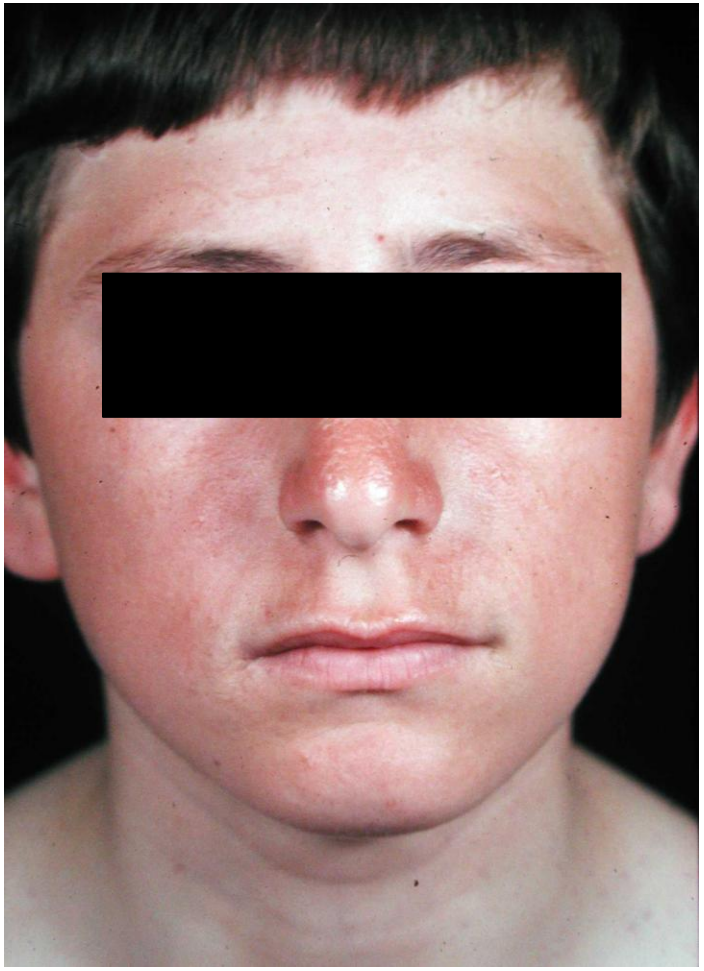
ERYTHROPOIETIC PROTOPORPHYRIA (EPP)



Erythropoietic Porphyrias
(Chronic)

- **Erythropoietic Protoporphyria**
  - **Pseudo-dominant or recessive**
  - **Coinheritance of one mutated *FECH* allele + one low expression *FECH* allele (IVS3 – 48C)**
- **Congenital Erythropoietic Porphyria (Günther's disease)**
  - **Autosomal recessive**

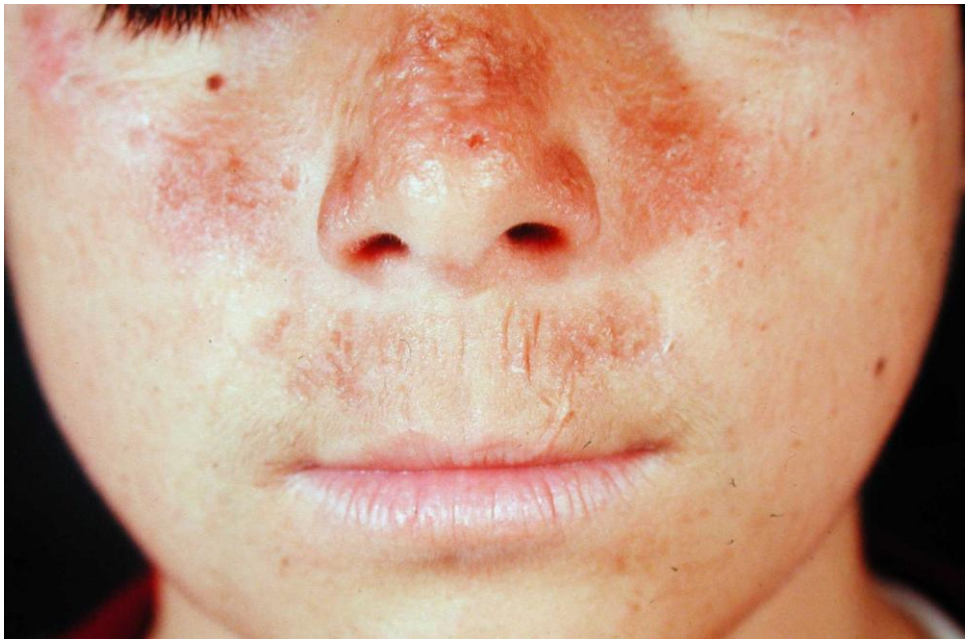
Erythropoietic Protoporphyria

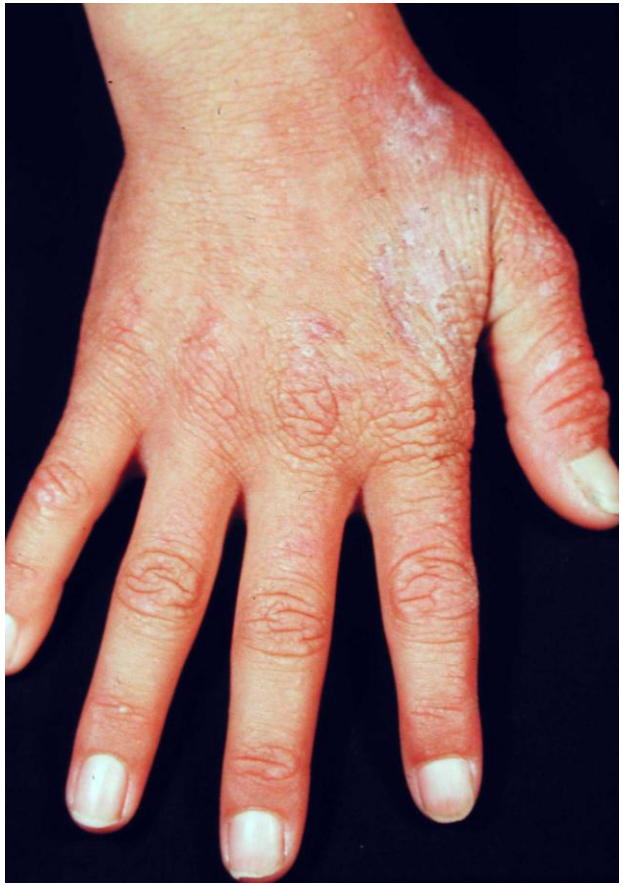


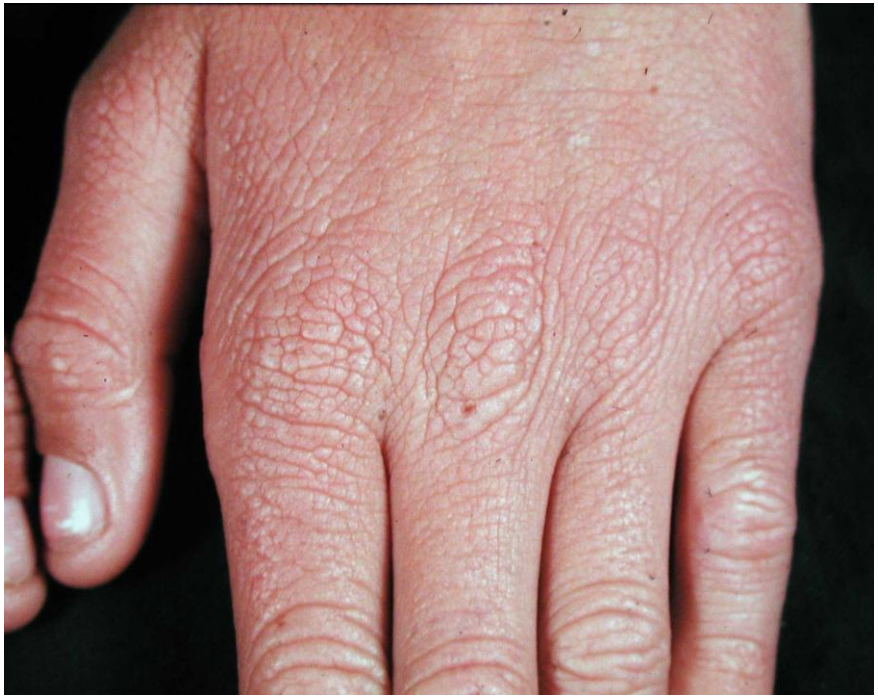
Light intolerance

eritema, edema, lesioni purpuric lesions and bolli

Erythropoietic Protoporphyria

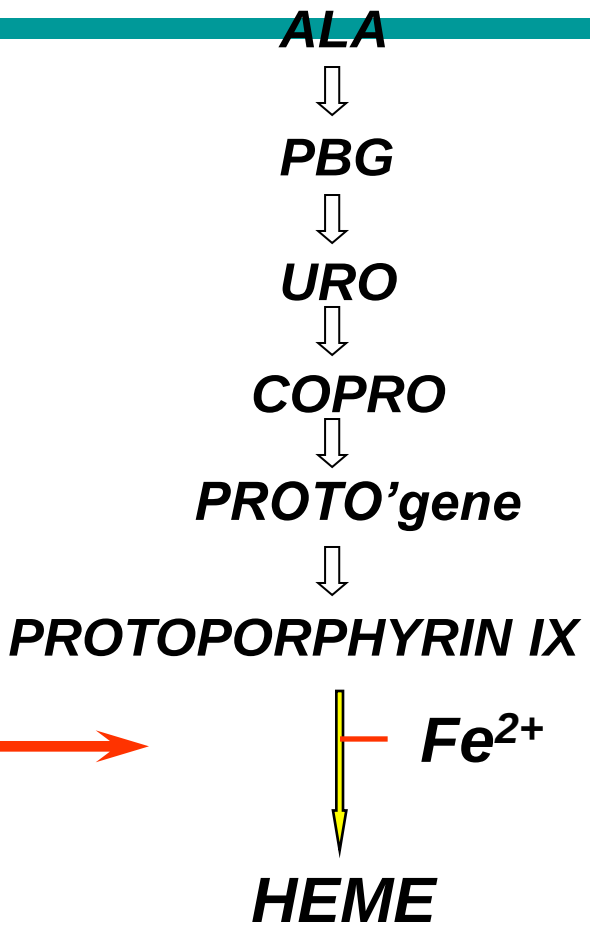






Erythropoietic Protoporphyria (EPP)

- cutaneous photosensitivity
- Protoporphyrin IX *bone marrow* overproduction
- Fatal liver disease (<5%)
- Ferrochelatase partial deficiency (FECH)

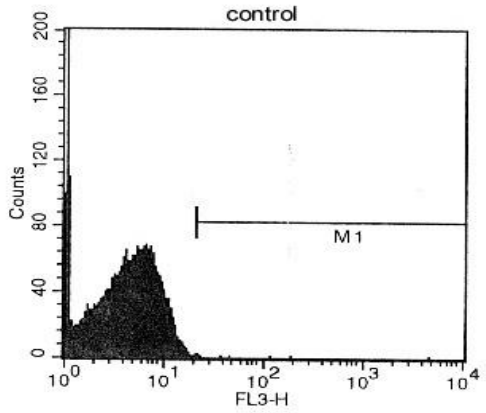


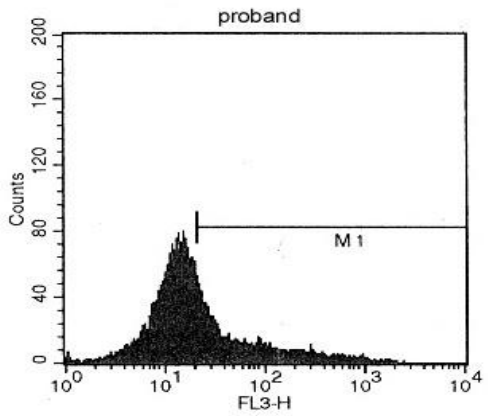
- 1/50 000 / 1/200000
- Autosomic dominant / recessive
- Incomplète Penetrance

Erythropoietic Protoporhyria (EPP)

•Prevalence: 1:50.000-1:200.000

•Accumulation of protoporphyrin IX in erythrocytes, plasma, urine, faeces and skin.





•Early childhood onset of lifelong acute photosensitivity of sun-exposed skin.

•In about 2% of patients, severe liver disease

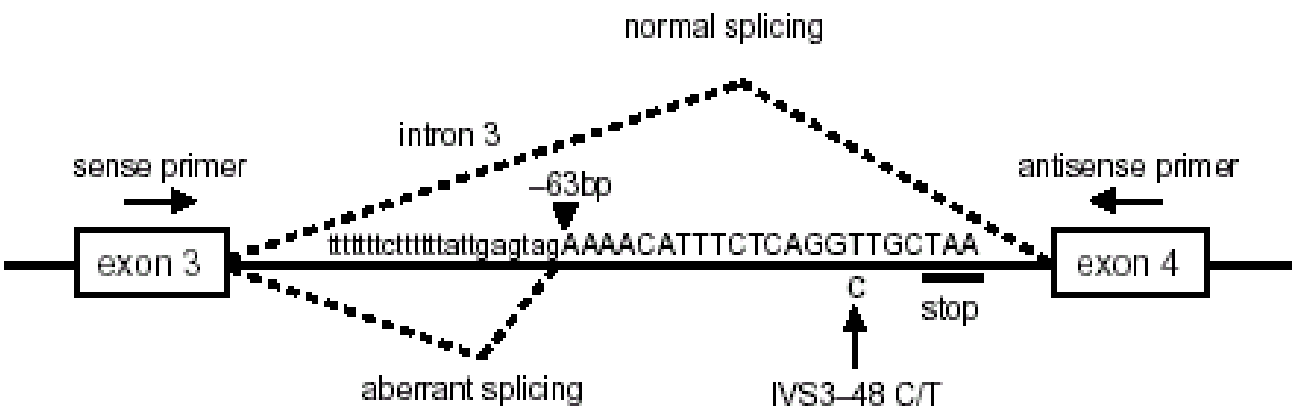
Erythropoietic Protoporhyria (EPP)

FECH mutation → abolishment of FECH activity

and

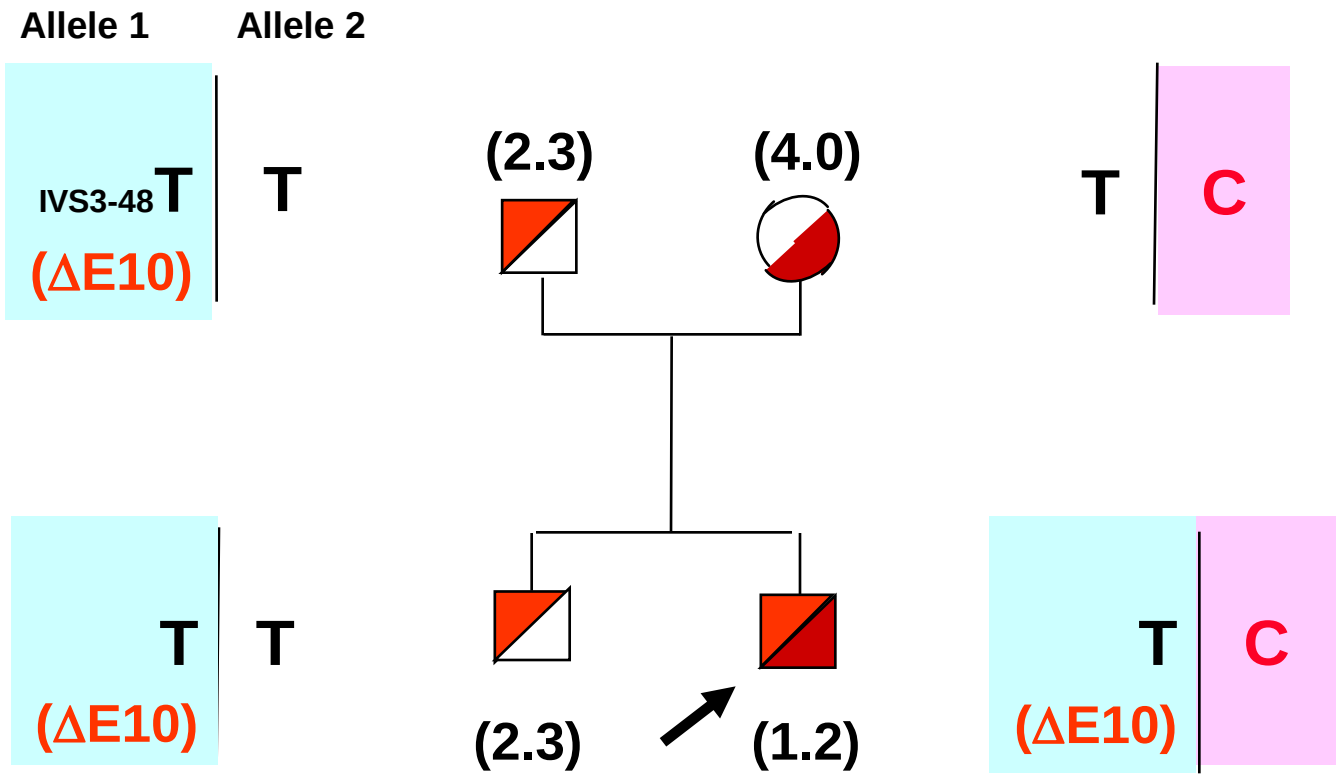
Low expressed *FECH* allele

a) IVS3-48 T/C

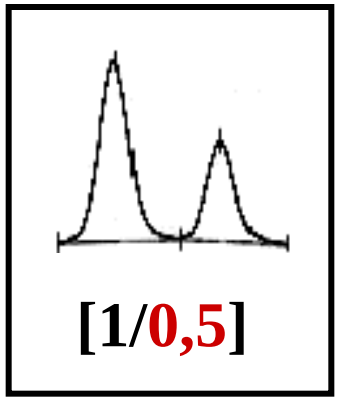


b) Haplotype:
–251 A/G
IVS1-23 C/T
IVS3-48 T/C

Inheritance in dominant EPP



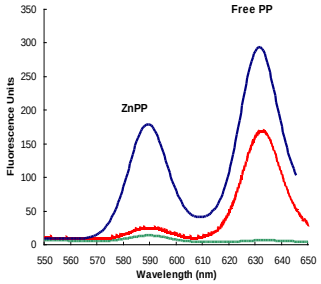
Fech mRNA ratio



In dominant EPP Family :
Co-inheritance of one mutated FECH allele and a low expression FECH allele IVS3 -48C

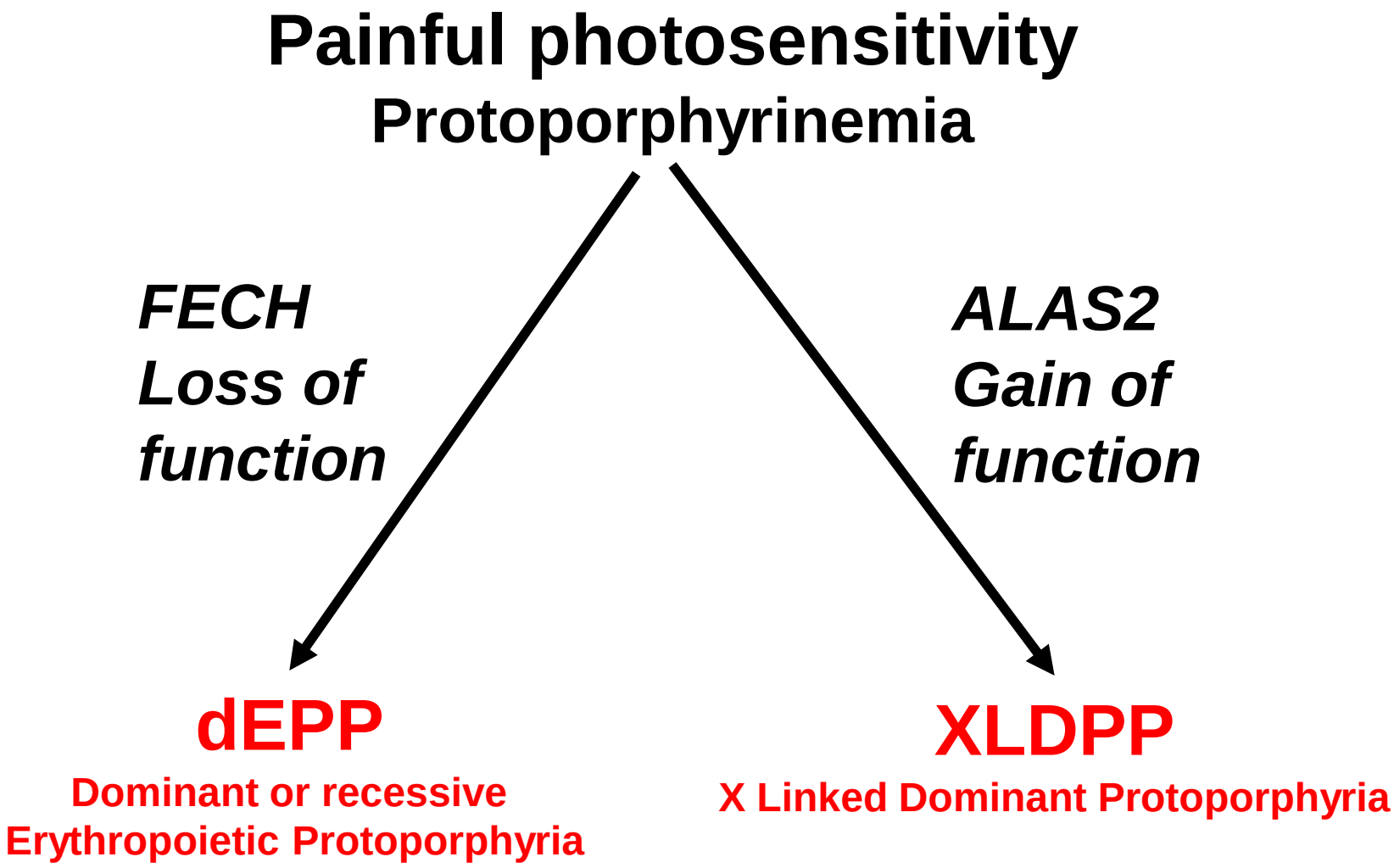
Atypical EPP

- Raised zinc protoporphyrin (44% vs 8% of total Protoporphyrin in dEPP)

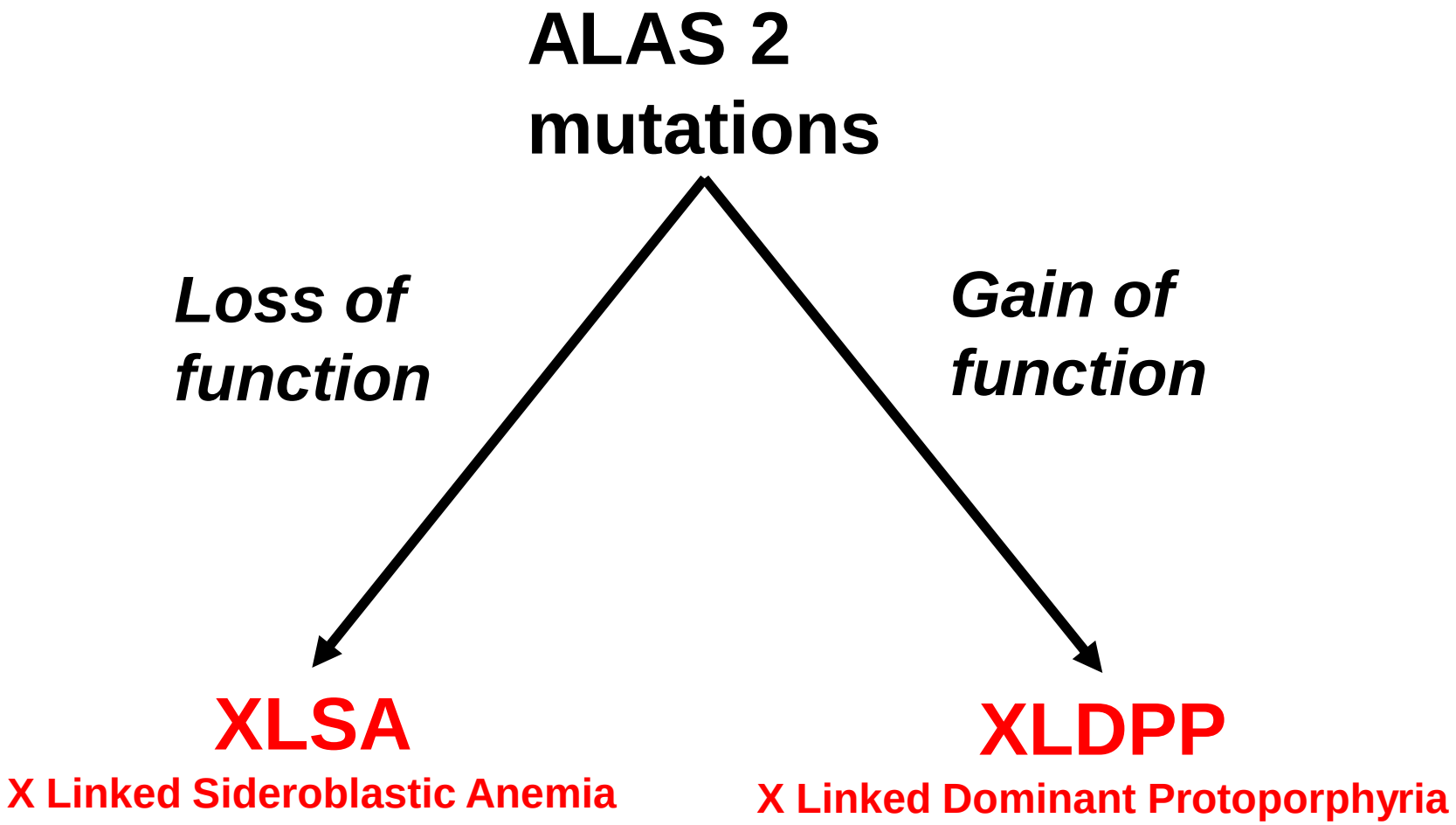


- FECH enzymatic activity normal
- No FECH mutation
- No FECH IVS3-48C hypomorphic allele

One disease …two different genes



One ALAS 2 gene…two different diseases



Therapy of Protoporphyria

- Avoid sun exposure, use protective procedures

- Sistemic Photoprotection with β carotene at high doses in spring :

  1/4 yrs:60/90 mg/die
  5/8 yrs:90/120 mg/die
  9/12 yrs:120/150/die`
  13/16 yrs:150/180/die
  from16 yrs:180 mg/die

- Alfa-melanotide, analog α–melanocites stimulating ormone

Therapy of Protoporphyria

- 10% of Protoporphyria patients develop colestatic chronic hepatitis due to protoporphyrine accumulation (protoporphyrines are insoluble, they form intra-hepatic cristals, reduction of bile flow)
- In presence of severe liver failure: colestiramina and active charcoals
- Liver trasplantation

Take Home Message

- In presence of cutaneous lesions linked to photosensitivity do not forget Porphyria cutanea in differential diagnosis
- Measure the urinary porphyrin precursors
- Remove risk factors
- Monitor liver and kidney functions

Erythropoietic Porphyrias
(Chronic)

- Erythropoietic Protoporphyria
  - Pseudo-dominant or recessive
  - Coinheritance of one mutated *FECH* allele + one low expression *FECH* allele (IVS3 – 48C)

- **Congenital Erythropoietic Porphyria (Günther's disease)**
  - **Autosomal recessive**

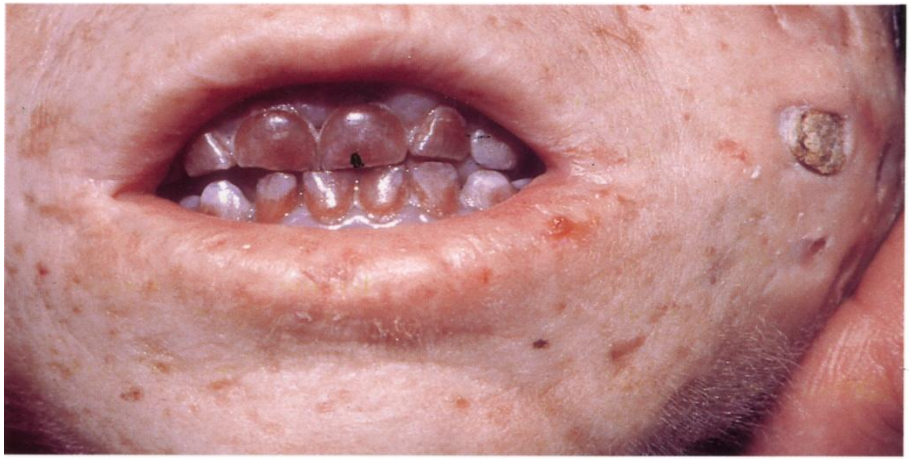
Congenital Erythropoïetic Porphyria (CEP, *Günther's disease*)

- ***Autosomal recessive***
- **Severe photodermatosis**
- **Bone marrow overproduction with massive porphyrinuria (*Uro, Copro, isomers I*)**
- **Hemolytic anemia**
- **Hepato-splenomegaly**
- **URO III Synthase (UROS) deficiency**

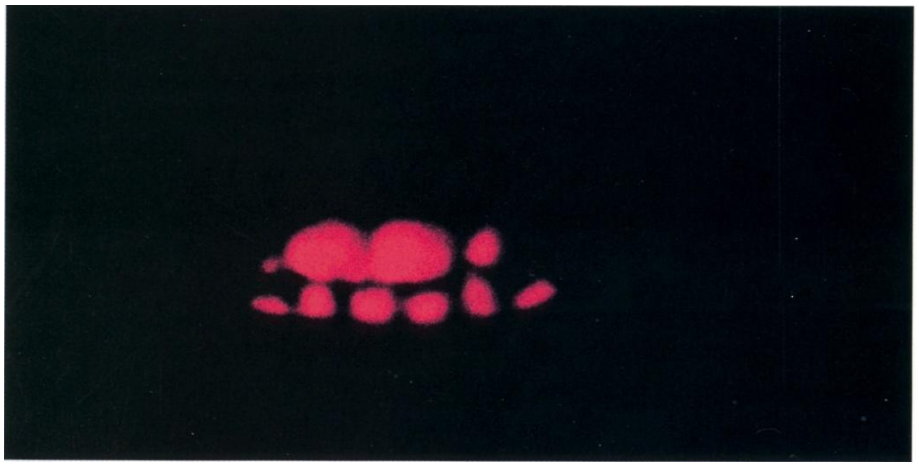
Congenital Erythropoïetic Porphyria (CEP, *Günther's disease*)

ERITRODONZIA

fluorescenza rossa alla luce di Wood



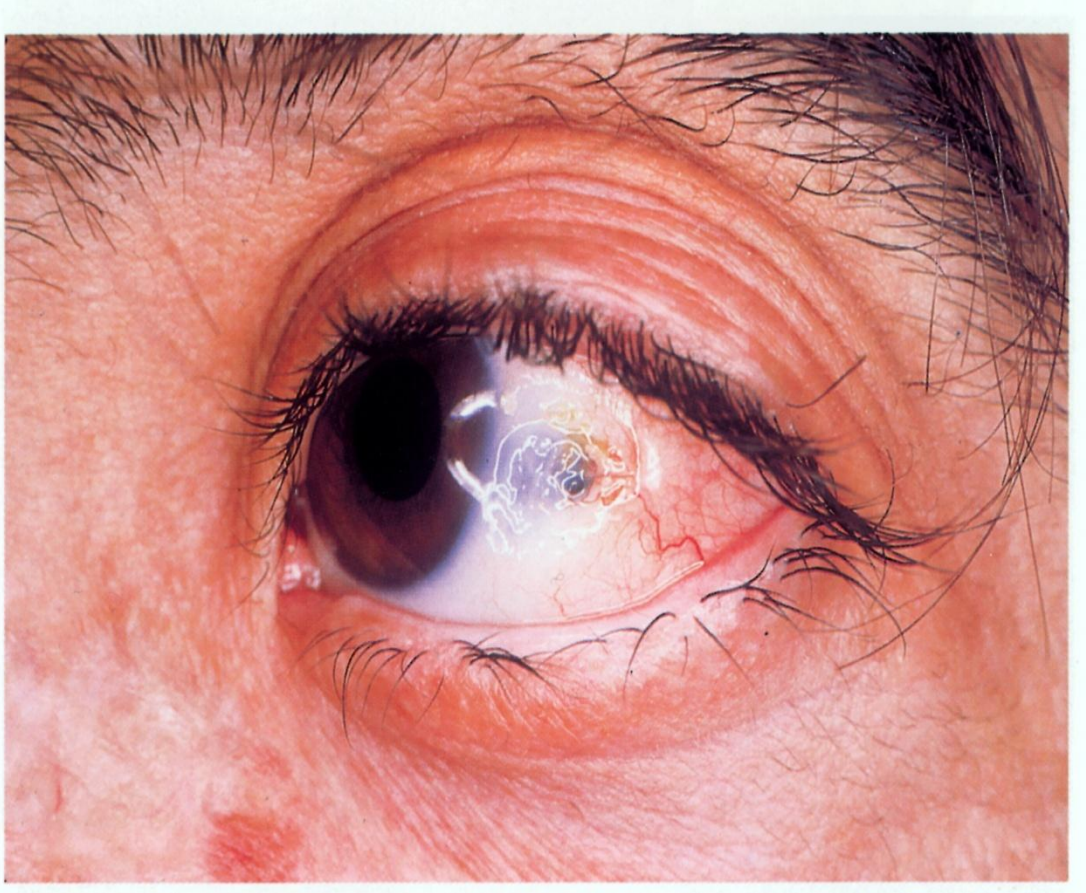
OSTEOLISI E OSTEODISTROFIA



Congenital Erythropoïetic Porphyria (CEP, *Günther's disease*)

CONGIUNTIVITE
CHERATITE
ECTROPION

SCLEROMALACIA PERFORANTE



Erythropoïetic Porphyrias
New therapeutic strategies

- **Bone Marrow Graft : CEP**
- **Gene therapy : CEP, EPP ?**

European Porphyria Initiative (EPI):

A platform to develop a common approach to the diagnosis and management of Porphyrias and to promote research in the field.

EPI General Assembly, Paris, France, 9-10 Dec 2005

Seminar

Porphyrias

Hervé Puy, Laurent Gouya, Jean-Charles Deybach

***Lancet* 2010; 375: 924–37**