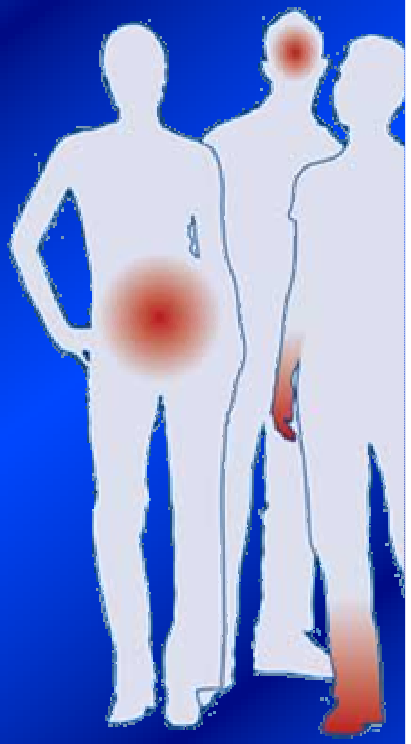
Les porphyries

Frédéric Cotton
Axelle Gilles

Centre Belge des Porphyries



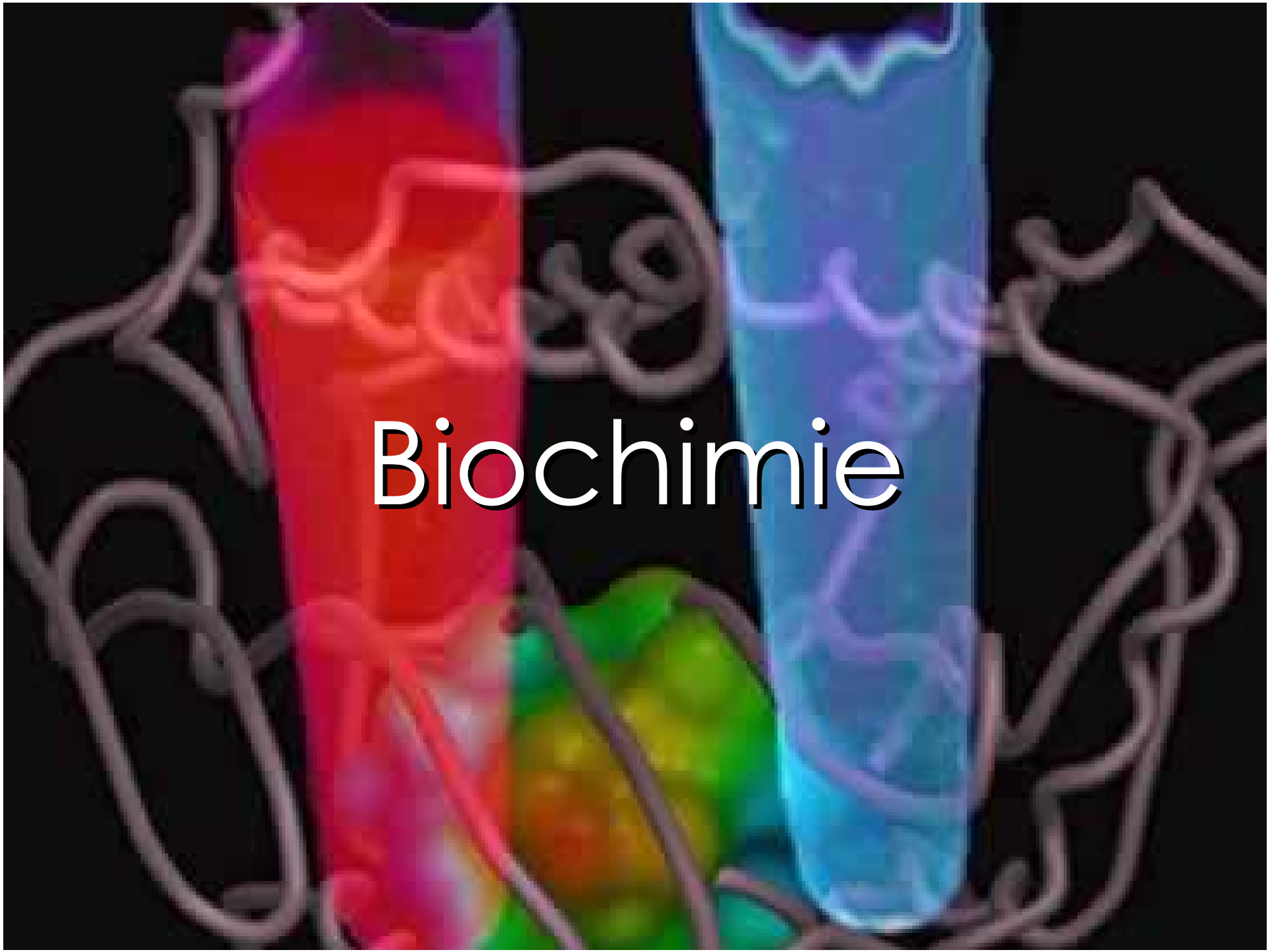
ULB ERASMUS

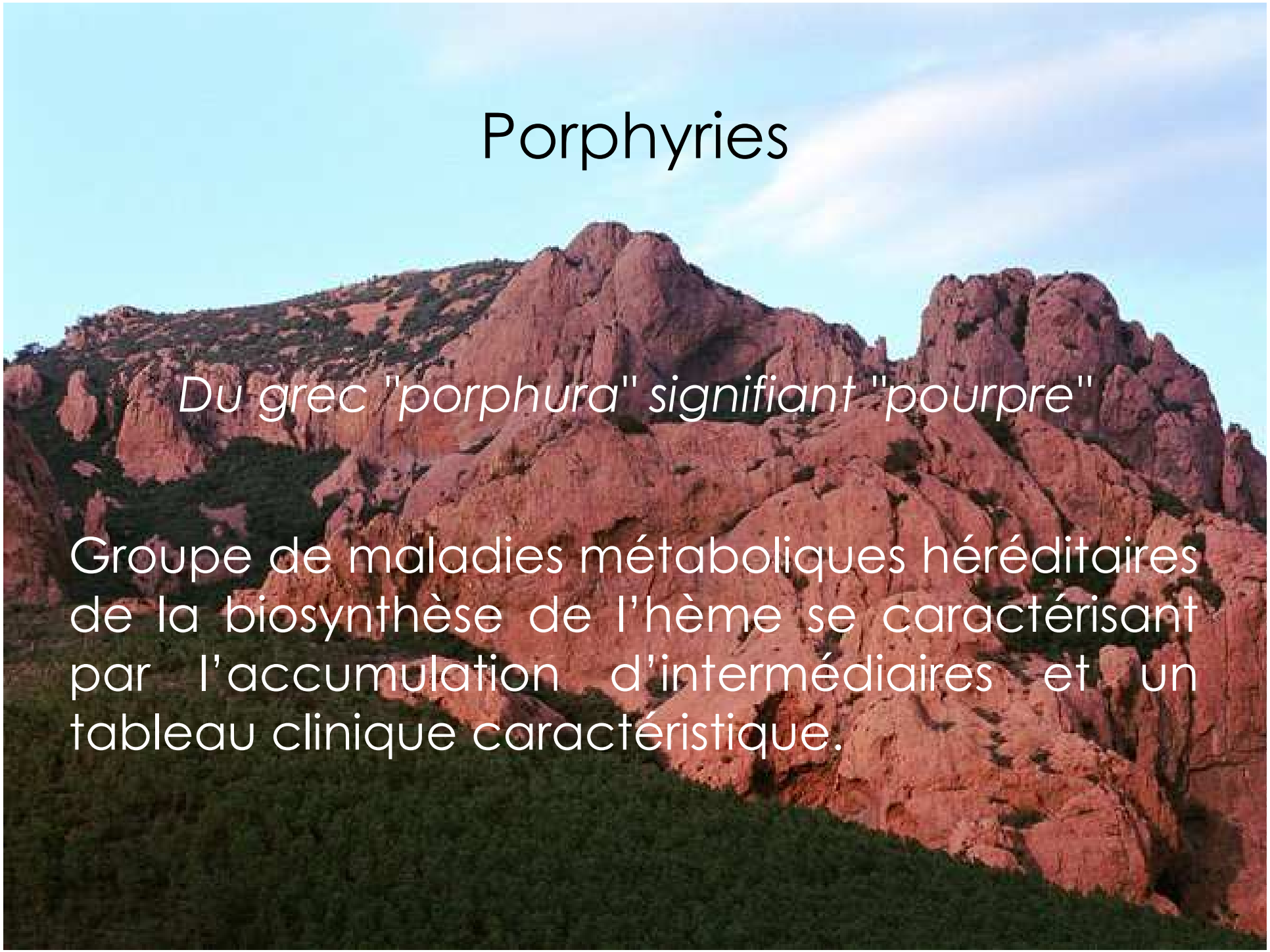
Porphyries: quelques chiffres

France:

- prévalence: 1 / 1 600 (porphyries aiguës)
- expression clinique: 1 / 75 000

- diagnostic trop rarement évoqué
- diagnostic biochimique mal mené
- prise en charge inadéquate


Biochimie



Porphyries

Du grec "porphura" signifiant "pourpre"

Groupe de maladies métaboliques héréditaires de la biosynthèse de l'hème se caractérisant par l'accumulation d'intermédiaires et un tableau clinique caractéristique.

Porphyrines

Les couleurs de la vie

Chlorophylle

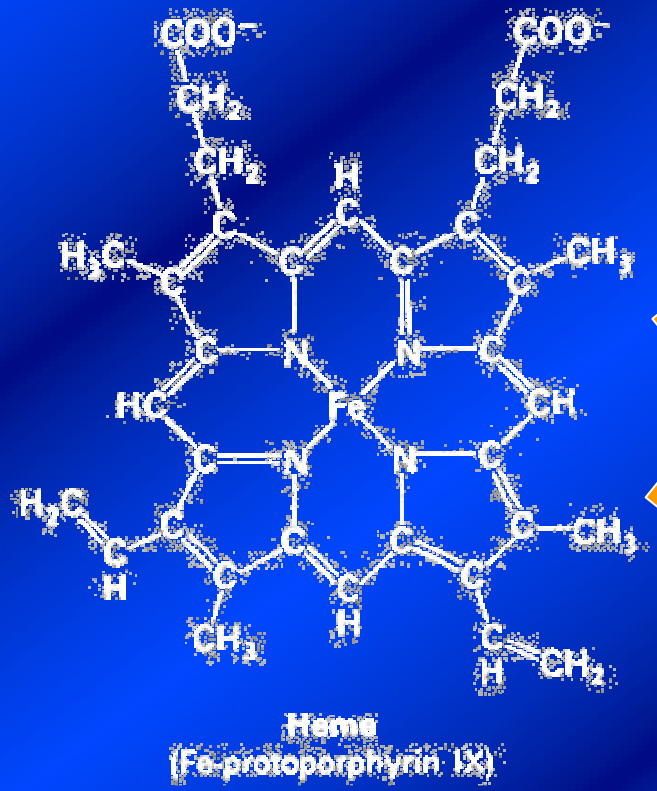
Vitamine B12

Coenzyme F430

Hème

"Molécule mère": Uroporphyrinogène III

L'hème

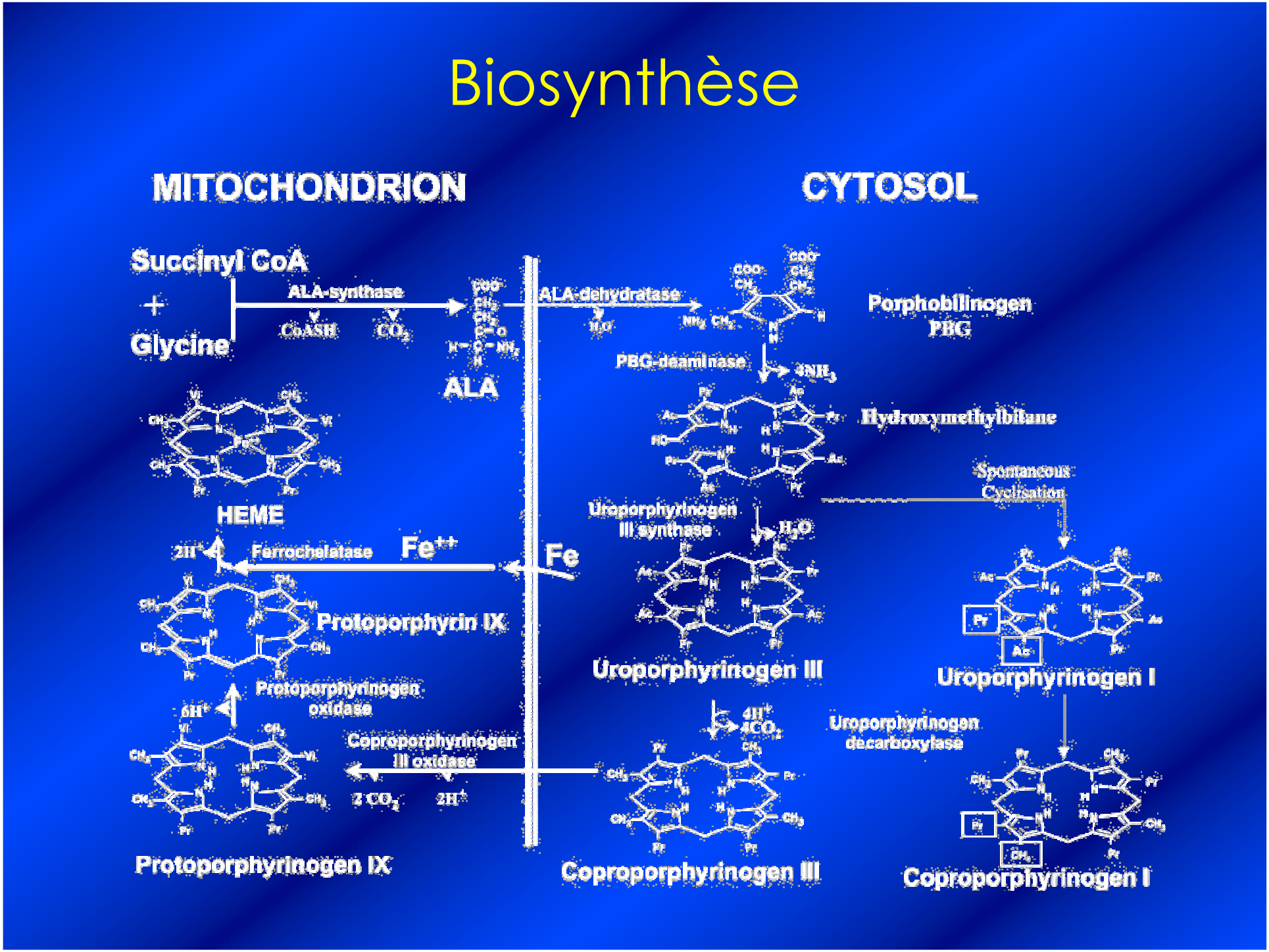


moelle 85% { Hémoglobine

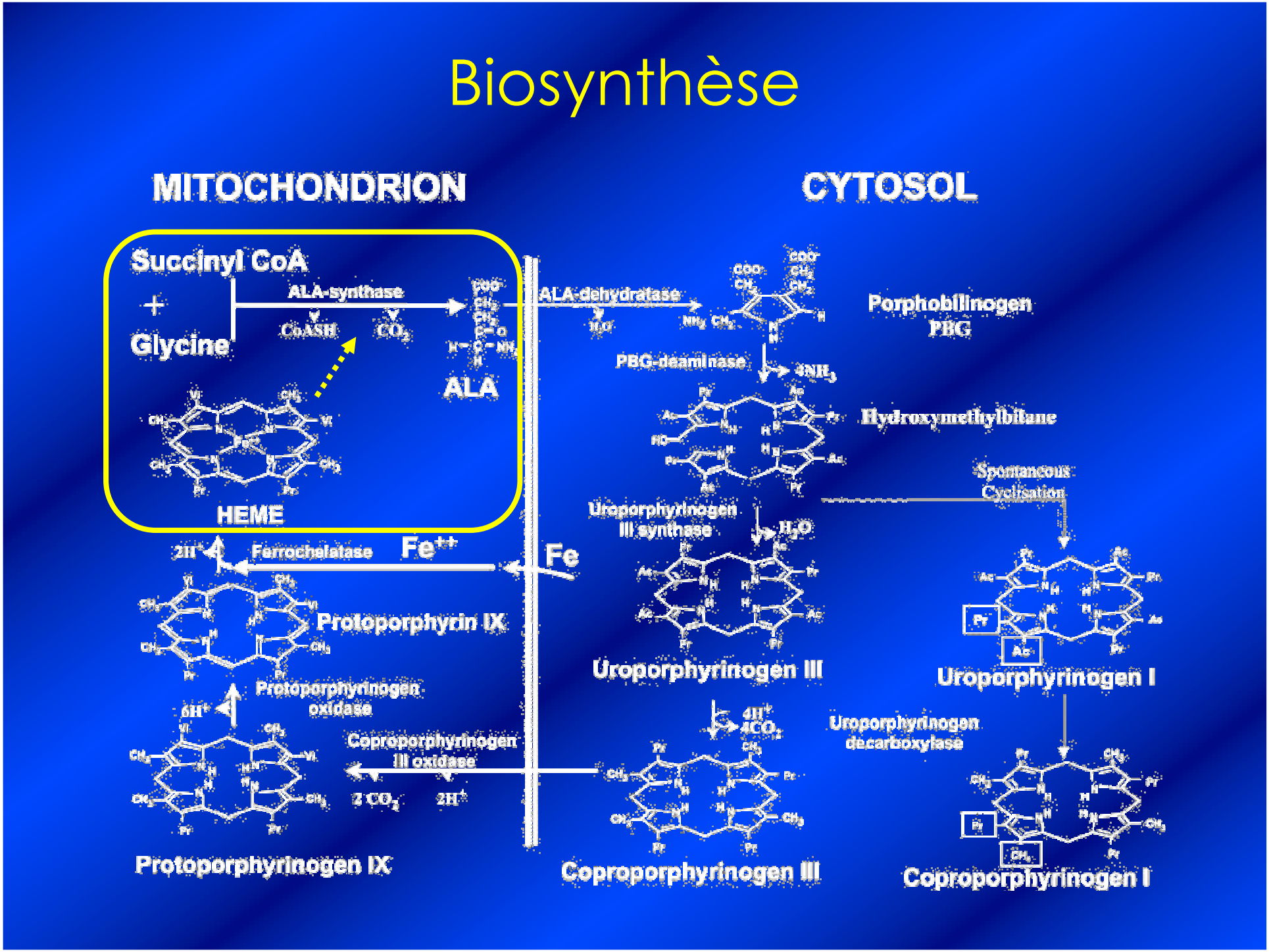
foie 14% { Cytochromes

autres 1% {
- Myoglobine
- Catalase
- Peroxydase
- Duodenal cytochrome b
- Tryptophane 2,3 dioxygénase
- Cyclooxygénase

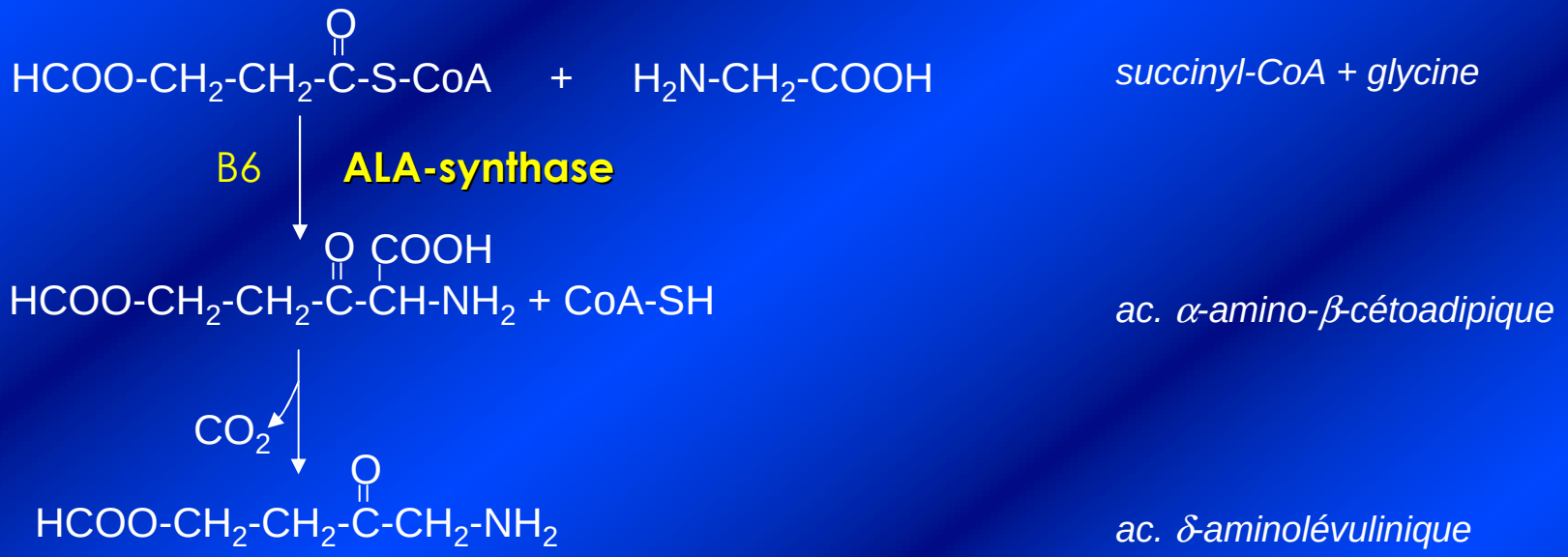
Biosynthèse



Biosynthèse

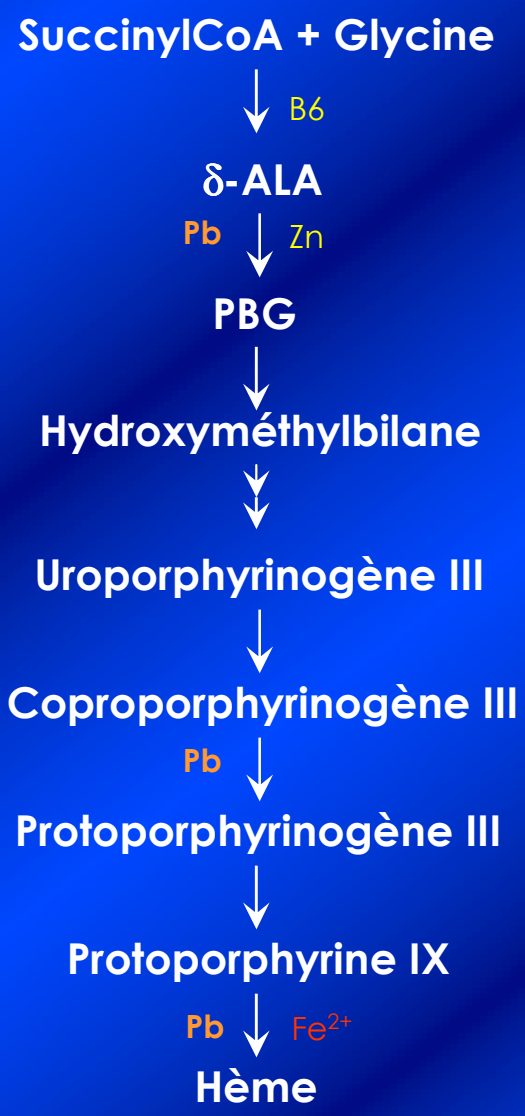


Biosynthèse de l'hème



- isoenzyme hépatique (ALAS1)
  - réprimée par hème
  - induite par médicaments, stéroïdes, alcool
- isoenzyme érythrocytaire (ALAS2)
  - stimulée par le fer
  - hème - stimule synthèse globines
    - inhibe entrée fer

Biosynthèse de l'hème



ALA-synthase	Protoporphyrie dominante liée X (?)
ALA-déhydratase	Déficience ALA-déhydratase
porphobilinogène déaminase	Porphyrie Intermittente Aiguë (1-2/100.000)
uroporphyrinogène III synthase	Porphyrie Erythrop. Congénitale (<1/1.000.000)
uroporphyrinogène décarboxylase	Porphyrie Cutanée Tardive (1/25.000)
coproporphyrinogène oxydase	Coproporphyrie Héréditaire (1/250.000)
protoporphyrinogène oxydase	Porphyrie Variegata (1/250.000)
ferrochélatase	Protoporphyrie Erythropoiétique (1/200.000)

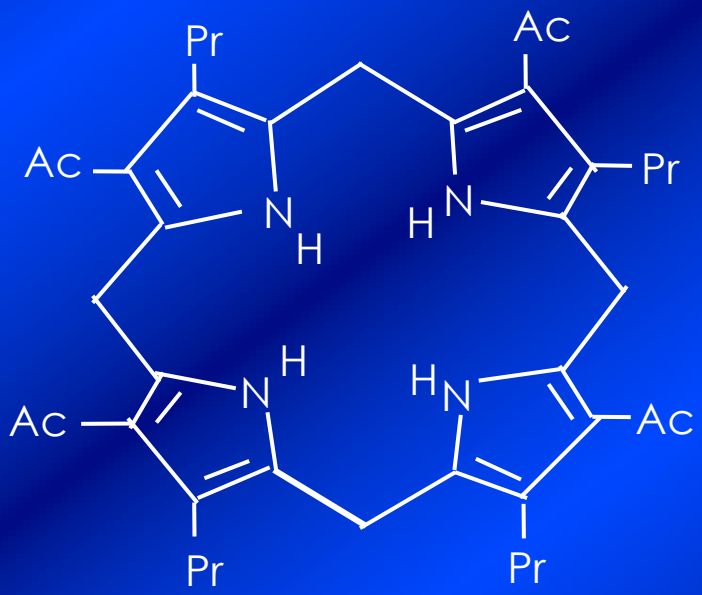
Génétique

Enzyme	Porphyrie	Mutations / Gènes	Transmission
ALA-déhydratase	Déf. ALA-d	7 (ALAD [7kn] - 9q34)	AR
PBG-déaminase	AIP	227 (PBGD [10kb] - 11q23.3)	AD
Uroporphyrinogène III synthase	CEP	35 (UROS - [34kb] 10q25.2-q26.3)	AR
Uroporphyrinogène décarboxylase	PCT	60 (UROD [3kb] - 1p34)	AD
Coproporphyrinogène oxydase	HC	36 (CPOX [14kb] - 3q12)	AD
Protoporphyrinogène oxydase	VP	121 (PPOX [5.5kb] - 1q22)	AR/AD
Ferrochélatase	EPP	74 (FECH [45kb] - 18q21.3)	AD

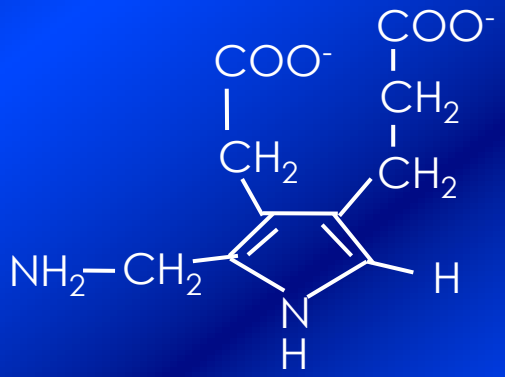
Lancet 2005;365:241

Physiopathologie

- Lésions cutanées
  - accumulation porphyrines
  - peau / liposolubilité

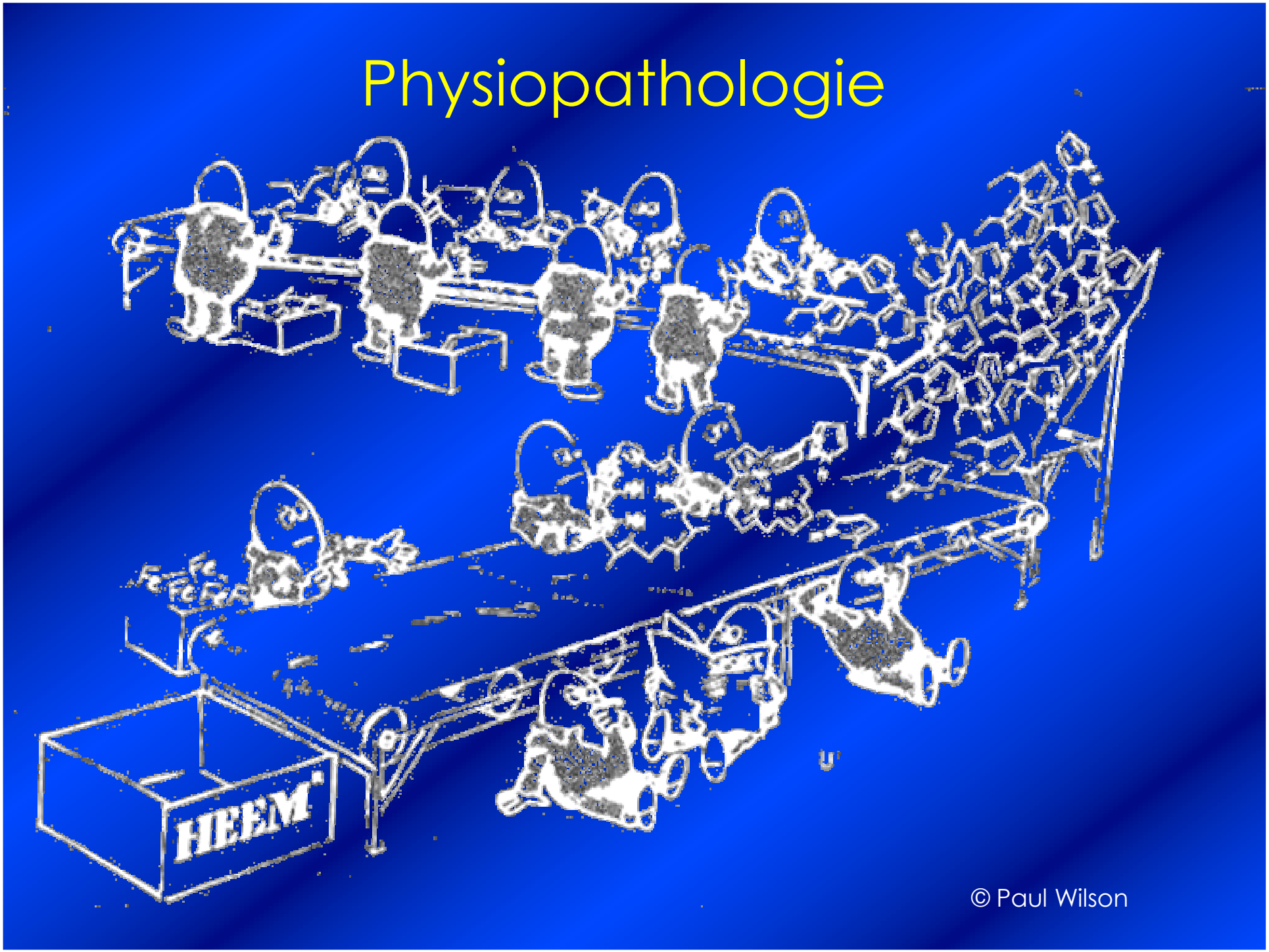


- Tableau neuroviscéral aigu
  - accumulation précurseurs (ALA, PBG)
  - déficience en hème

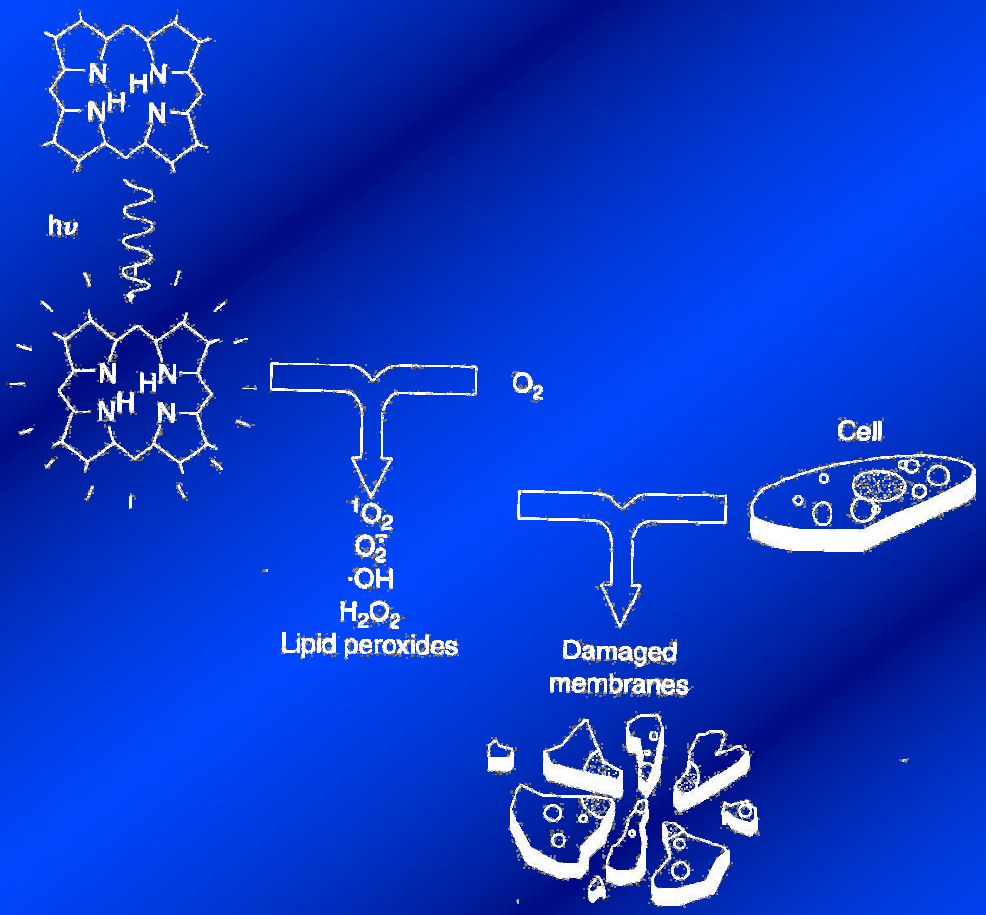


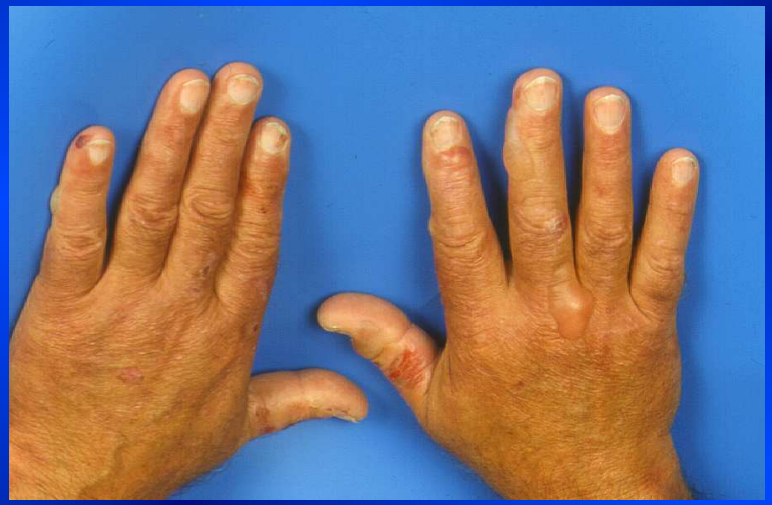
Porphyries cutanées

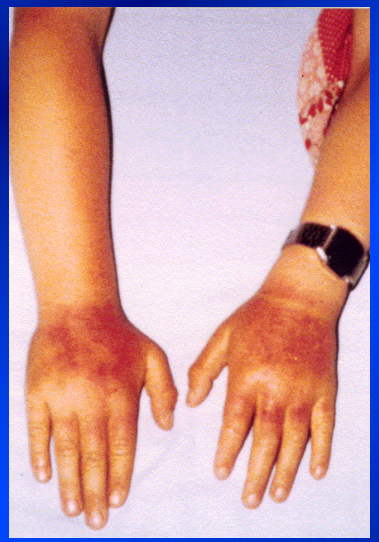
Physiopathologie

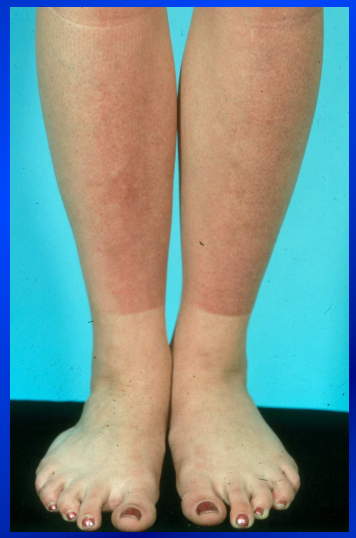


Physiopathologie



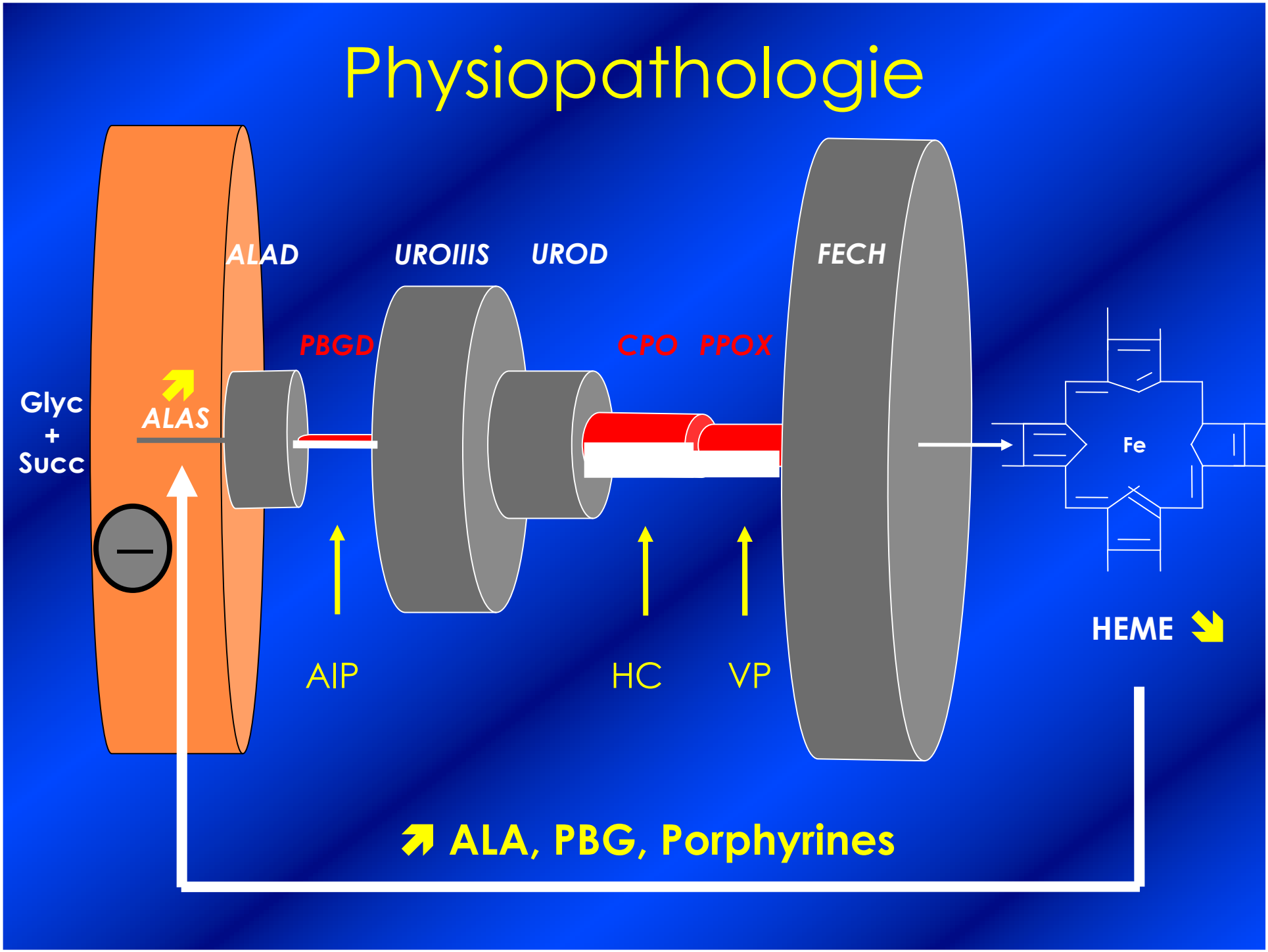






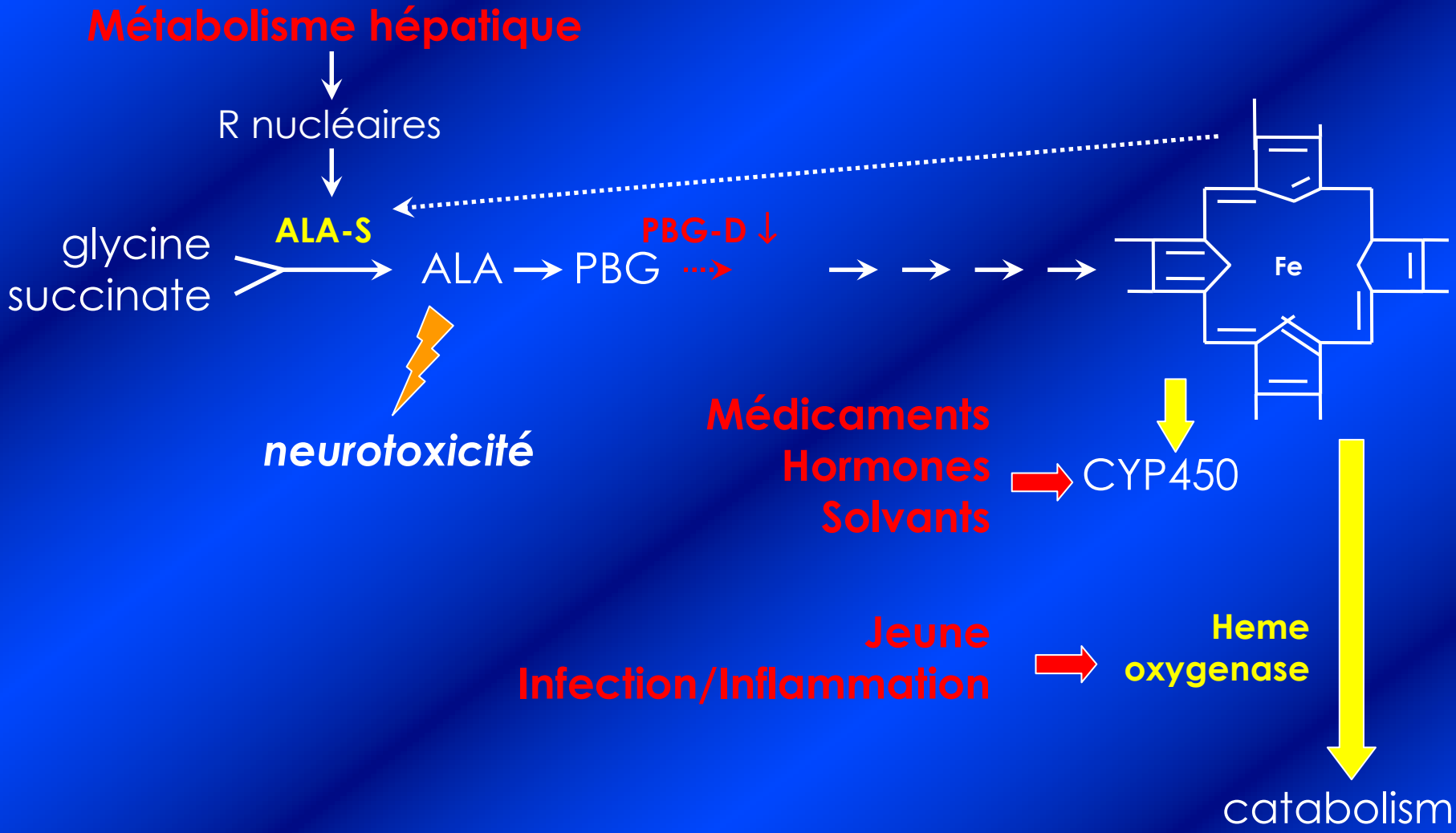

Porphyries aiguës

Physiopathologie



Facteurs précipitants

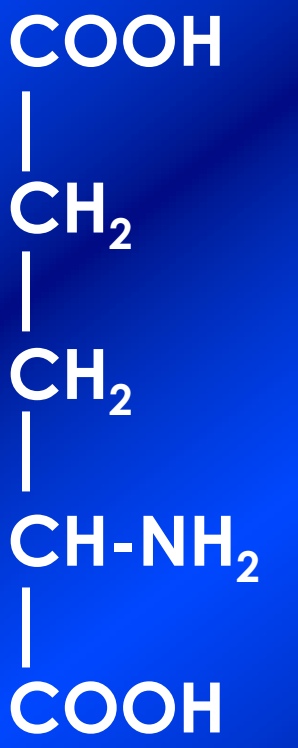
Phase latente → phase active



Physiopathologie

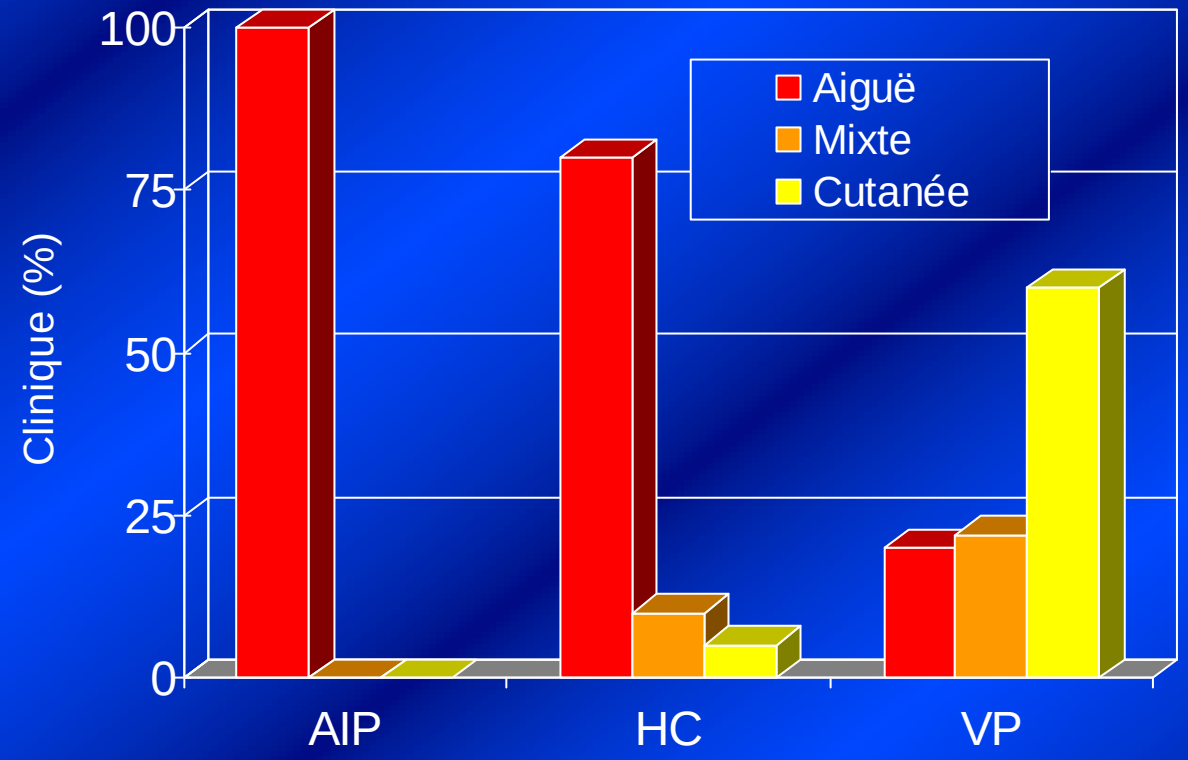
ALA

GABA



Ac. glutamique

Porphyries aiguës

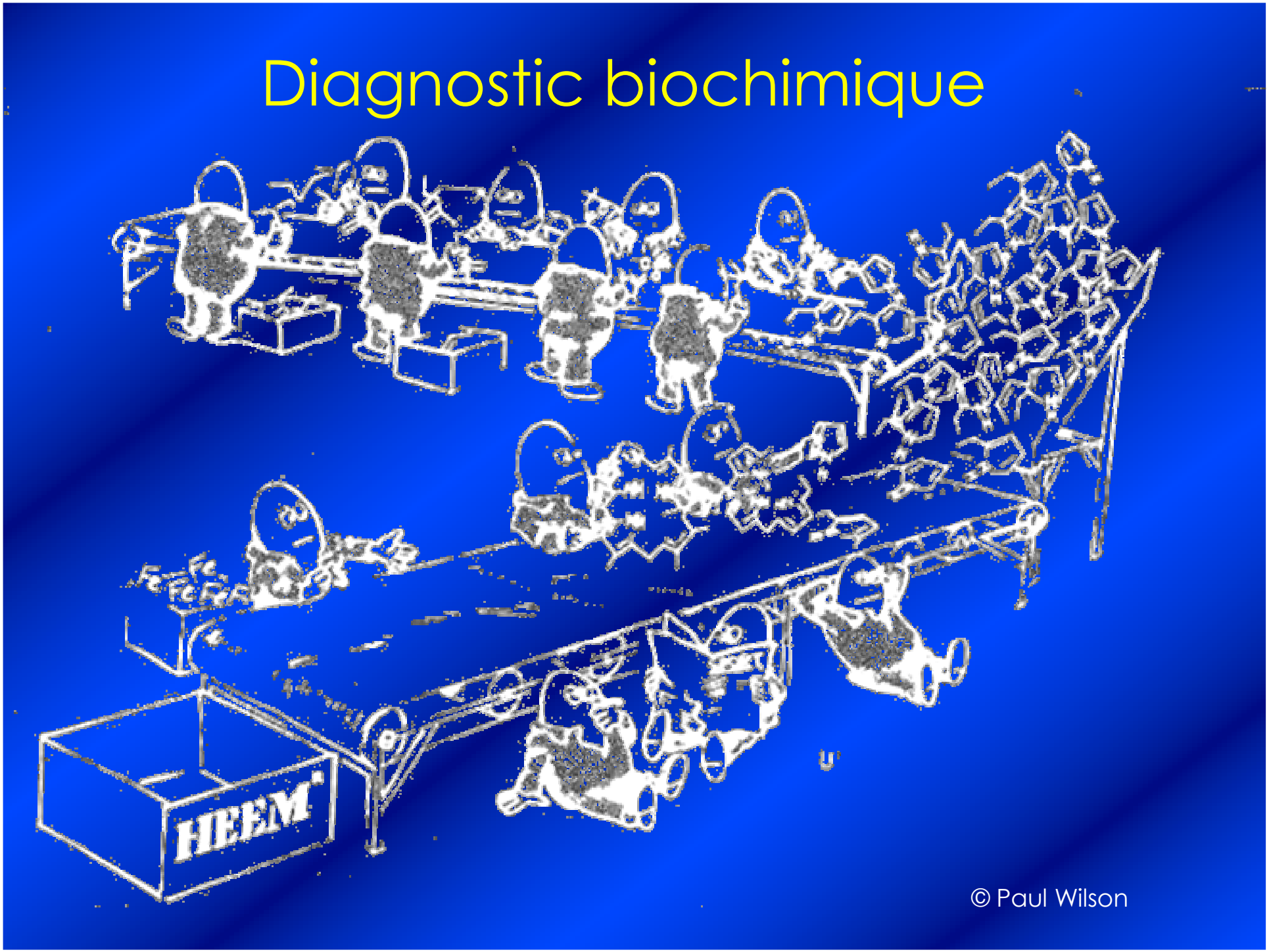



Diagnostic

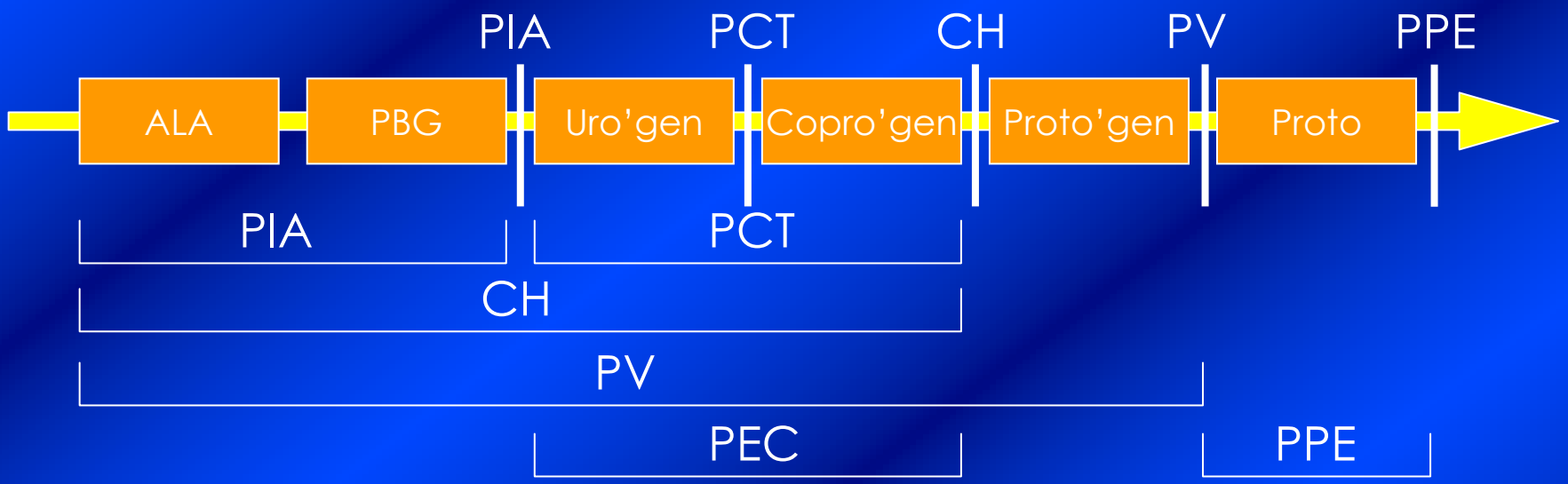
Démarche diagnostique

1. Screening
2. Caractérisation
3. Activité enzymatique
4. Génétique

Diagnostic biochimique



Diagnostic biochimique



Urines

Selles

Clin Biochem 1999;8:609

Diagnostic biochimique

- Urine
  - δ-ALA, PBG
  - porphyrines totales
  - porphyrines fractionnées
- Selles
  - porphyrines fractionnées
  - (porphyrines totales)
- Erythrocytes
  - Protoporphyrine libre
  - Zn-protoporphyrine
  - activité enzymatique
- Plasma
  - pic de fluorescence
  - porphyrines fractionnées

Echantillons ~~(24h)~~

Abri de la lumière !

Diagnostic biochimique

	Urines				Selles			G.R.
	d-ALA	**PBG**	**Uro**	**Copro**	**Uro**	**Copro**	**Proto**	**Proto**
d.AD	+++	-	-	++	-	-	-	-
AIP	+++	+++	+++	+	+	+	(+)	-
HC	+++	+++	++	+++	+	+++	+	-
VP	+++	+++	++	+++	+	++	++	-
PCT	-	-	+++ (1)	+	++	++ (2)	-	-
CEP	-	-	++	++	++	+++	-	-
EPP	-	-	(+)	(+)	-	(+)	+++	+++
Pb	+++	(+)	-	+	-	+	+/++	(+)

(1) + heptacarboxyporphyrine
(2) + isocoproporphyrine

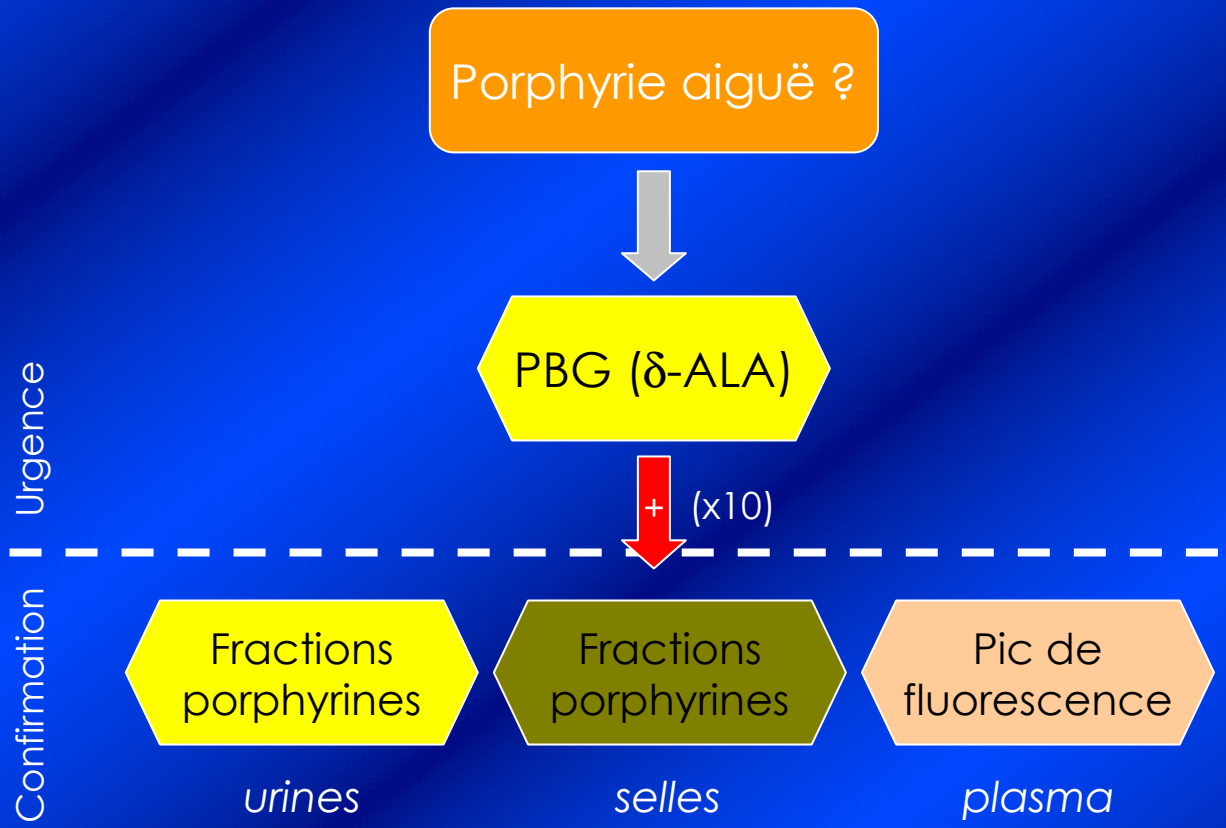
Recommandations EPNET

- PBG_{ur}: méthode spécifique et quantitative
- δ-ALA_{ur}: méthode spécifique et quantitative
- Fluorescence plasmatique
- Porphyrines urines: fractions
- Porphyrines selles : fractions
- Séparation des isomères I et III
- Protoporphyrines érythrocytaires

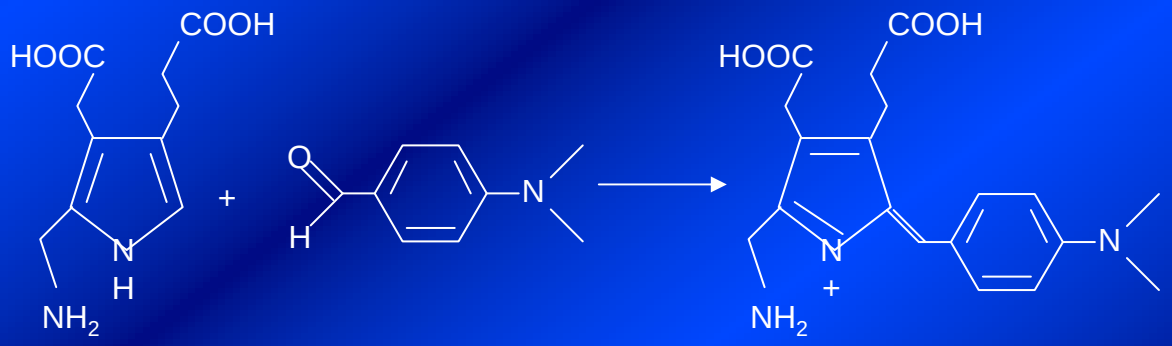
Nomenclature INAMI

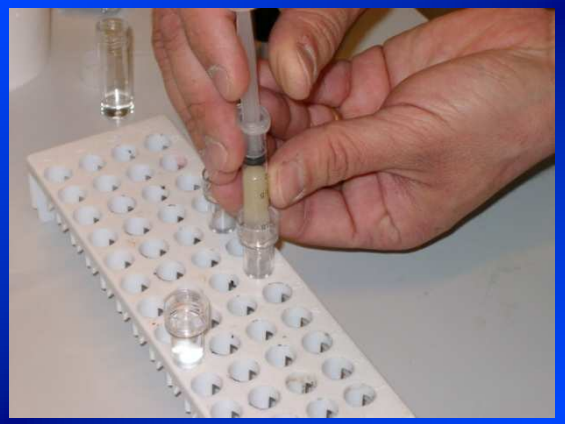
- PBG_{ur}: recherche puis dosage ♣
- δ-ALA_{ur}: dosage ♥
- Fluorescence plasma ♠
- Urines: recherche puis HPLC ♥
- Selles: HPLC ♣
- Isomères I et III ♣
- Protoporphyrines érythrocytaires ♥

Diagnostic des porphyries aiguës



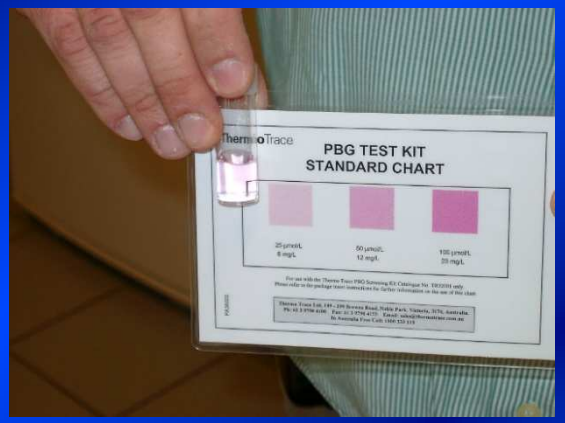
Diagnostic des porphyries aiguës





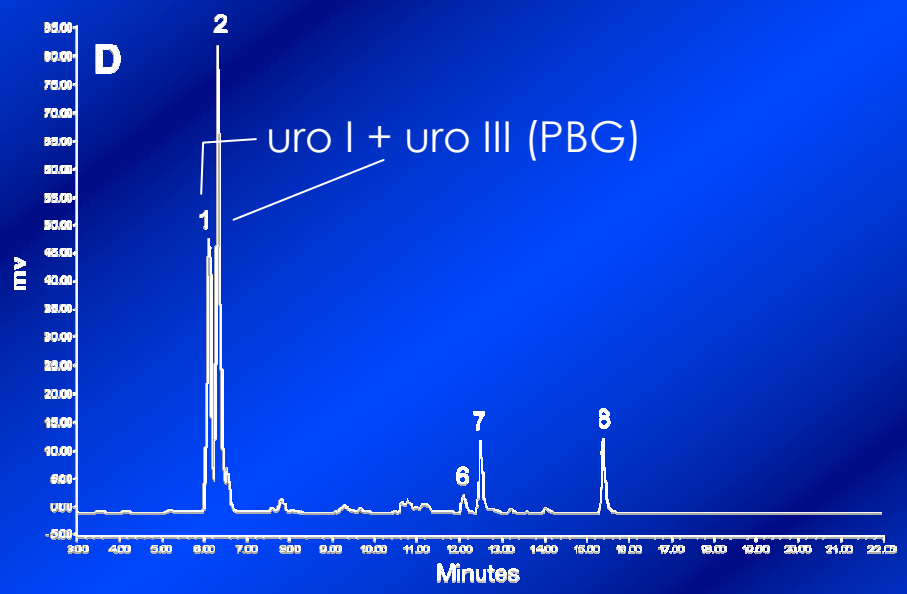
< 0.8 µmol/mmol créatinine

- tests quantitatifs (Mauzerall-Granick)
- tests semi-quantitatifs
- [tests qualitatifs (Watson-Schwartz)]
  - faux négatifs: sensibilité insuffisante +++
  - faux positifs: médicaments, urines concentrées

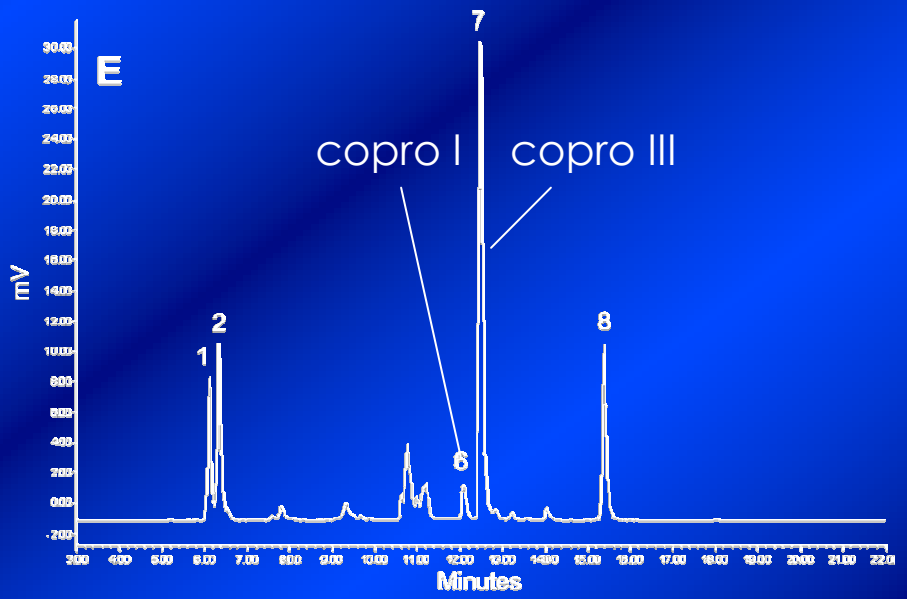


Diagnostic des porphyries aiguës

AIP: urine

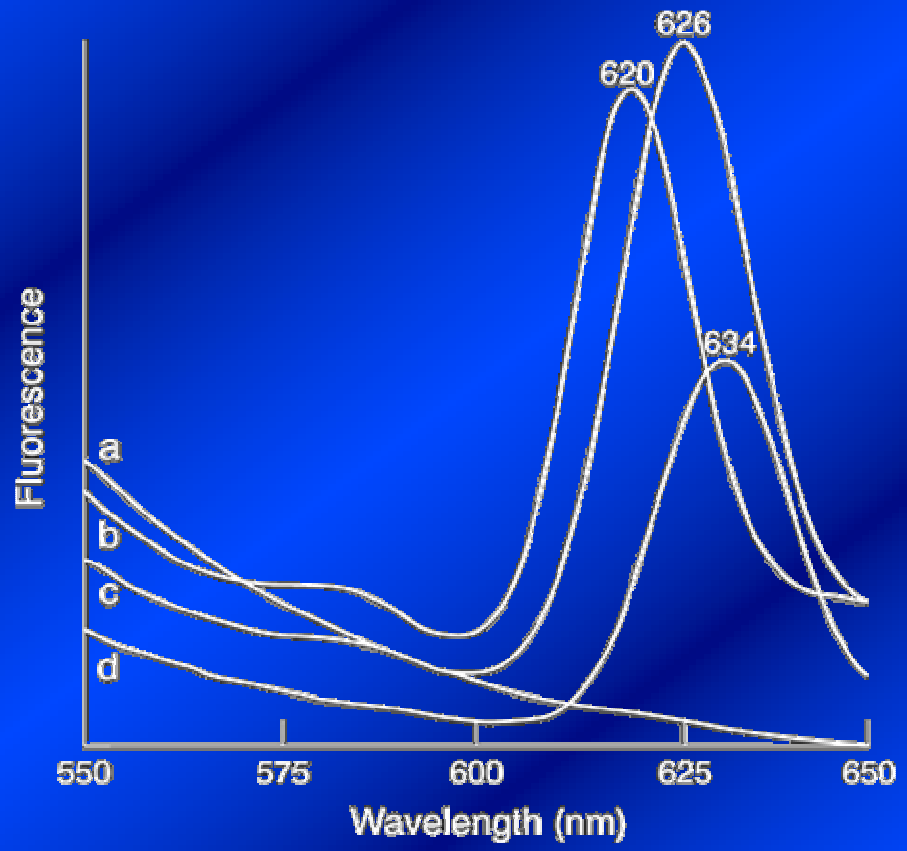


HC: urine



Clin Chem Lab Med 2006;44:1433

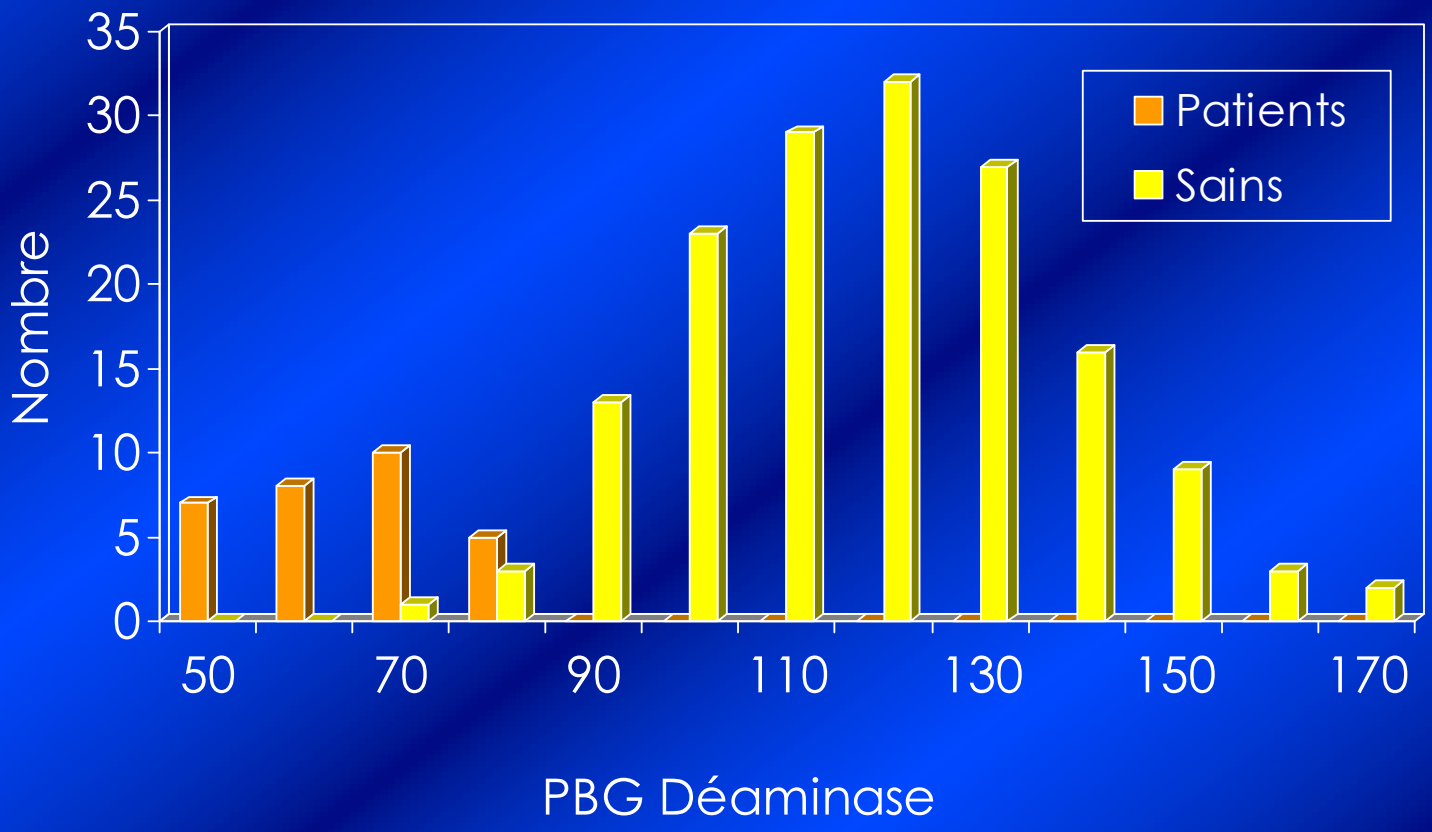
Diagnostic des porphyries aiguës



Porphyrie	λ (nm)
AIP	619-620
HC	619-620
VP	624-627
CEP	619-620
PCT	619-620
EPP	626-634

Clin Chem 2004;50:915
Ann Clin Biochem 1990;27:395

Diagnostic des porphyries aiguës

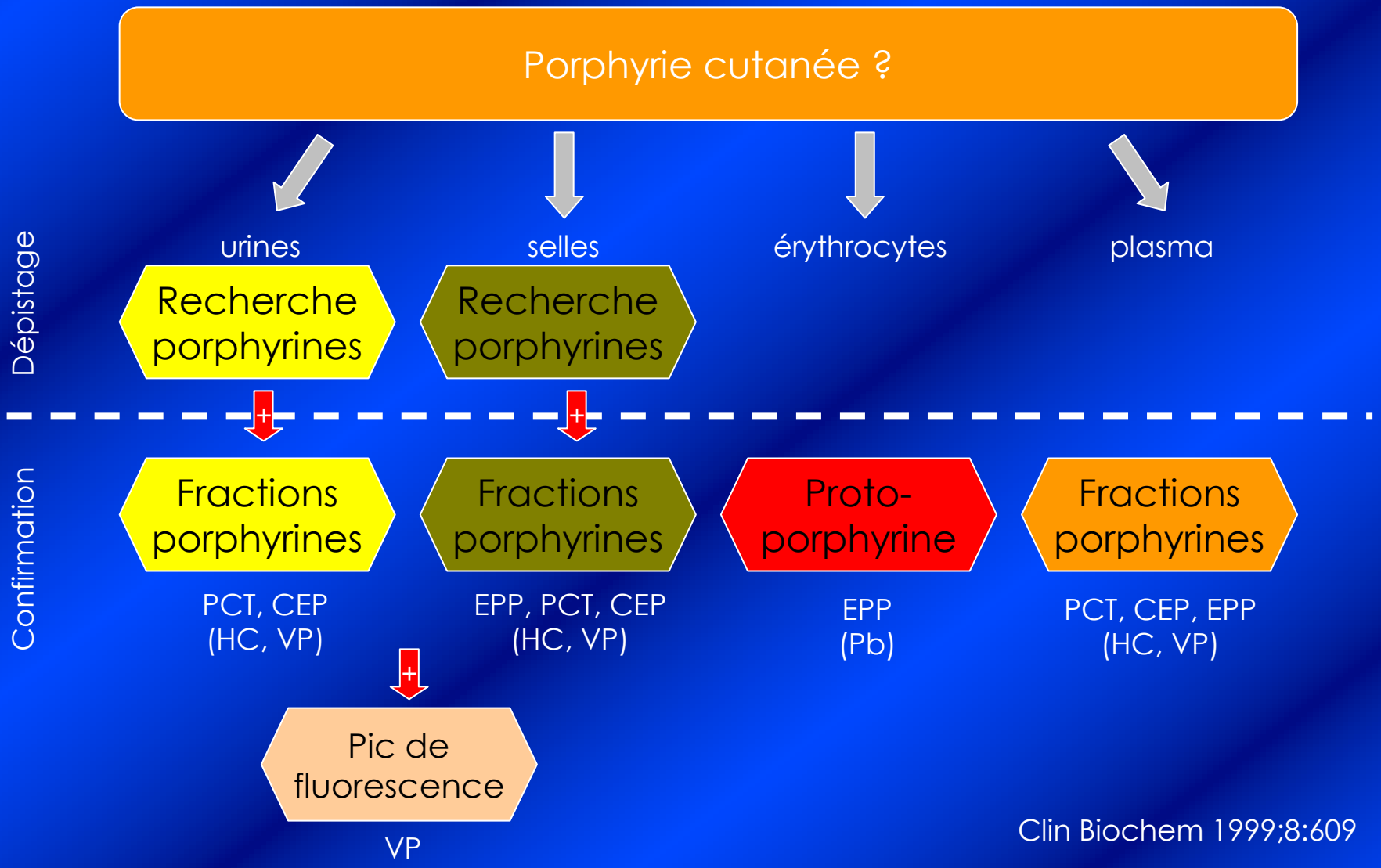


Diagnostic des porphyries aiguës en dehors des crises

- PBG, δ-ALA
- porphyrines fécales
- fluorescence plasmatique
- PBG-déaminase érythrocytaire

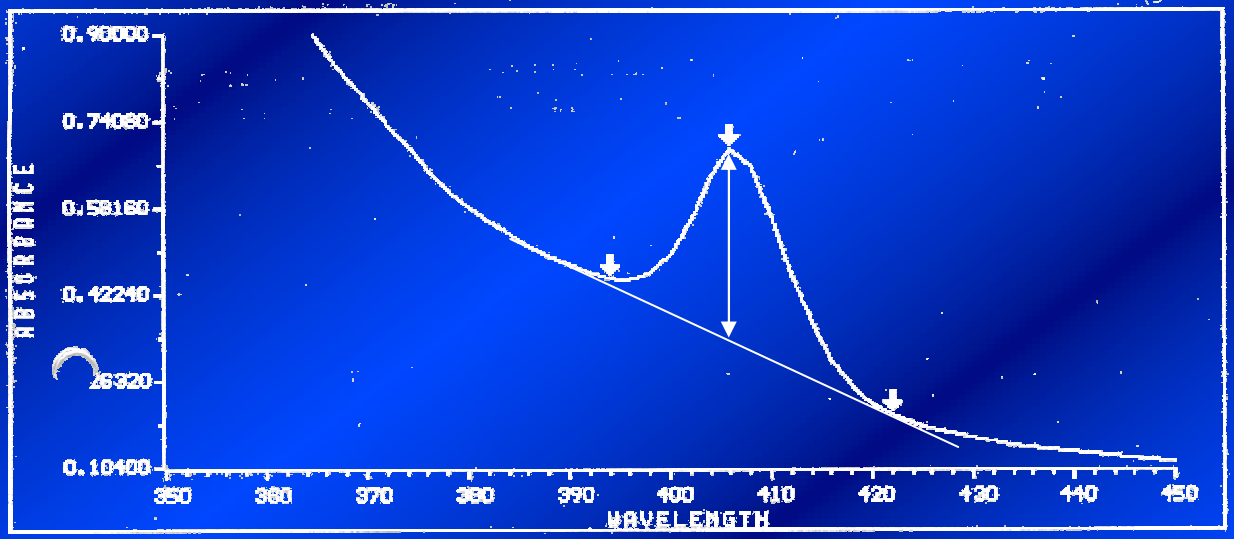
- Séquençage gènes: pas recommandé

Diagnostic des porphyries cutanées



Clin Biochem 1999;8:609

Diagnostic des porphyries cutanées



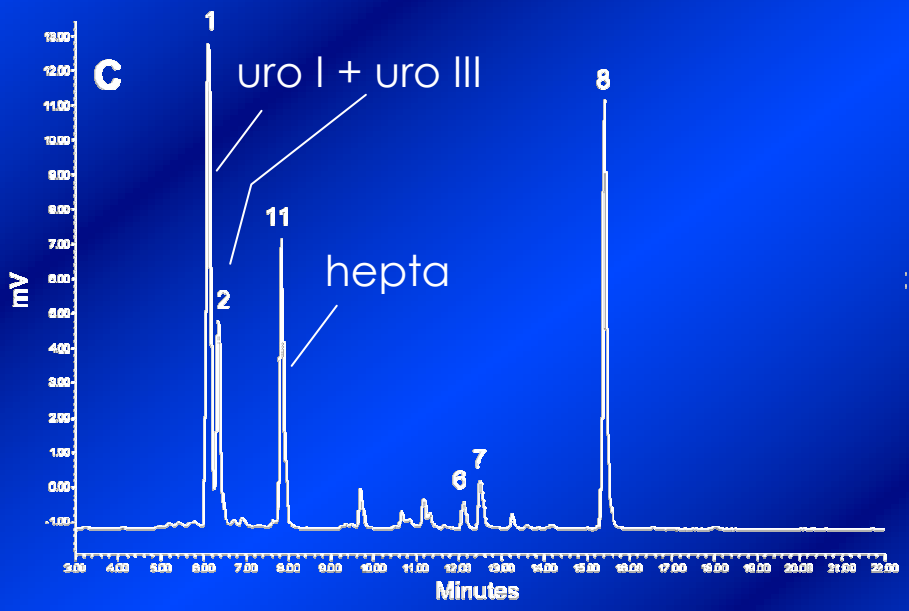
[porphyrines totales] (nmol/L) = $(A_{405} - (A_{405-x} + A_{405+x})/2) \times 2520$
V.R. < 110 nmol/L

- faux positifs:
  - cholestase
  - (pigments, hémoglobine)
- faux négatifs: test inapproprié

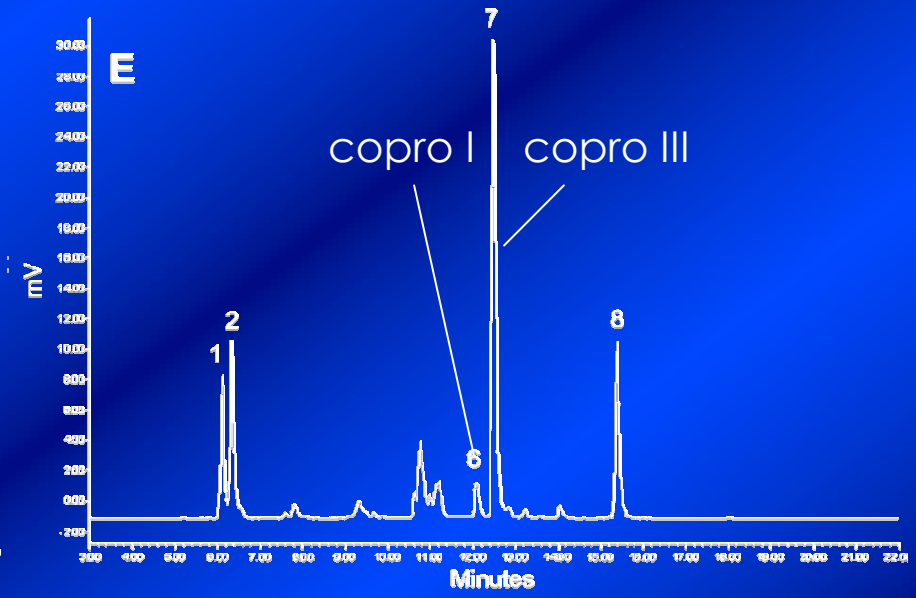
Ann Clin Biochem 1988;25:392
Ann Clin Biochem 1995;32:186

Diagnostic des porphyries cutanées

PCT: urine



VP: urine

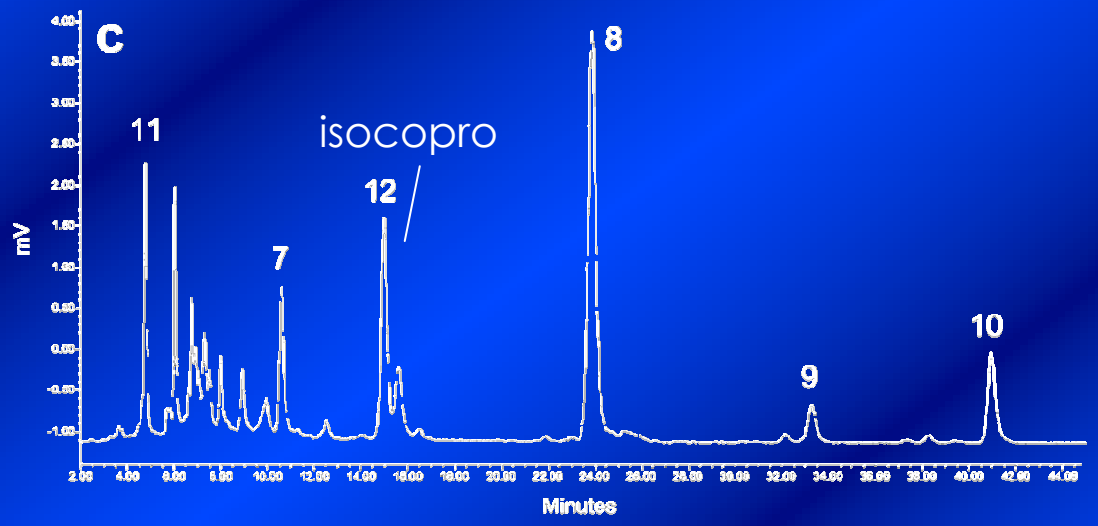


Cholestase: ↑ copro (I > III)

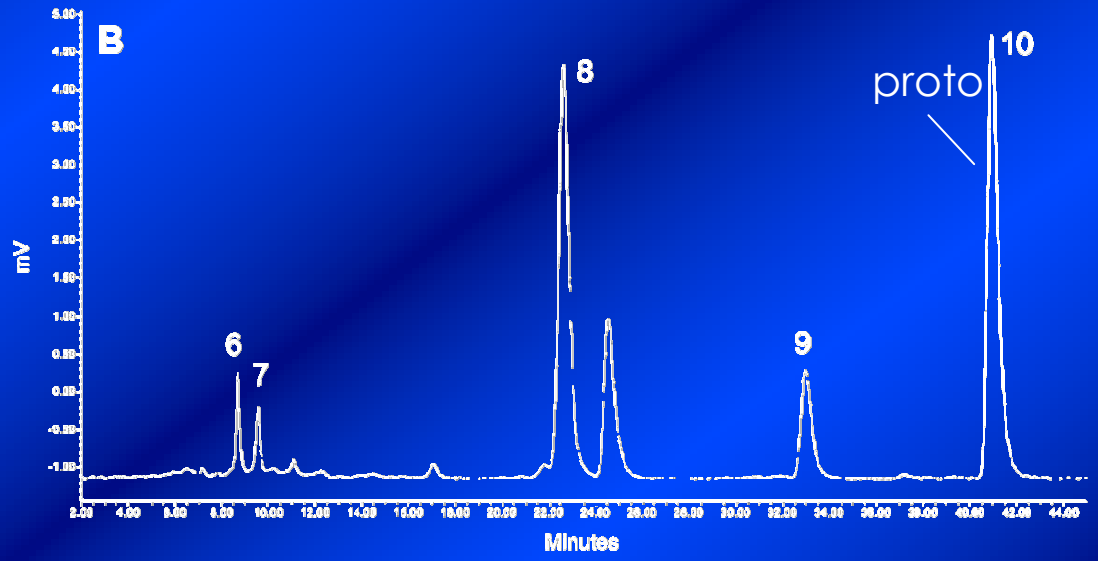
Clin Chem Lab Med 2006;44:1433

Diagnostic des porphyries cutanées

PCT: selles

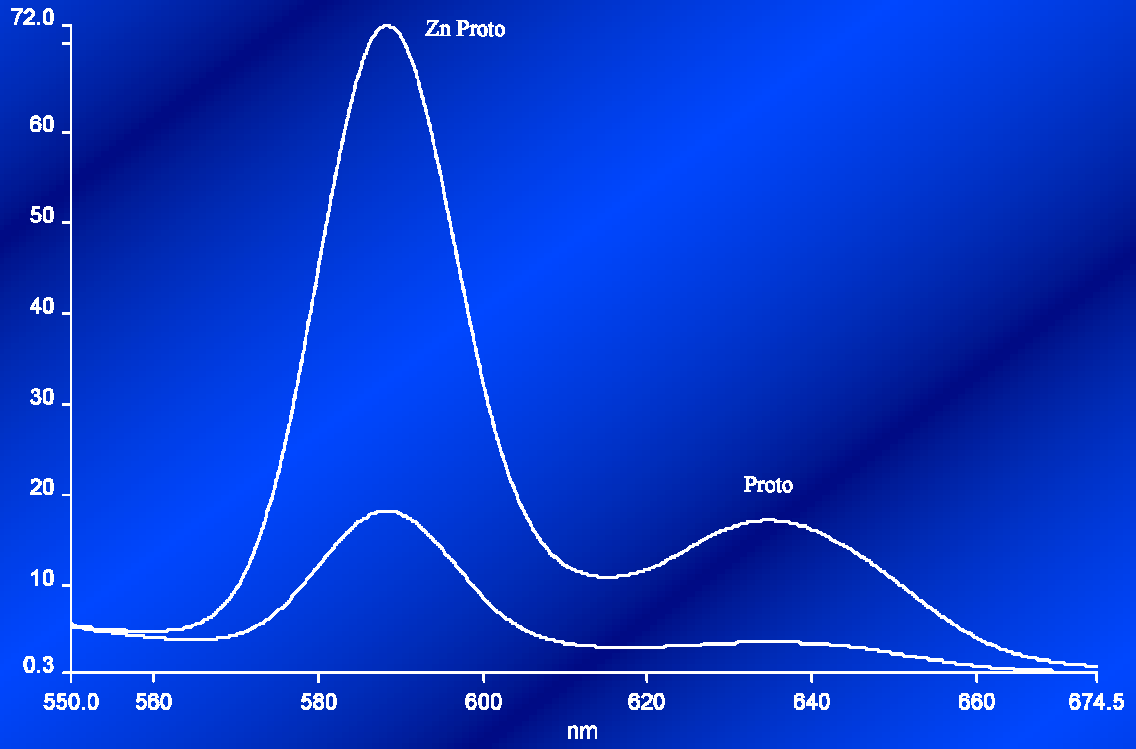


EPP: selles



Clin Chem Lab Med 2006;44:1433

Diagnostic des porphyries cutanées



- faux positifs:
  - carence martiale
  - Métaux lourds
- faux négatifs: test inapproprié

Aide à la prescription

- δ-ALA
- PBG
- Porphyrines

} urines

- Protoporphyrines érythrocytaires

- porphyrie cutanée
  - bulles ⟹ porphyrines (urines ou selles)
  - érythème ⟹ protoporphyrine libre (+ Zn-PP)
- porphyrie aiguë ⟹ PBG (+ δ-ALA)


EPI
European Porphyria Initiative
EVROPA
recens descripta
à
Guilielmo Blaeuw.
AMSTERDAM
PRAGA
VENETIA
ROMA
PARIS
LONDON
TOLEDO
LISBONA
OCEANVS SEPTENTRIONALIS
MYRMANSKOY MORE
OCEANVS DEVCALEDONIVS
RVSSIA
ASIÆ
TARTARIÆ PARS
HIBERNIA
OCCIDENTALIS
PONTVS EVXINVS
MARE ATLANTICVM
BARBARIA
MARE MEDITERRANEVM
MARMARICA
AFRICÆ PARS
Cyprus
Candia ol Creta

European Porphyria Initiative

Missions:

- aider à la compréhension des porphyries
- favoriser la prévention et le traitement
- fournir de l'information et de l'aide aux familles
- soutenir la recherche médicale

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Seminar

Porphyrias

Hervé Puy, Laurent Gouya, Jean-Charles Deybach

Lancet 2010; 375: 924–37

Assistance Publique Hôpitaux de Paris, Centre Français des Porphyries, Hôpital Louis Mourier, Colombes, France (Prof H Puy MD, Prof L Gouya MD, Prof J-C Deybach MD); Institut National de la Santé et de la Recherche Medicalé Unit 773, Centre de Recherches Biomédicales Bichat-Beaujon, Université Paris Diderot, Paris, France (Prof H Puy, Prof L Gouya, Prof J-C Deybach); and Université de Versailles, Saint Quentin en Yvelines, France (Prof L Gouya)

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Hereditary porphyrias are a group of eight metabolic disorders of the haem biosynthesis pathway that are characterised by acute neurovisceral symptoms, skin lesions, or both. Every porphyria is caused by abnormal function of a separate enzymatic step, resulting in a specific accumulation of haem precursors. Seven porphyrias are the result of a partial enzyme deficiency, and a gain of function mechanism has been characterised in a new porphyria. Acute porphyrias present with acute attacks, typically consisting of severe abdominal pain, nausea, constipation, confusion, and seizure, and can be life-threatening. Cutaneous porphyrias present with either acute painful photosensitivity or skin fragility and blisters. Rare recessive porphyrias usually manifest in early childhood with either severe cutaneous photosensitivity and chronic haemolysis or chronic neurological symptoms with or without photosensitivity. Porphyrias are still underdiagnosed, but when they are suspected, and dependent on clinical presentation, simple first-line tests can be used to establish the diagnosis in all symptomatic patients. Diagnosis is essential to enable specific treatments to be started as soon as possible. Screening of families to identify presymptomatic carriers is crucial to decrease risk of overt disease of acute porphyrias through counselling about avoidance of potential precipitants.

Introduction

Porphyrias are a group of eight panethnic inherited metabolic disorders of haem biosynthesis. Each results from a specific enzymatic alteration in the haem biosynthesis pathway (figure 1). Specific patterns of accumulation of the haem precursors 5-aminolaevulinic acid, porphobilinogen, and porphyrins are associated

5-aminolaevulinic acid. The first enzyme, 5-aminolaevulinic acid synthase (ALAS), is coded by two genes[3]—one erythroid specific (*ALAS2* on chromosome X) and one ubiquitous (*ALAS1* on chromosome 3). ALAS1 is the rate-limiting enzyme in the production of haem in the liver and is controlled via negative-feedback regulation by the intracellular uncommitted haem pool[4,5] (figure 2).

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Merci de votre
attention