UNIVERSITY OF KWAZULU-NATAL ™

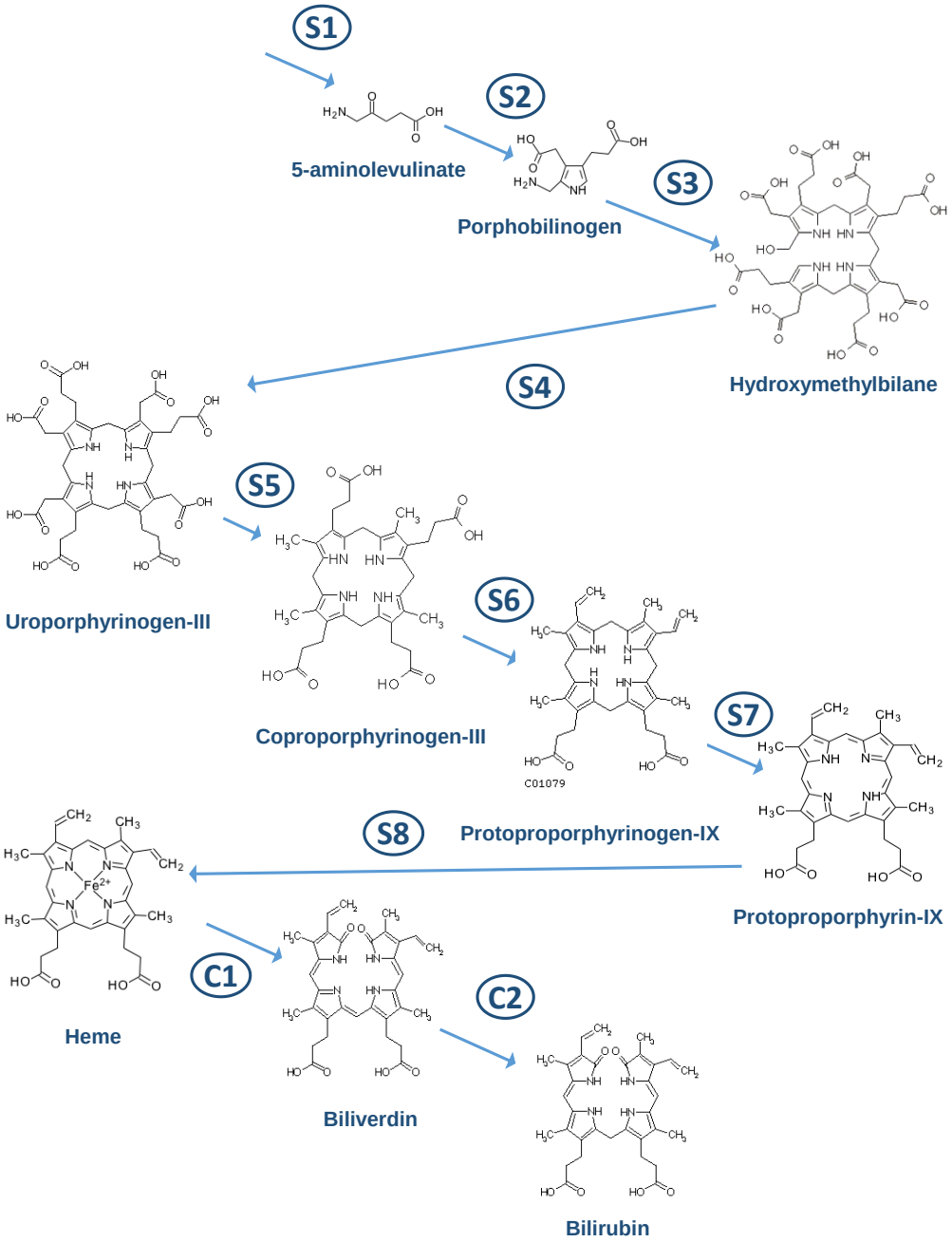
INYUVESI YAKWAZULU-NATALI

ACUTE PORPHYRIA

R J HIFT

SCHOOL OF CLINICAL MEDICINE
COLLEGE OF HEALTH SCIENCES

UKZN - INSPIRING GREATNESS



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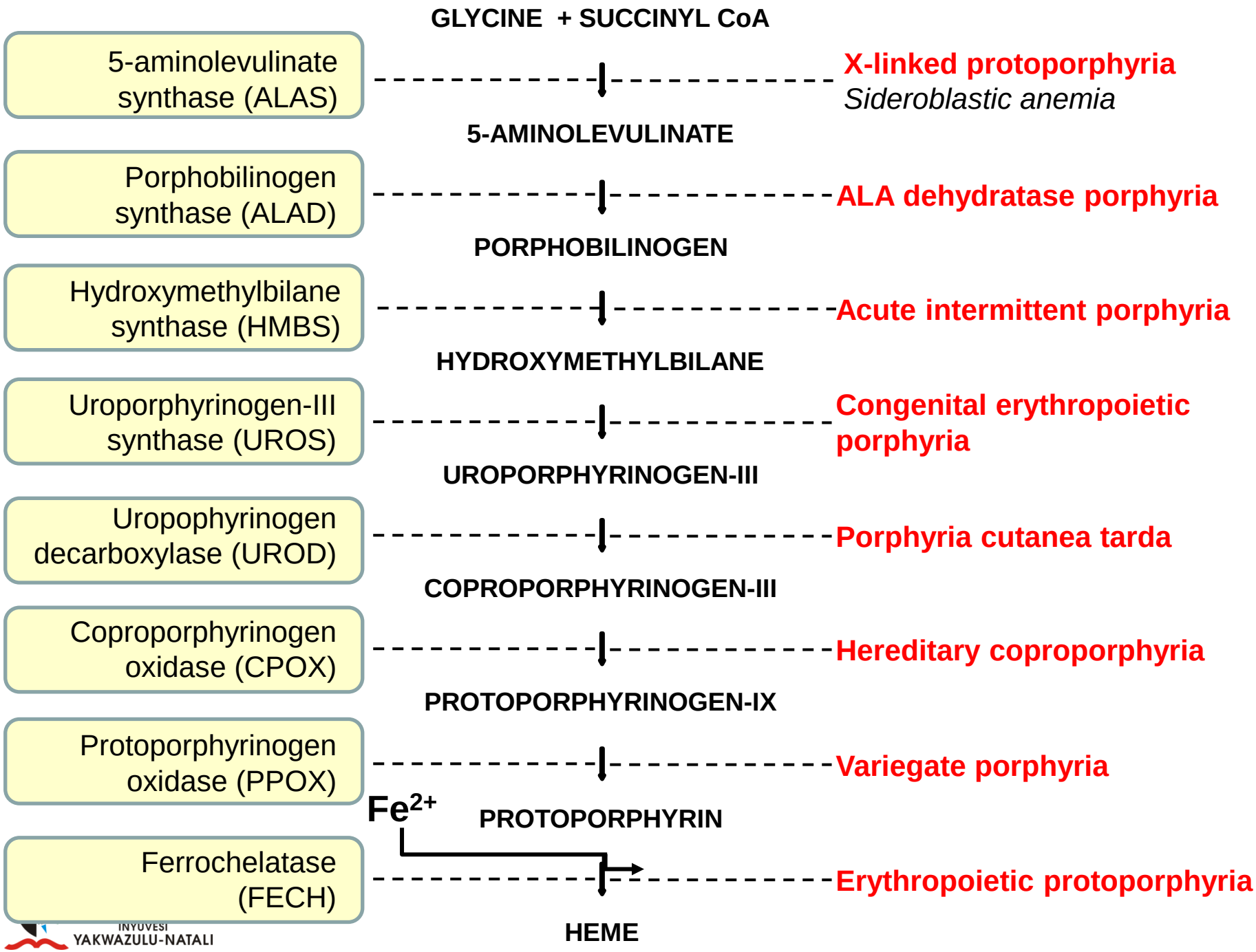
GLYCINE + SUCCINYL CoA
5-aminolevulinate synthase (ALAS)
X-linked protoporphyria
Sideroblastic anemia
5-AMINOLEVULINATE
Porphobilinogen synthase (ALAD)
ALA dehydratase porphyria
PORPHOBILINOGEN
Hydroxymethylbilane synthase (HMBS)
Acute intermittent porphyria
HYDROXYMETHYLBILANE
Uroporphyrinogen-III synthase (UROS)
Congenital erythropoietic porphyria
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Uropophyrinogen decarboxylase (UROD)
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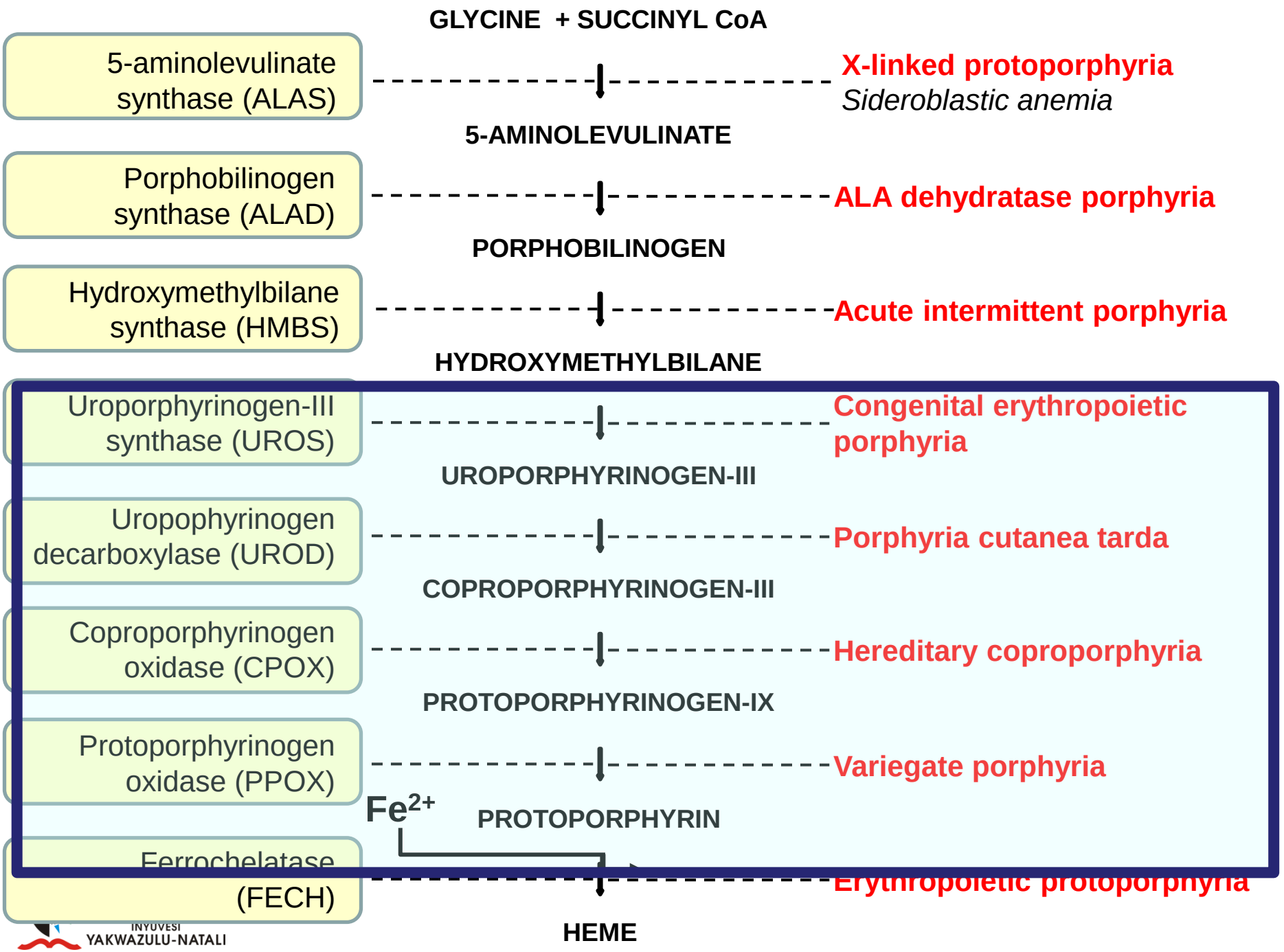
Coproporphyrinogen oxidase (CPOX)
Hereditary coproporphyria
PROTOPORPHYRINOGEN-IX
Protoporphyrinogen oxidase (PPOX)
Variegate porphyria
Fe2+
PROTOPORPHYRIN
Ferrochelatase (FECH)
Erythropoietic protoporphyria
HEME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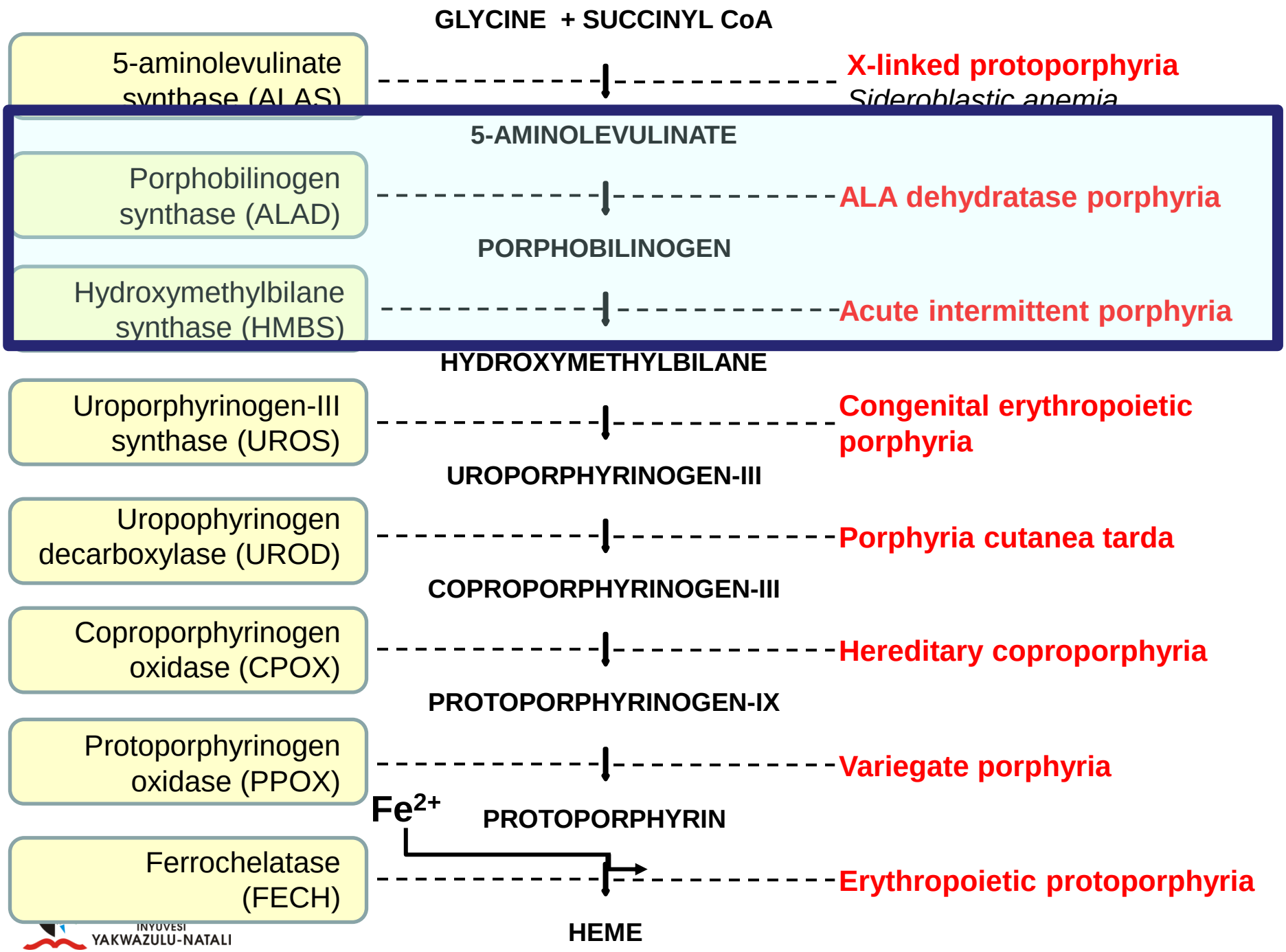
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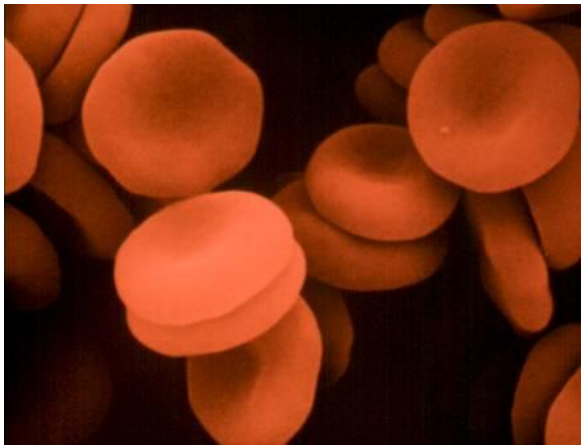
HEME

Disposition of haem



GLYCINE + SUCCINYL CoA

↓

AMINOLEVULINIC ACID

↓

PORPHOBILINOGEN

↓

HYDROXYMETHYLBILANE

↓

UROPORPHYRINOGEN

↓

COPROPORPHYRINOGEN

↓

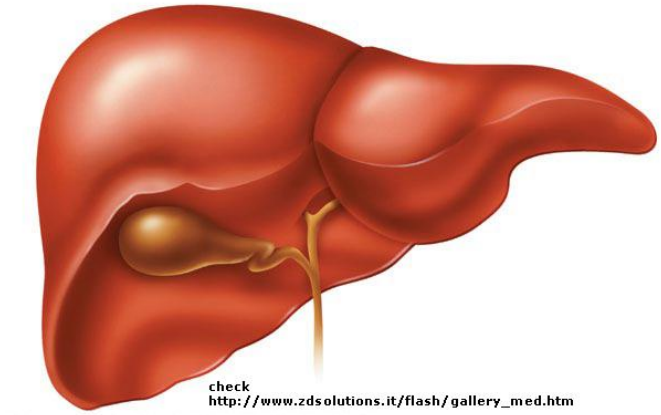
PROTOPORPHYRINOGEN

↓

PROTOPORPHYRIN

↓ ← Fe^{2+}

HAEM

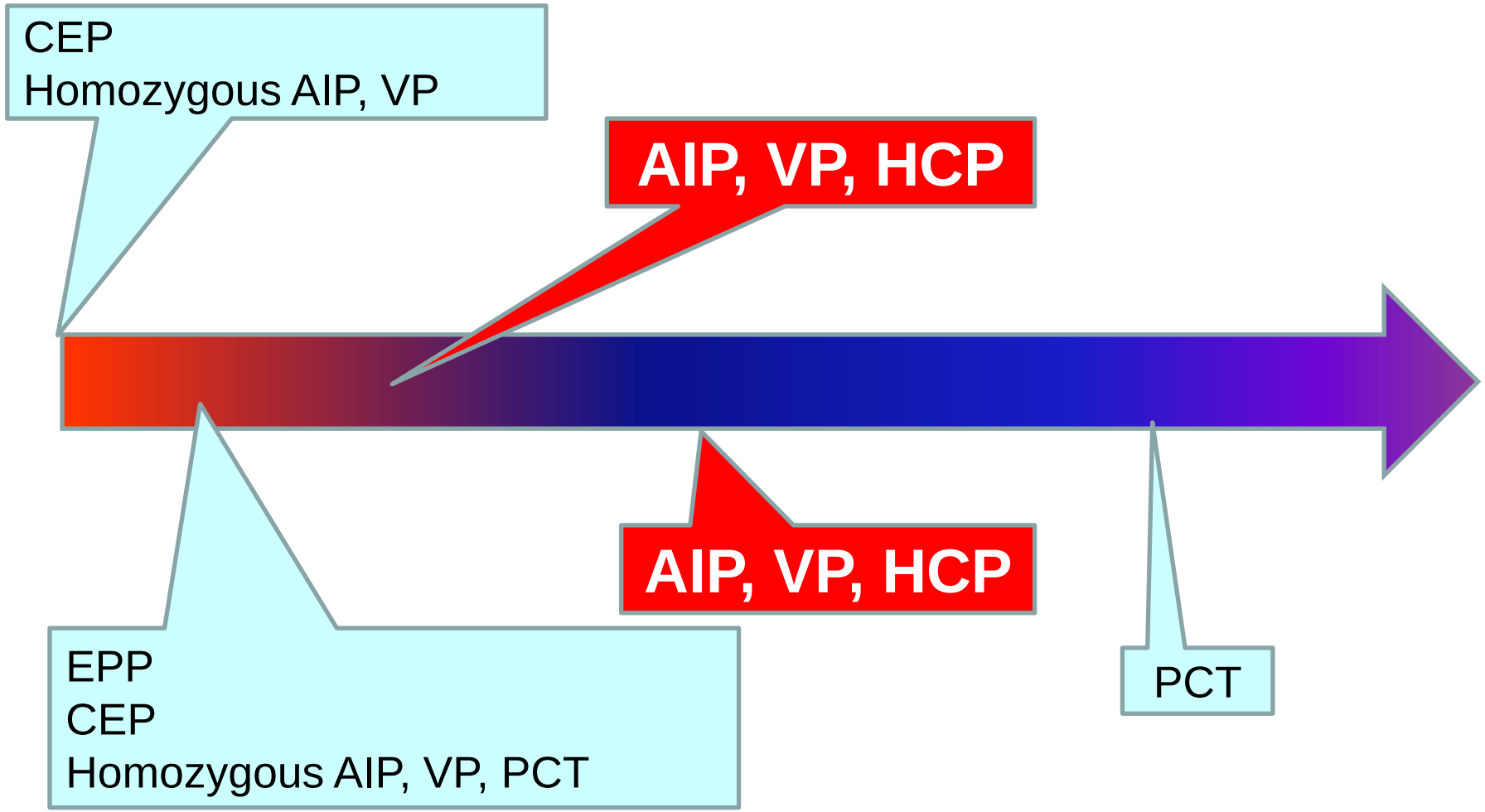


check
http://www.zdsolutions.it/flash/gallery_med.htm

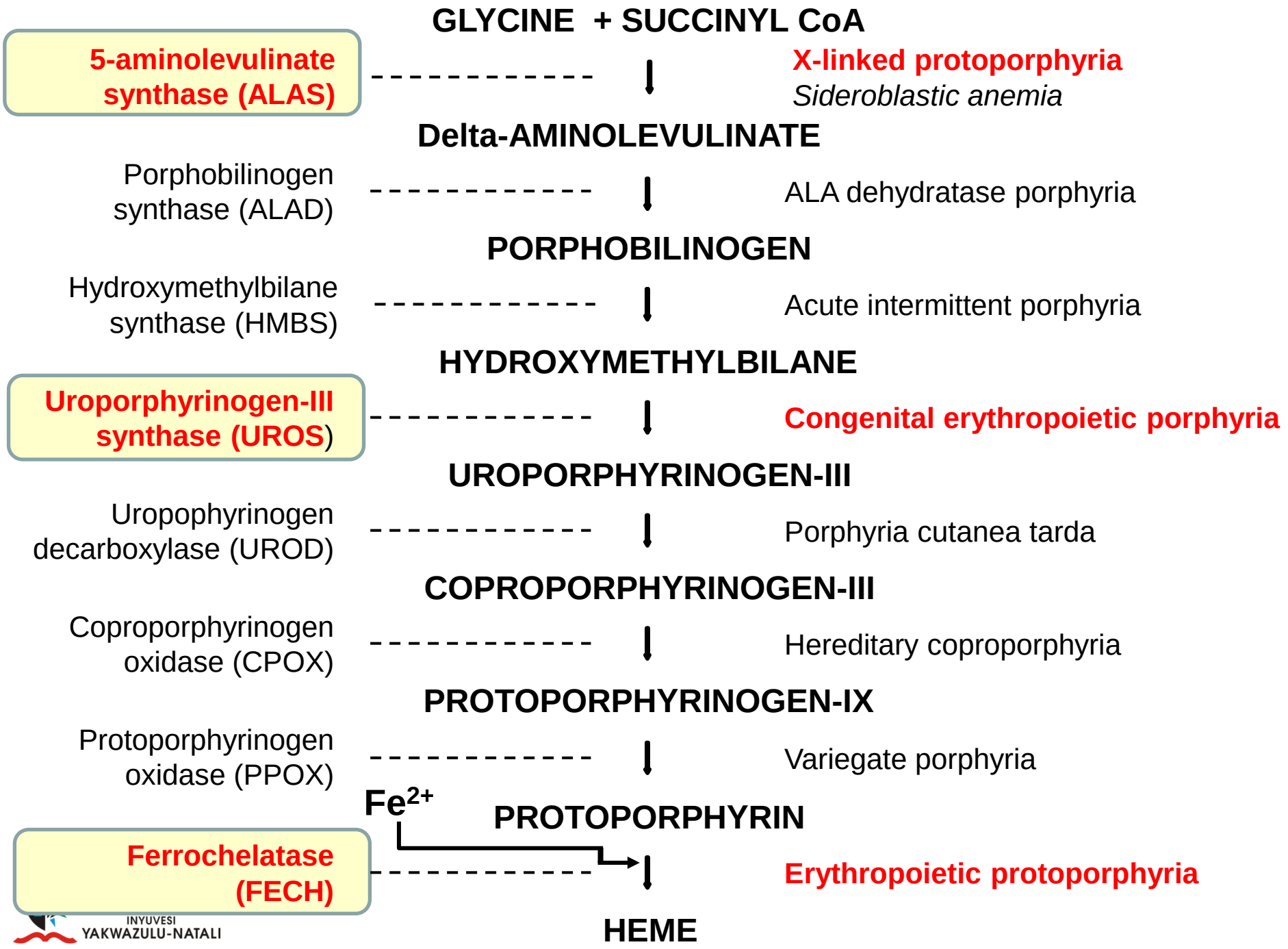
ERYTHROCYTE (80%)

LIVER (20%)

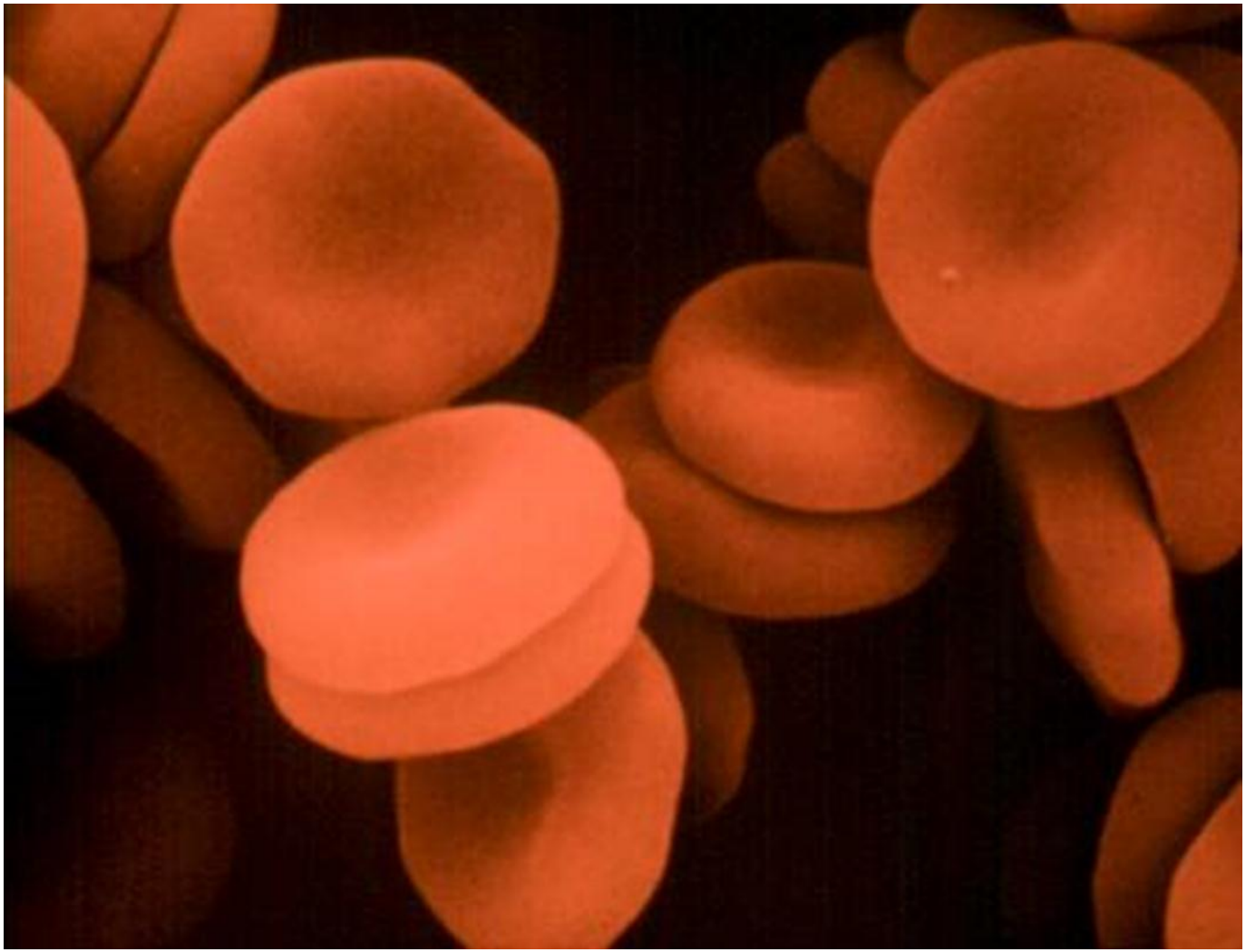
Age of onset


CEP
Homozygous AIP, VP
AIP, VP, HCP
AIP, VP, HCP
EPP
CEP
Homozygous AIP, VP, PCT
PCT

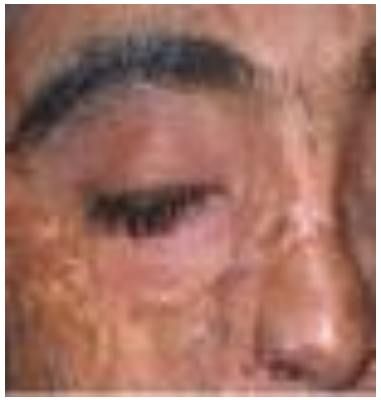
ERYTHROPOIETIC PORPHYRIAS

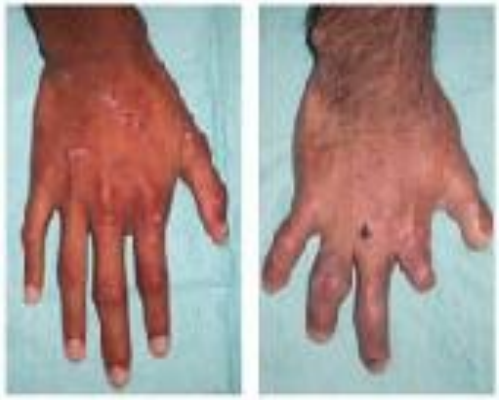


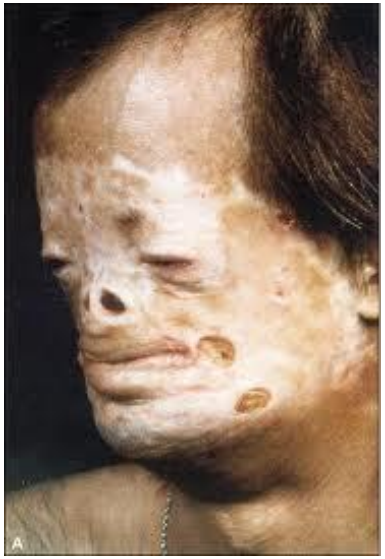
Fluorescence



Congenital erythropoietic porphyria







Hematological complications

- Associated with early-onset CEP
- Predictive of poor prognosis
- Features
  - Neonatal jaundice
  - Splenomegaly
  - Hemolytic anemia
    - May be transfusion-dependent
  - Thrombocytopenia

Erythropoietic protoporphyria

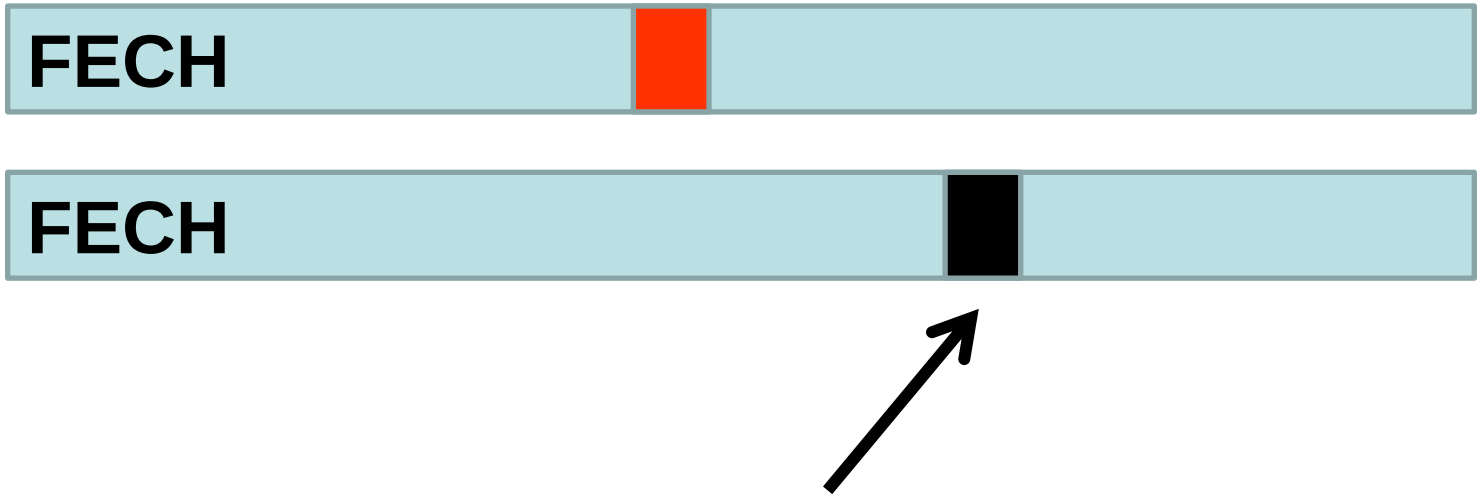
Immediate photosensitivity

Early onset...

Late diagnosis

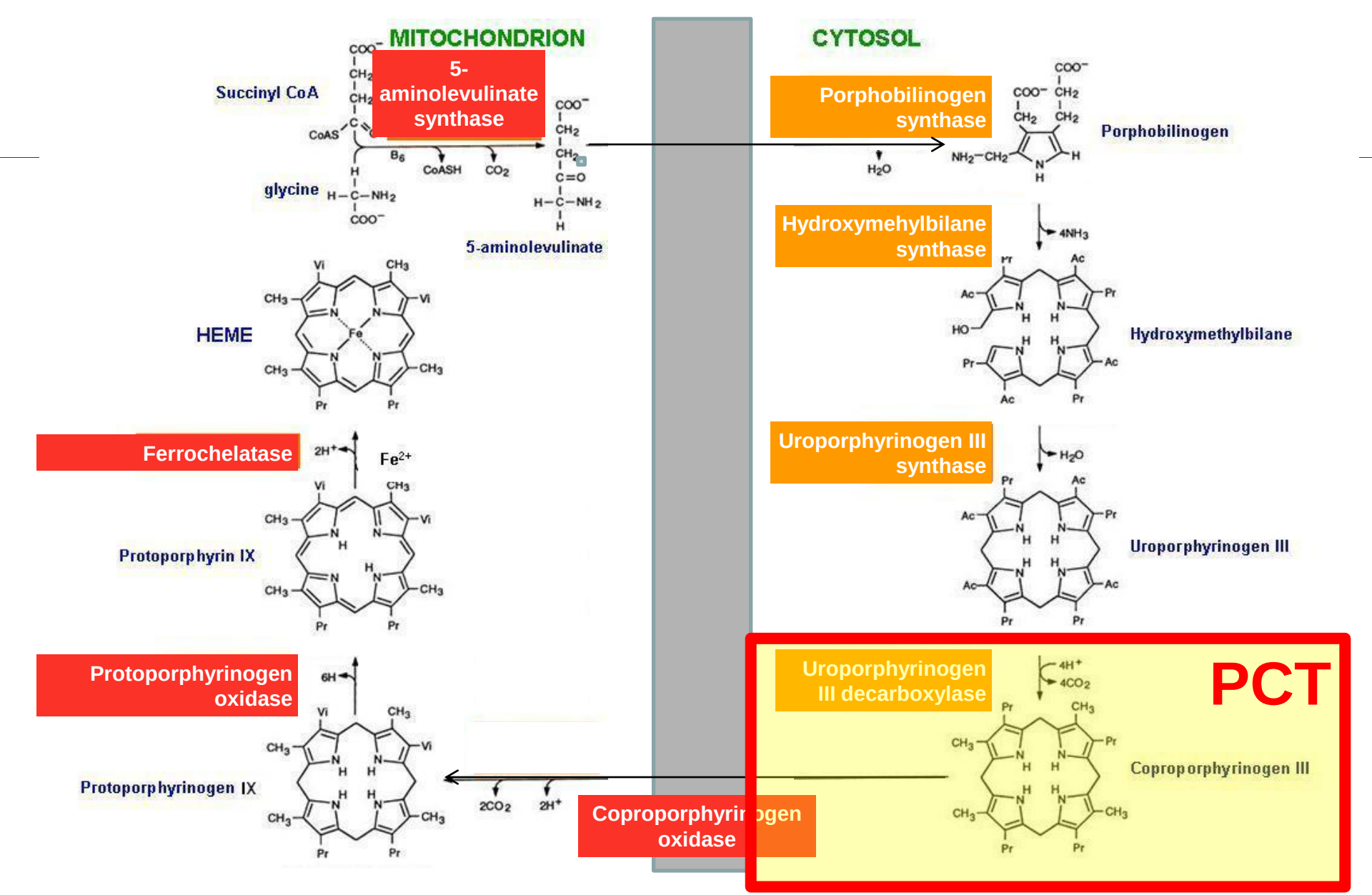
http://www.mommymdguides.com/wp-content/uploads/2011/02/QuestionsBabysFirstYearSunProtection.jpg

“Pseudodominant” inheritance of EPP



Alternative splice site
Polymorphism
10% of European populations

HEPATIC PORPHYRIAS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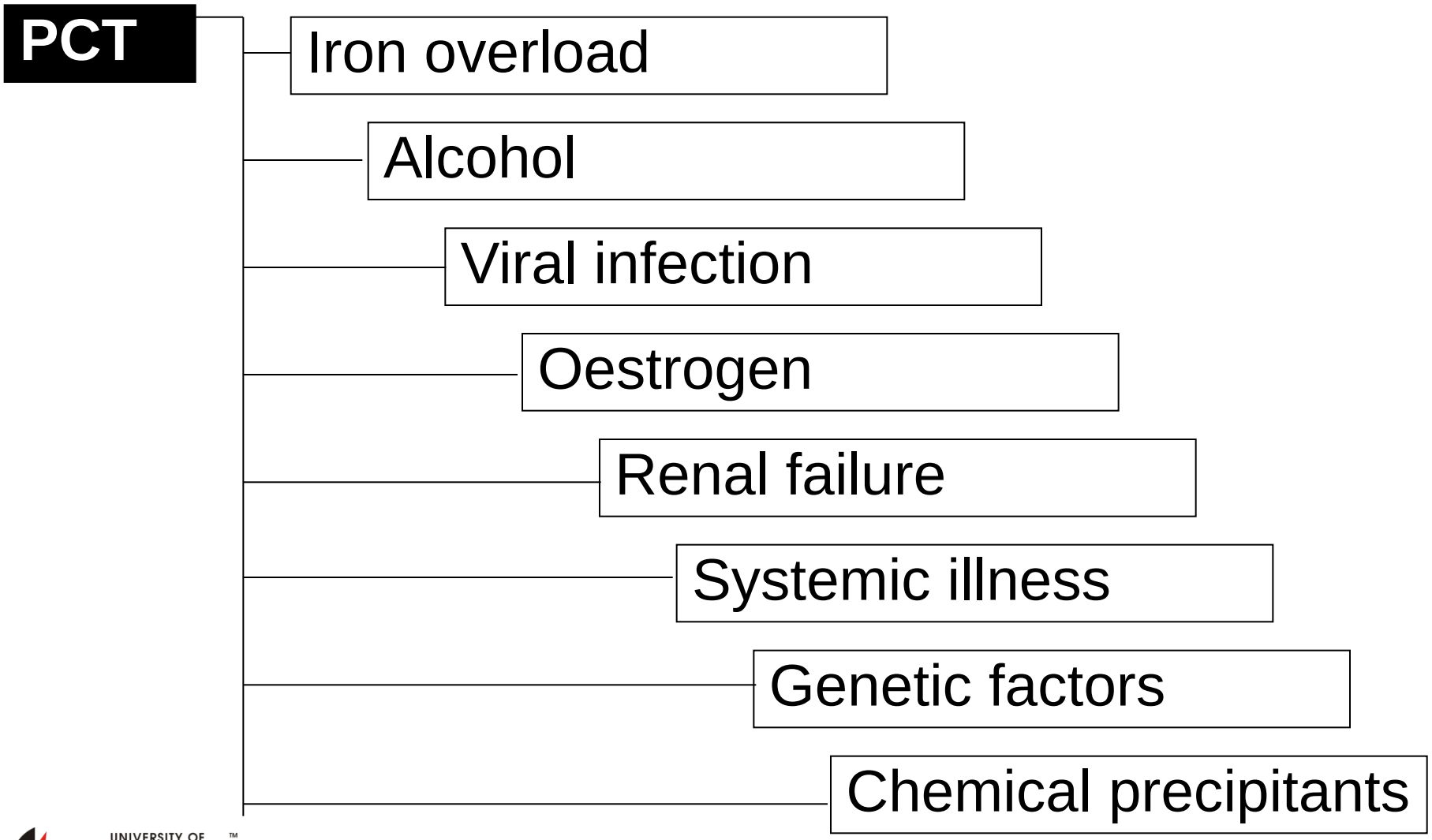
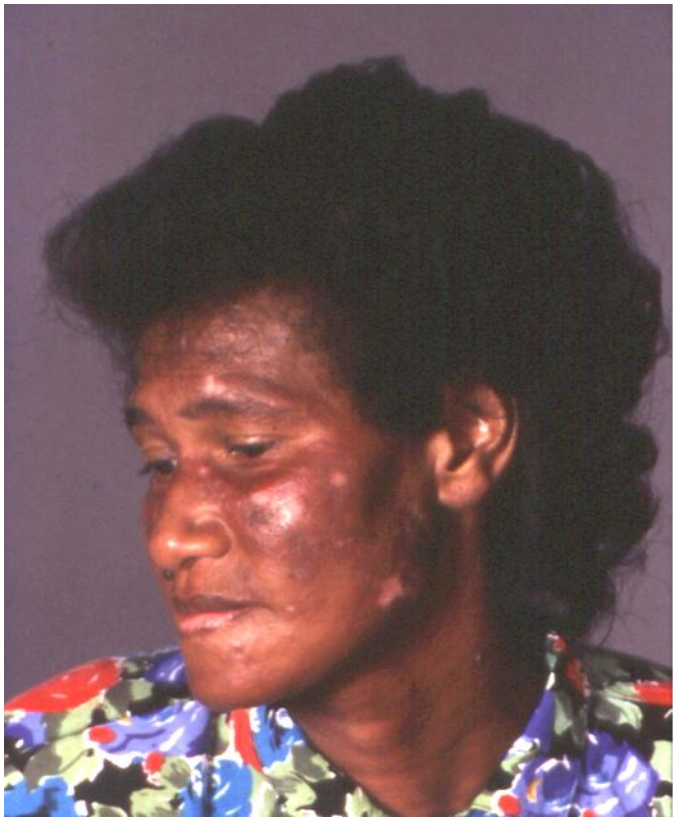
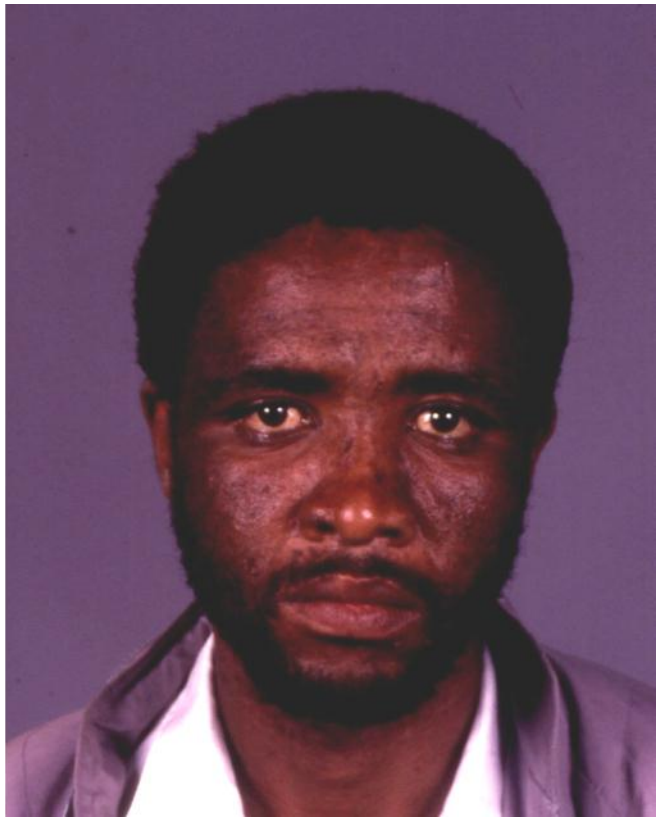
Uroporphyrinogen III
Protoporphyrinogen oxidase
Protoporphyrinogen IX
Uroporphyrinogen III decarboxylase
PCT
Coproporphyrinogen III
Coproporphyrinogen oxidase

Precipitants of PCT

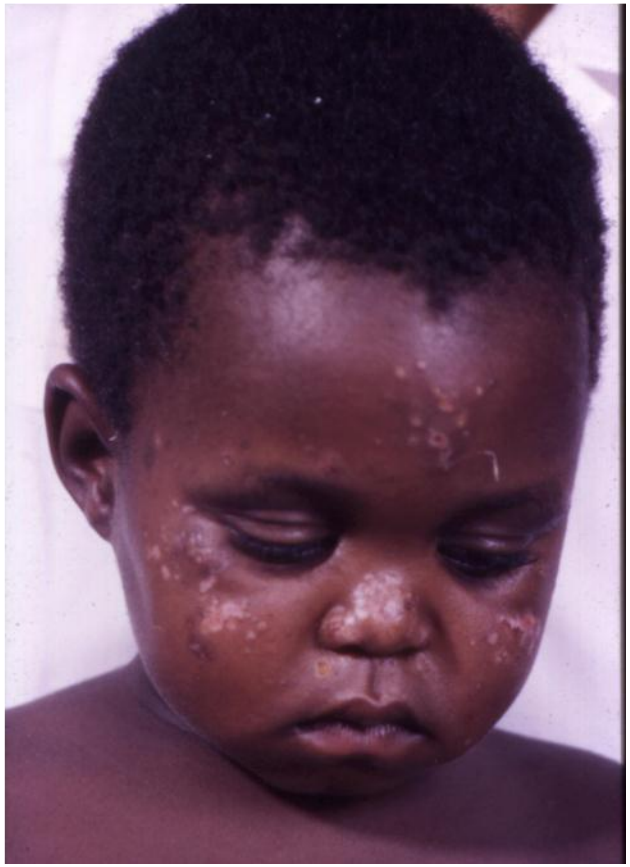


Porphyia cutanea tarda (PCT)





Infantile PCT



Suid-Afrikaanse Tydskrif vir Geneeskunde : South African Medical Journal

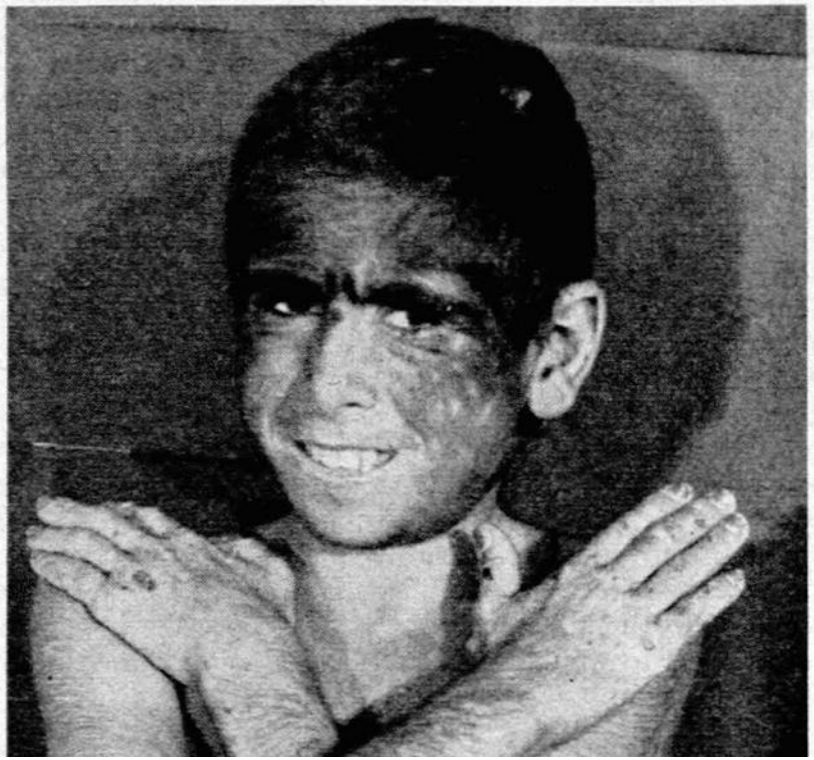
Kaapstad, 24 Junie 1961 Deel 35 No 25 Volume 35 Cape Town, 24 June 1961

THE TURKISH EPIDEMIC OF PORPHYRIA

GEOFFREY DEAN, M.D., M.R.C.P.

Senior Physician, Provincial Hospital, Port Elizabeth

In 1955 Dr. Cihad Cam, who is the Director of the skin clinic in Diyarbakir in Eastern Turkey, found that he was seeing a large number of children with sores and blisters on the face and on the back of their hands. These children had dark pigmented skins and great hairiness of their faces. The urine of the children was reddish-brown in colour and when Dr. Cam examined the urine in ultraviolet light, using a Wood's filter, it gave a brilliant red fluorescence. He realized these children had porphyria. He had not seen children with porphyria before 1955, but in that year and in each subsequent year he saw many hundreds of affected children[1,2] (Fig. 1).

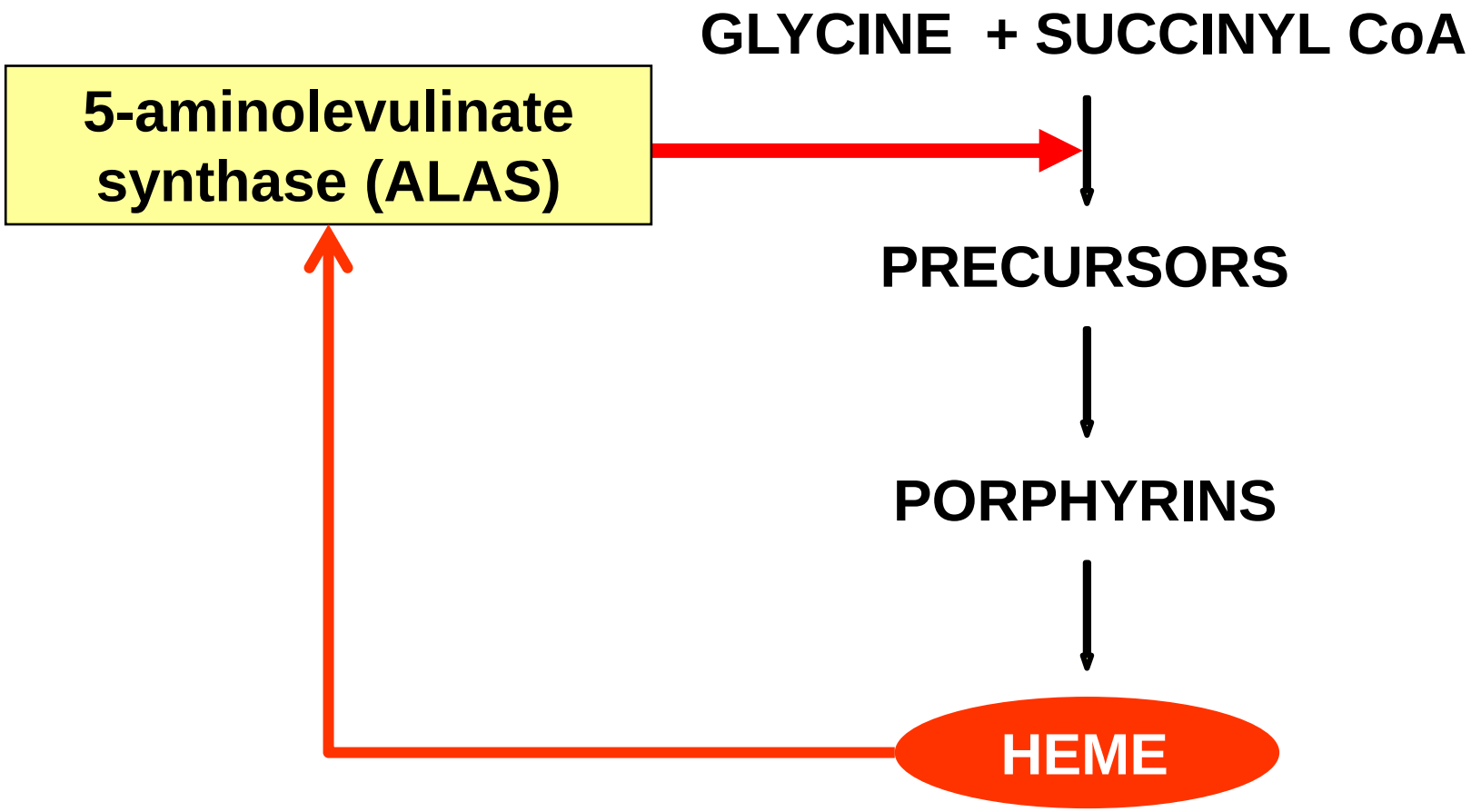


This epidemic aroused great interest and concern in Turkey. Children were admitted for further study under the care of Dr. Joseph Wray to the Hacettepe Children's Hospital in Ankara and also to a hospital in Istanbul. Prof. Cecil Watson of Minneapolis, renowned for his porphyria research, sent one of his outstanding research assistants to assist in the biochemical investigation of the children, and Dr. Rudi Schmid, an American expert on porphyria, visited Turkey and made a report on the epidemic.[3]

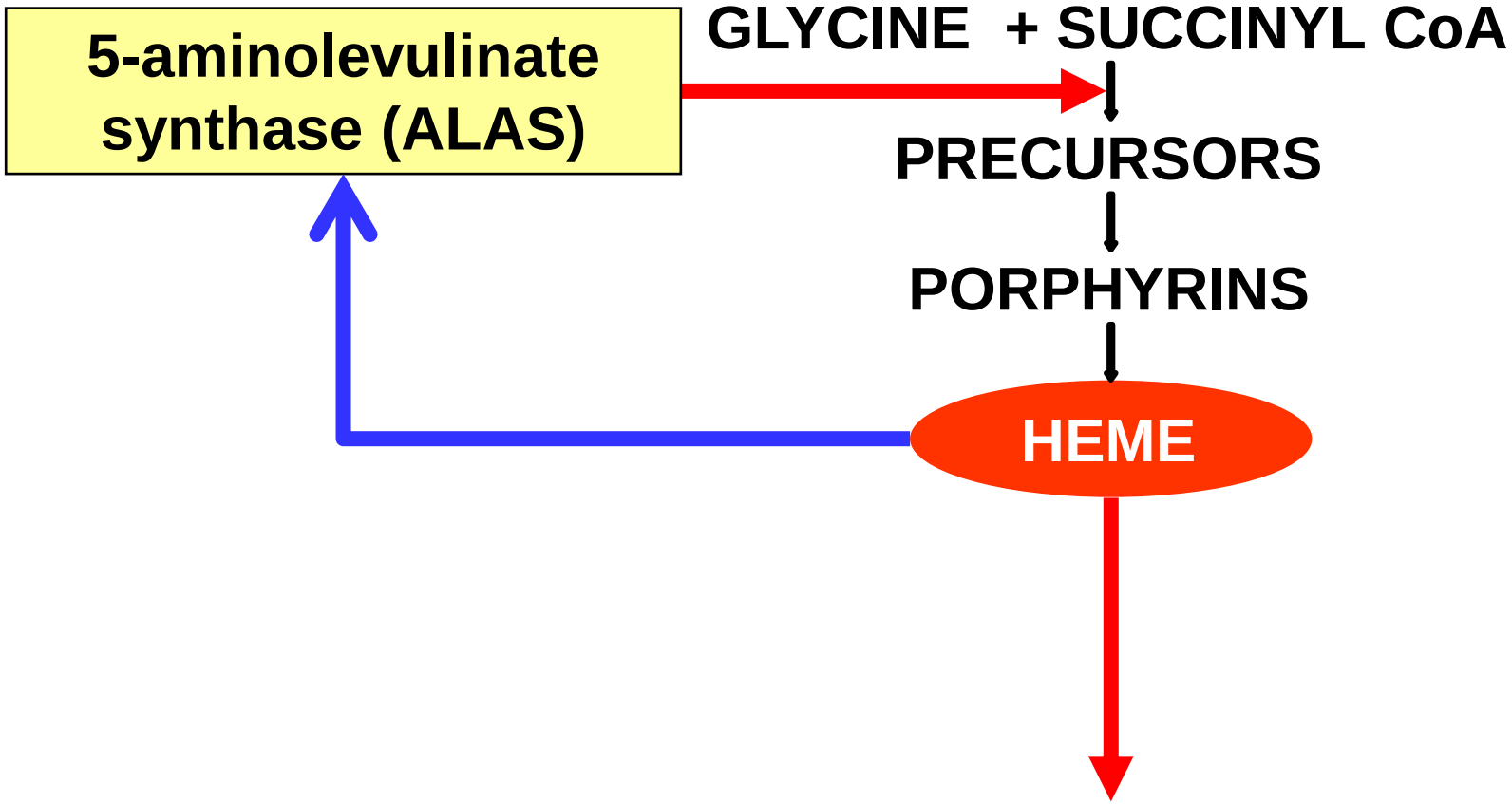
ACUTE HEPATIC PORPHYRIAS

Age of onset

Control of heme biosynthesis



Drug induction of the acute porphyrias



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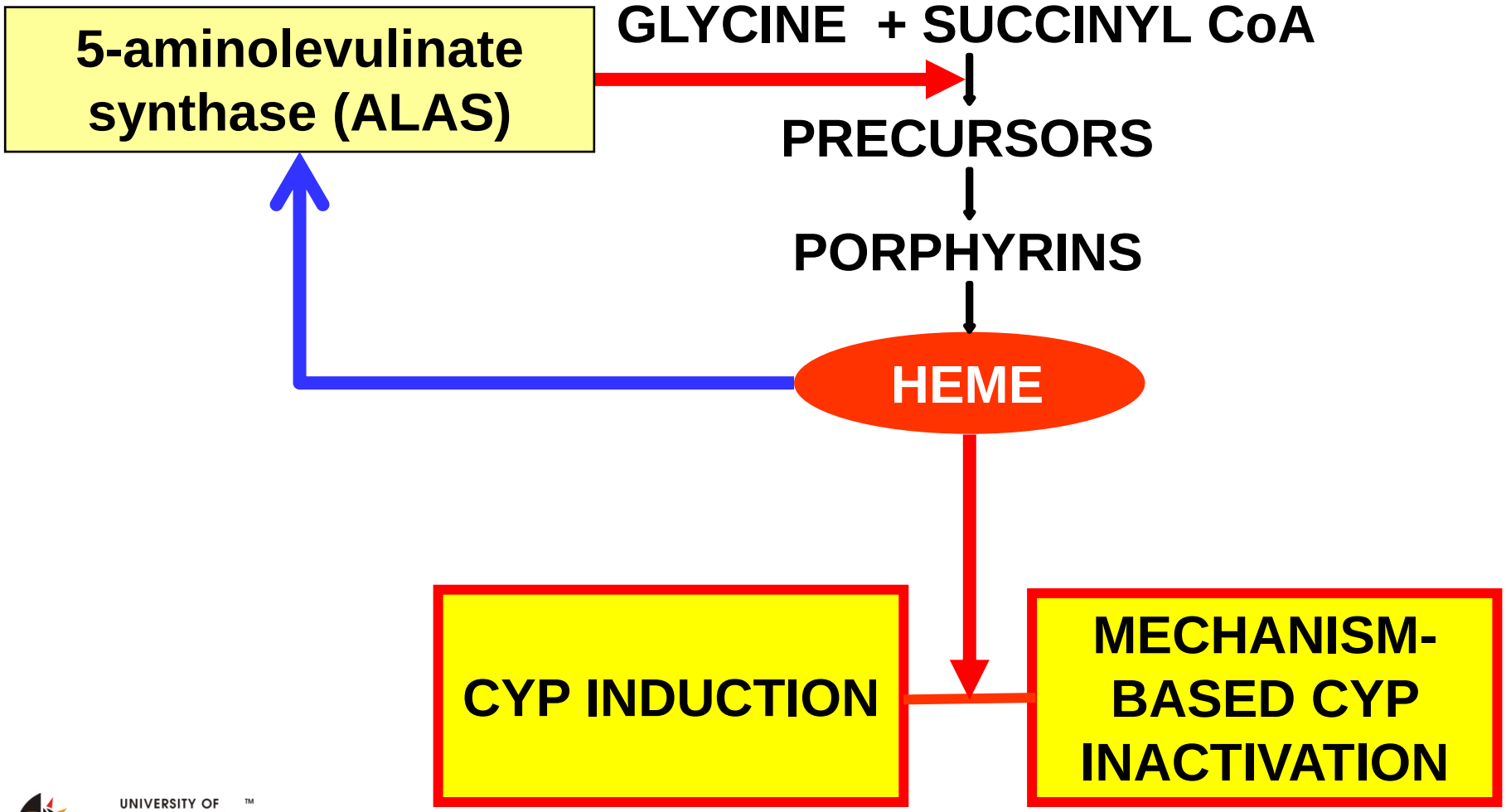

Prediction of porphyrogenicity

Pharmacology & Therapeutics 132 (2011) 158–169

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Drugs in porphyria: From observation to a modern algorithm-based system for the prediction of porphyrogenicity

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[b] Porphyria Centre Sweden, Department of Laboratory Medicine, Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden
[c] Norwegian Porphyria Centre, Haukeland University Hospital, Bergen, Norway
[d] Institute of Medicine, University of Bergen, Bergen, Norway

ARTICLE INFO

Keywords:
Porphyria
Porphyrogenicity
Drug metabolism

ABSTRACT

The acute porphyrias are a group of disorders which result from inherited defects in the enzymes of the heme biosynthetic pathway. Affected patients are prone to potentially fatal acute attacks. These attacks are frequently precipitated by exposure to commonly used drugs. Correctly identifying the safety or otherwise of drugs in porphyria is therefore important. In this review we describe how clinical experience and the findings of experimental systems using whole animal or cell culture models have been interpreted to determine porphyrogenicity, that is the potential of a drug to induce an acute attack in a patient carrying a gene for acute porphyria.

It is now well established that induction of delta-aminolevulinic acid synthase, the rate controlling enzyme of the heme biosynthetic pathway, is fundamental to porphyrogenicity, and that drug-induced hepatic heme depletion via induction or suicidal inactivation of cytochrome P450 is central to this process. The process is now sufficiently well understood that prediction of porphyrogenicity from structural and functional information alone would appear to be justified.

Contents

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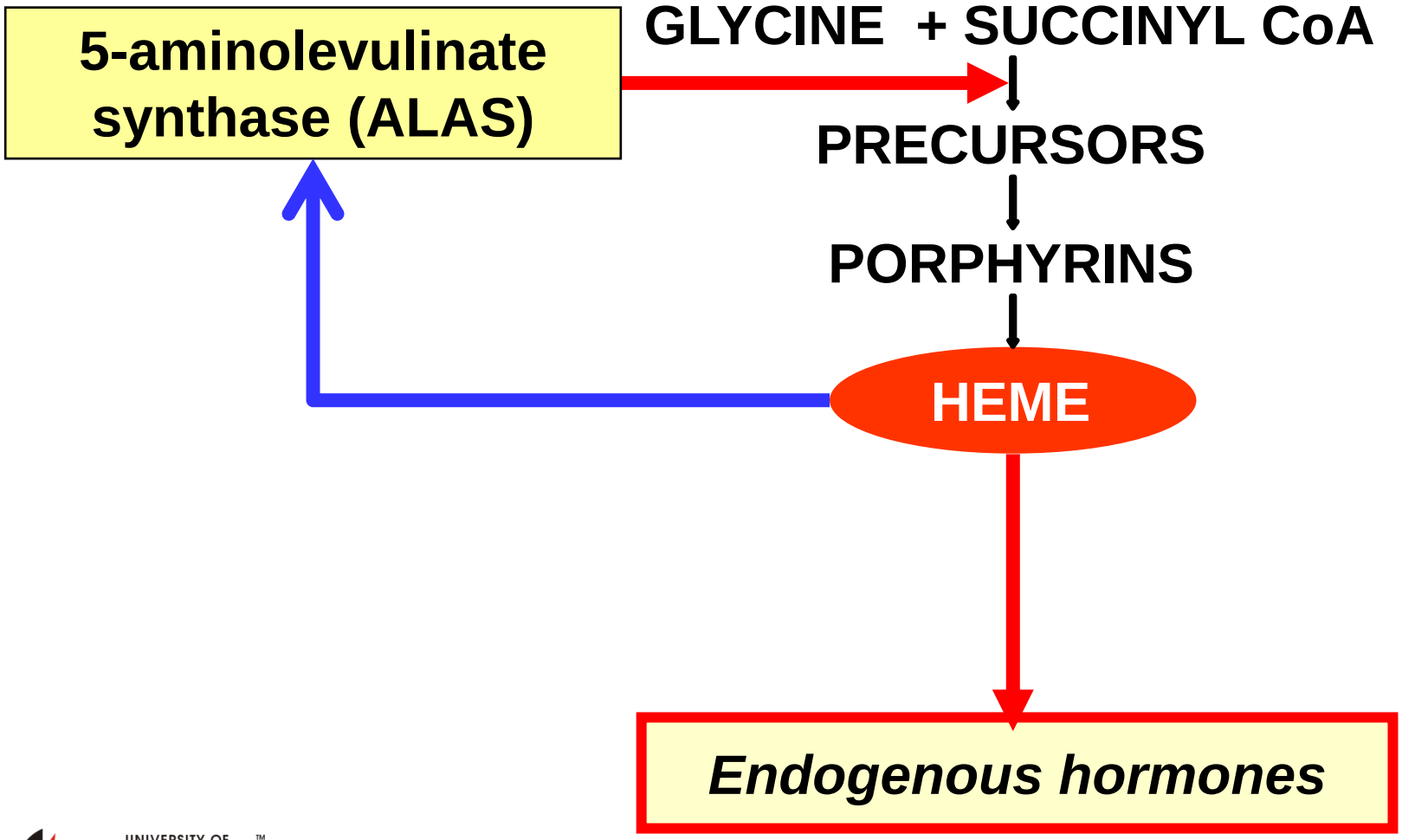
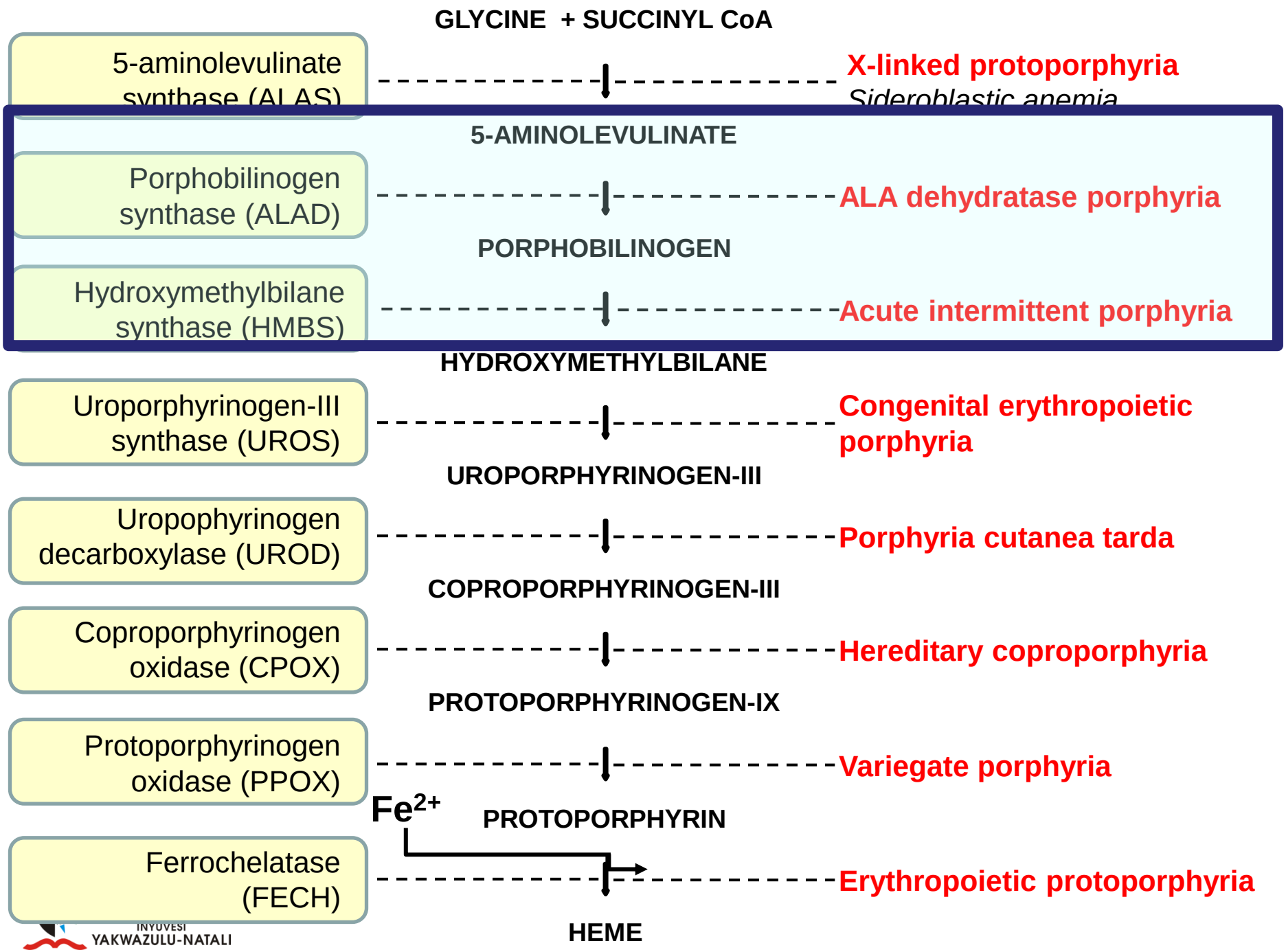
Hift RJ, Thunell S, Brun A. Pharmacol Ther *(2011).*

Induction of the acute porphyrias

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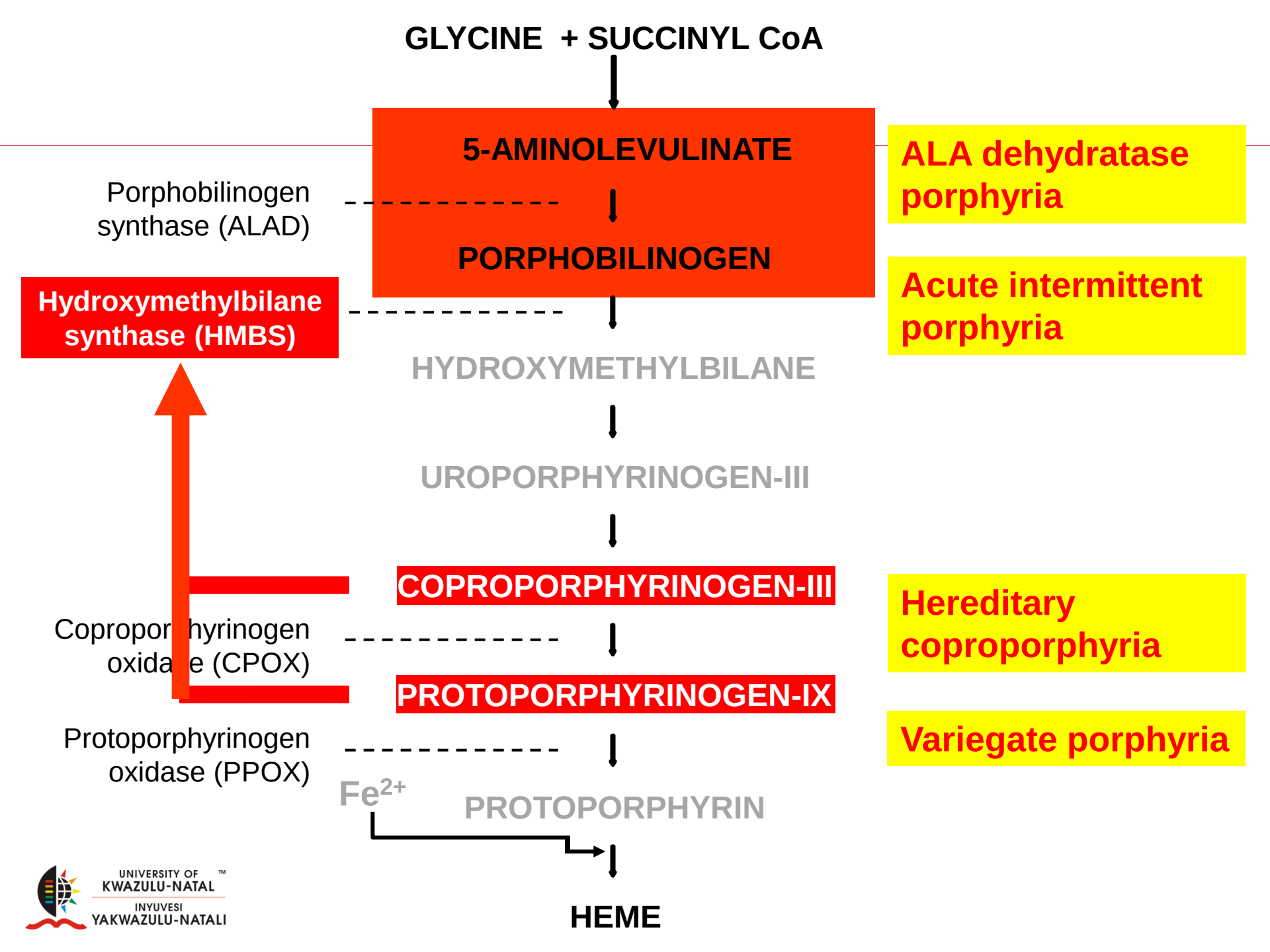

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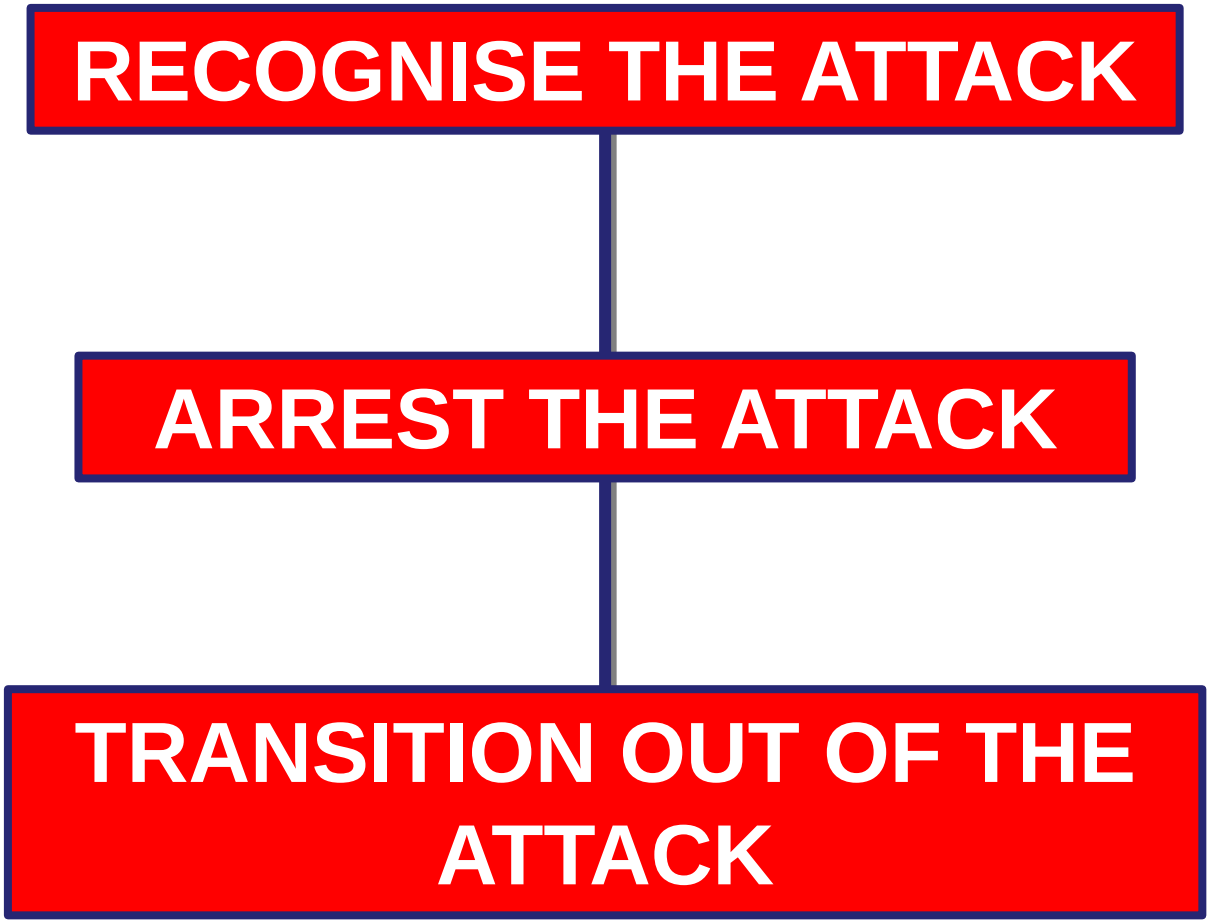
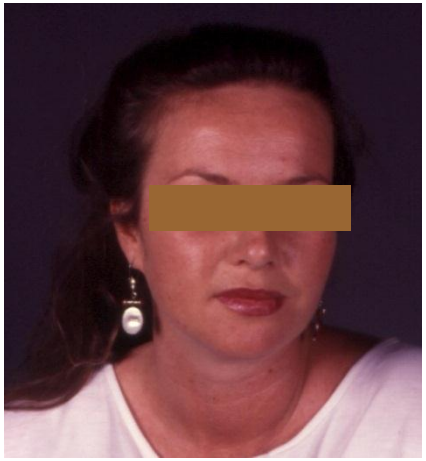
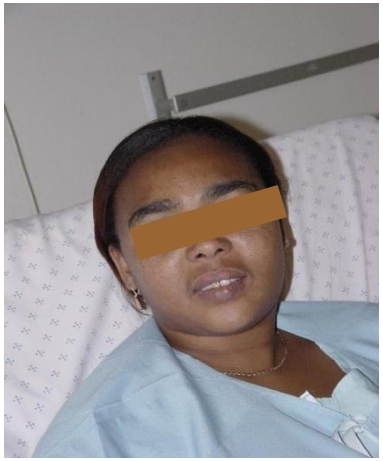
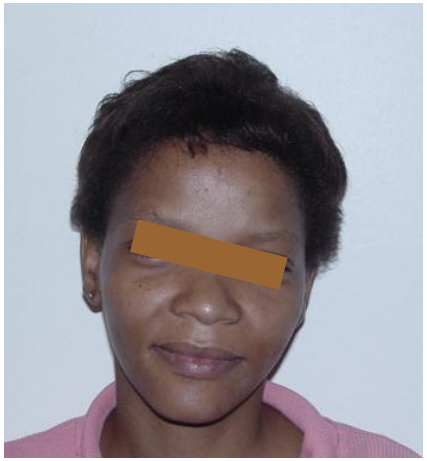
Steps in management

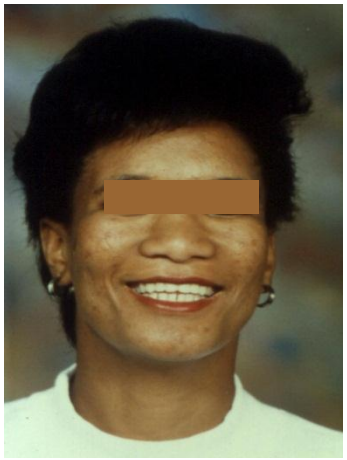


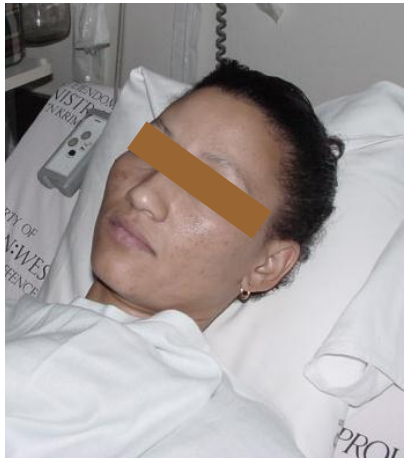
Acute intermittent porphyria

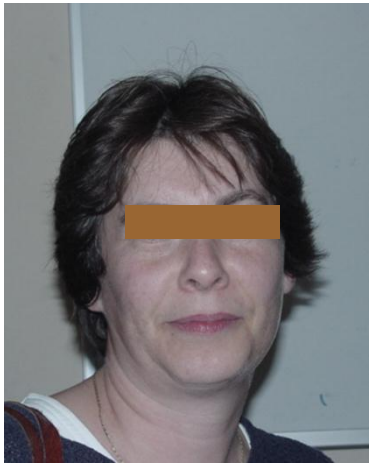


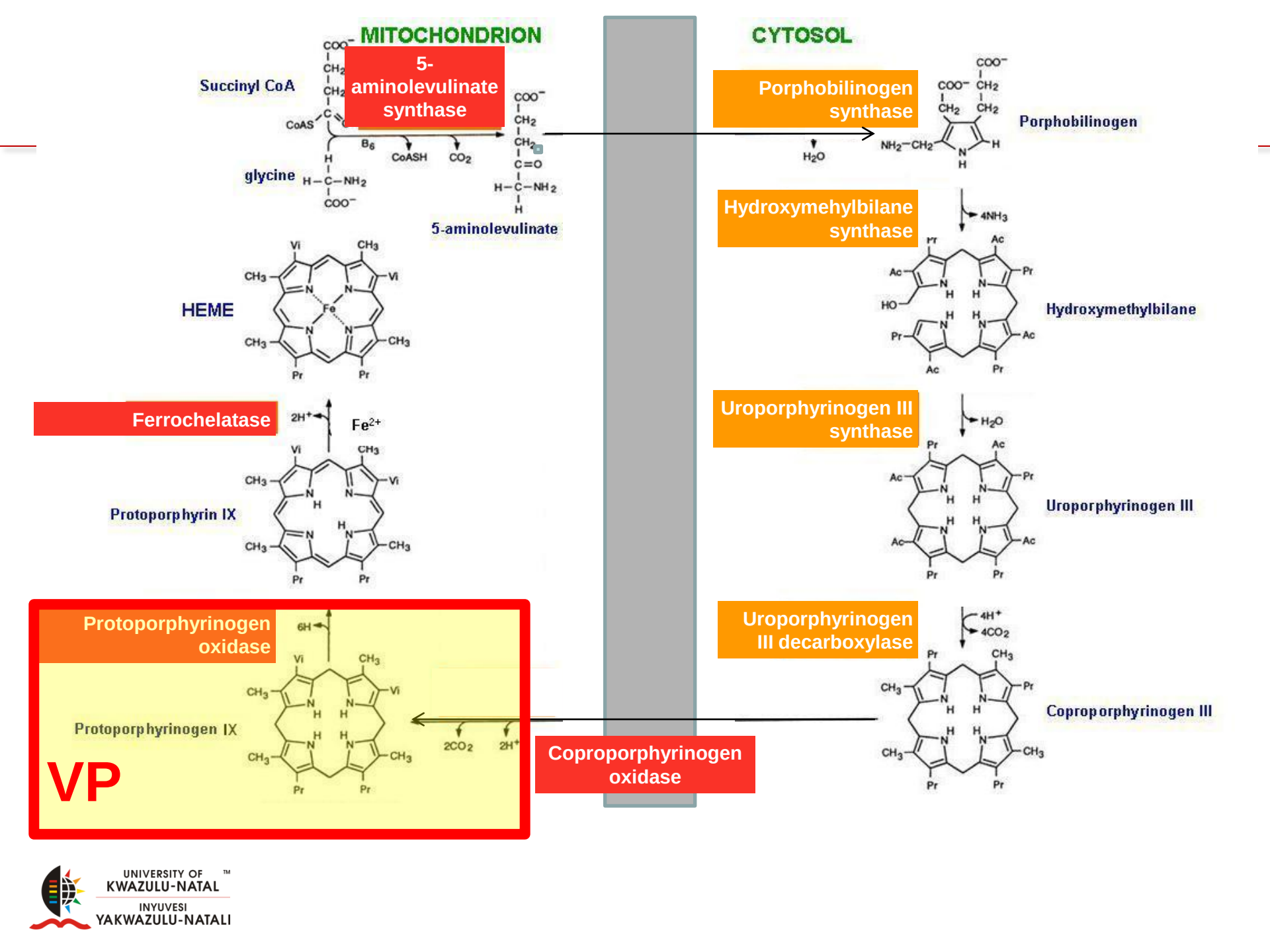












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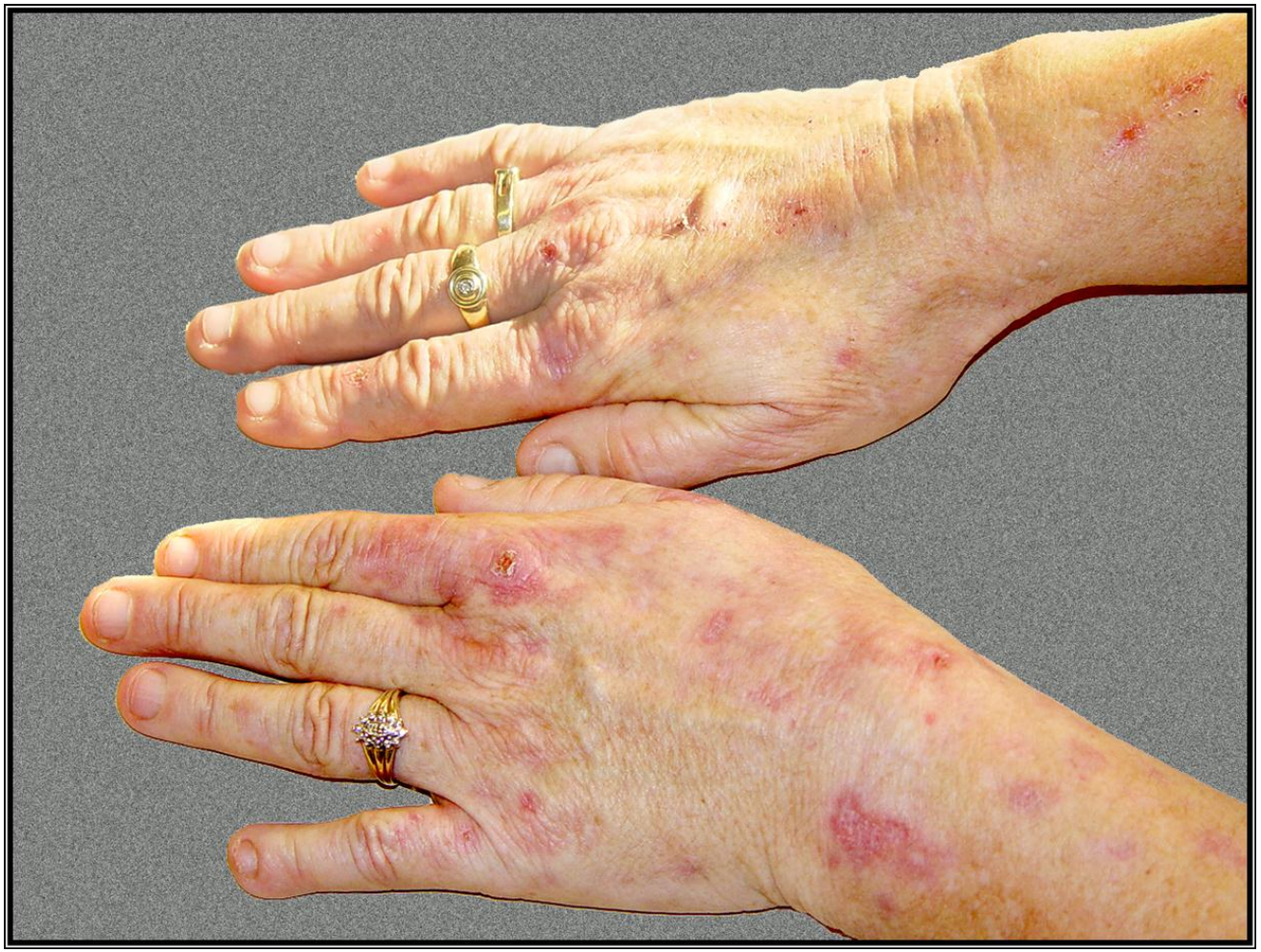
Variegate porphyria



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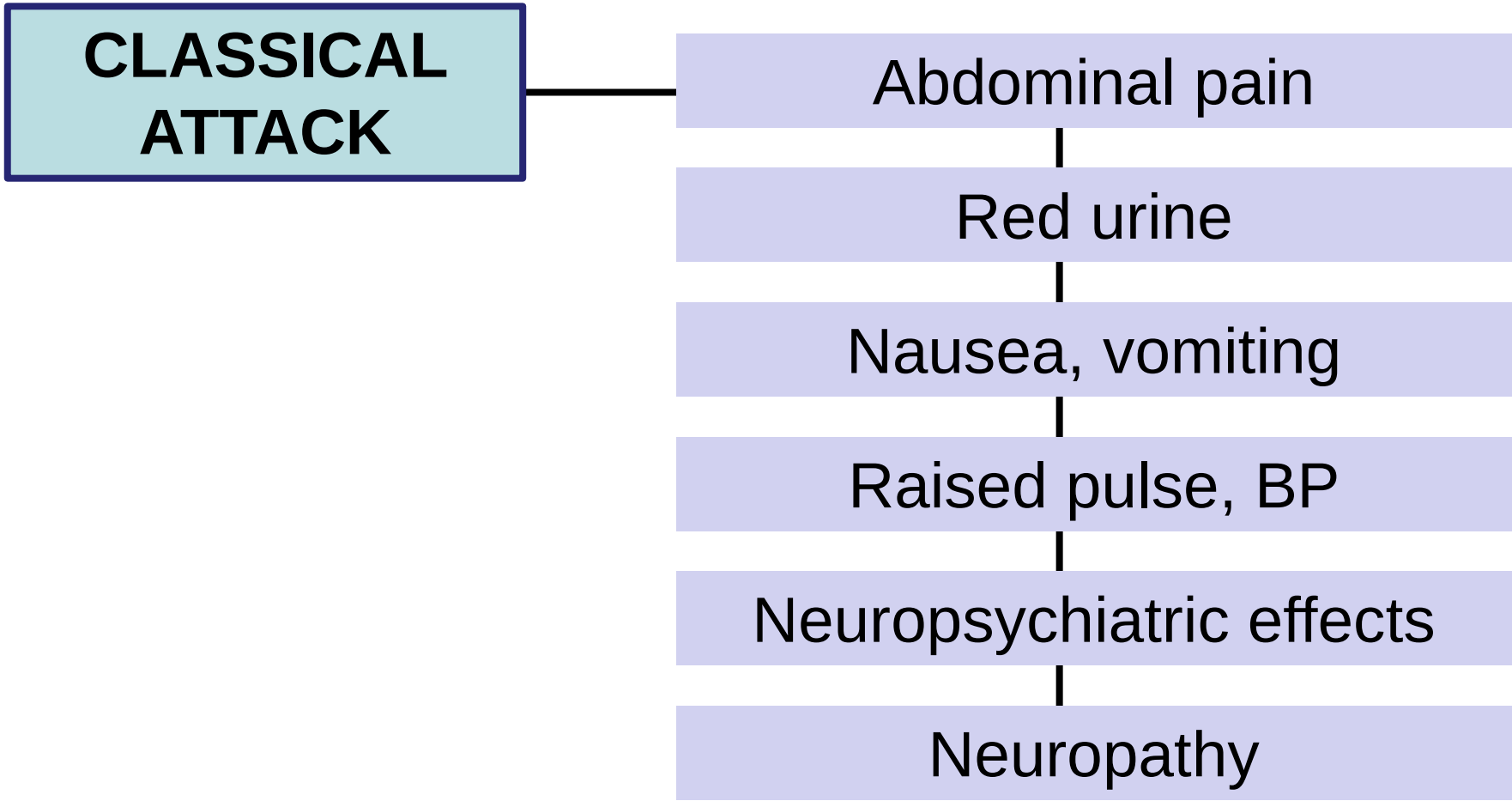
Symptoms of the acute attack

- The symptoms are mediated via an autonomic and, eventually motor, neuropathy

Recognising an acute attack



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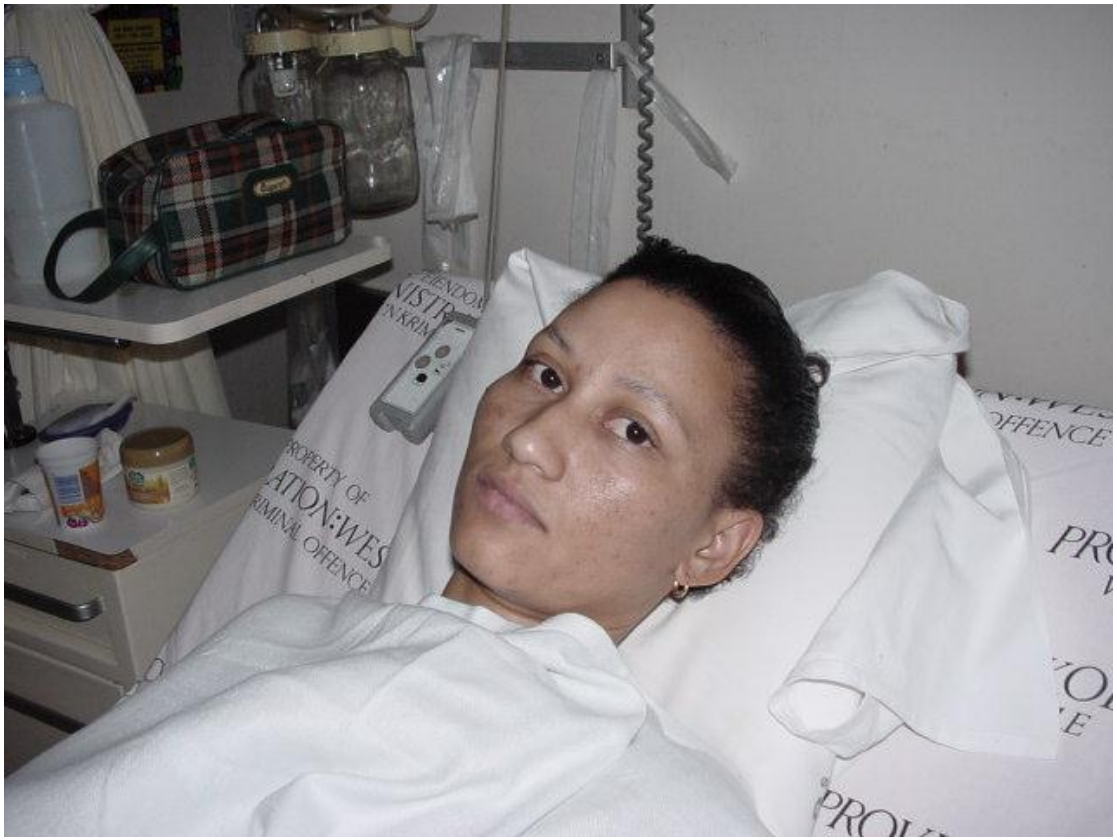
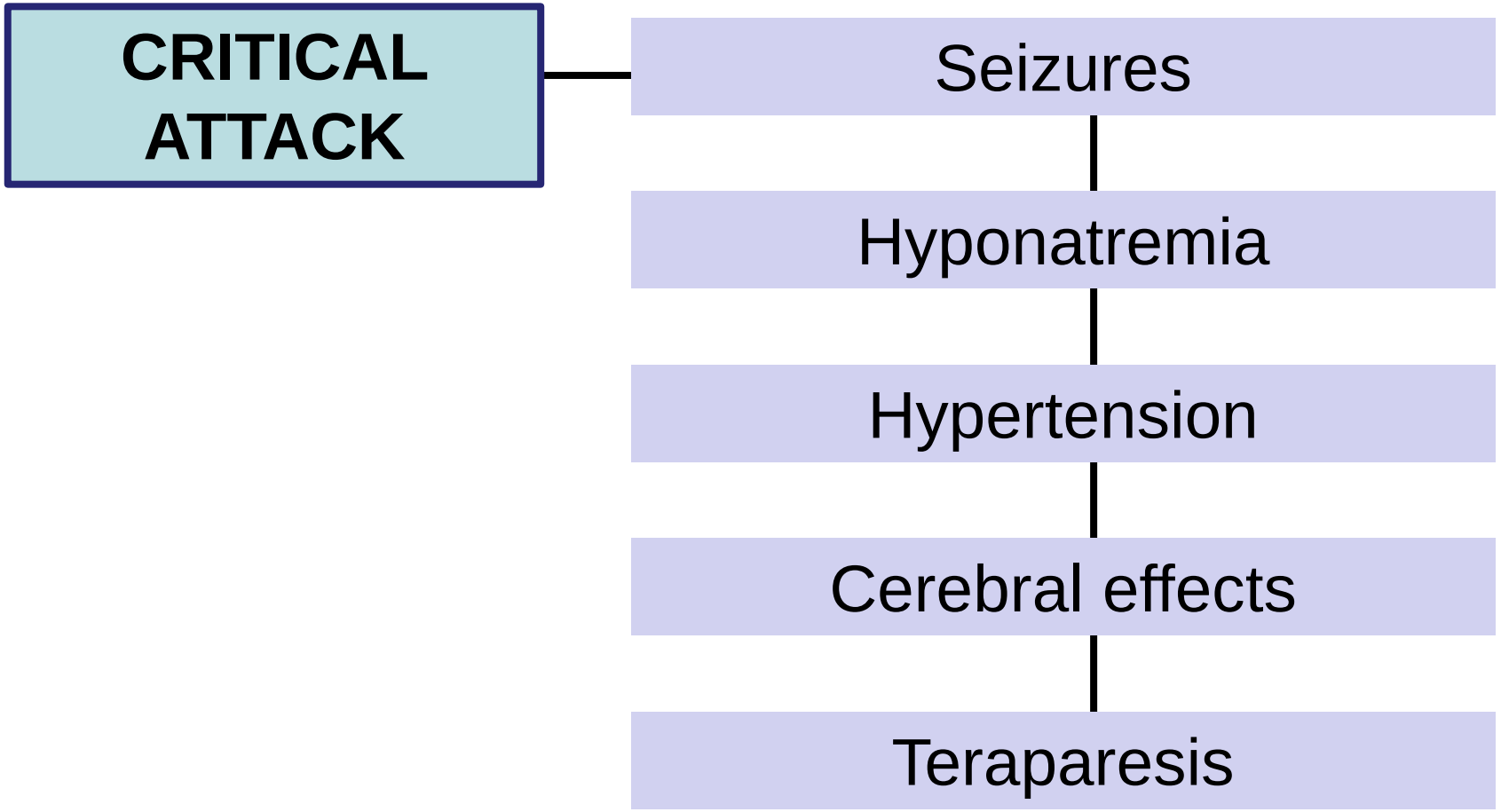
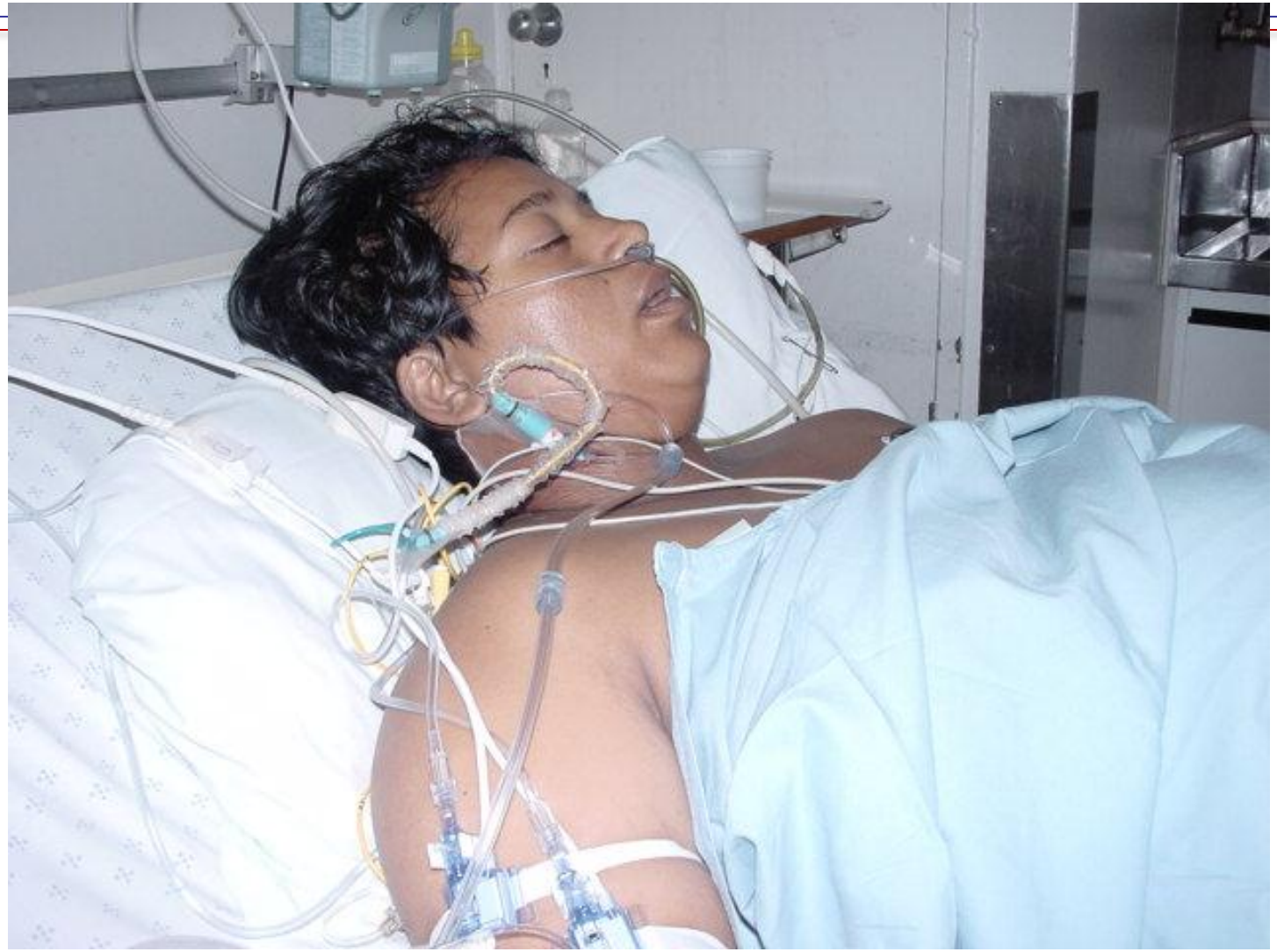


AIP

Recognising an acute attack



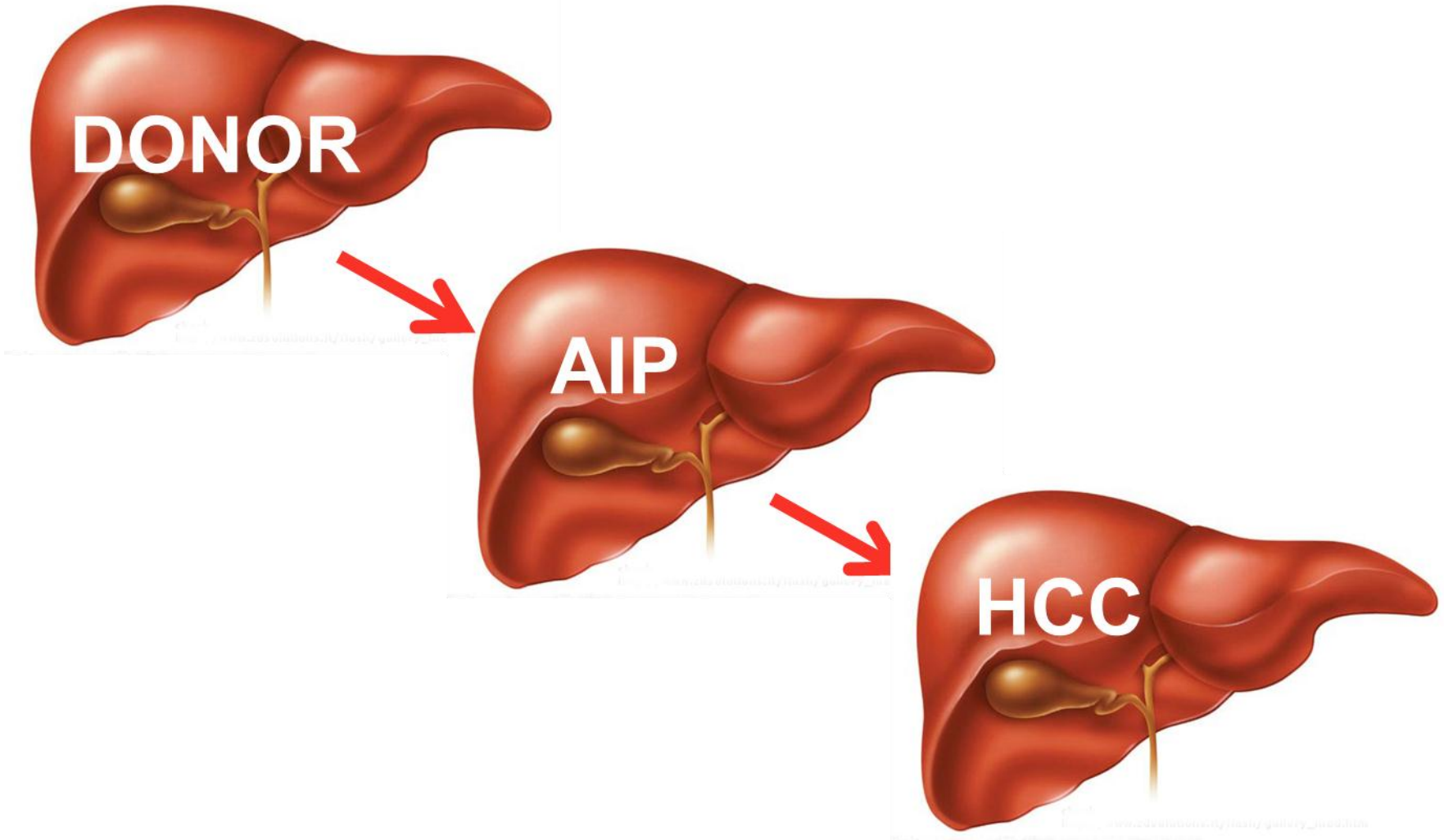
The acute attack



Liver or nerve?

- Liver
  - Site of overproduction
  - Potentially toxic precursors
- Nerve
  - Ultimate target of damage
  - Metabolically active, heme requiring
  - Heme-containing neurotransmitters

Domino transplant for AIP



Moinia M, Mistry P, Schilsky ML. Curr Opin Organ Transplant *(2010).*
Dowman JK, Gunson BK, Bramhall S et al. Ann Intern Med *(2011).*

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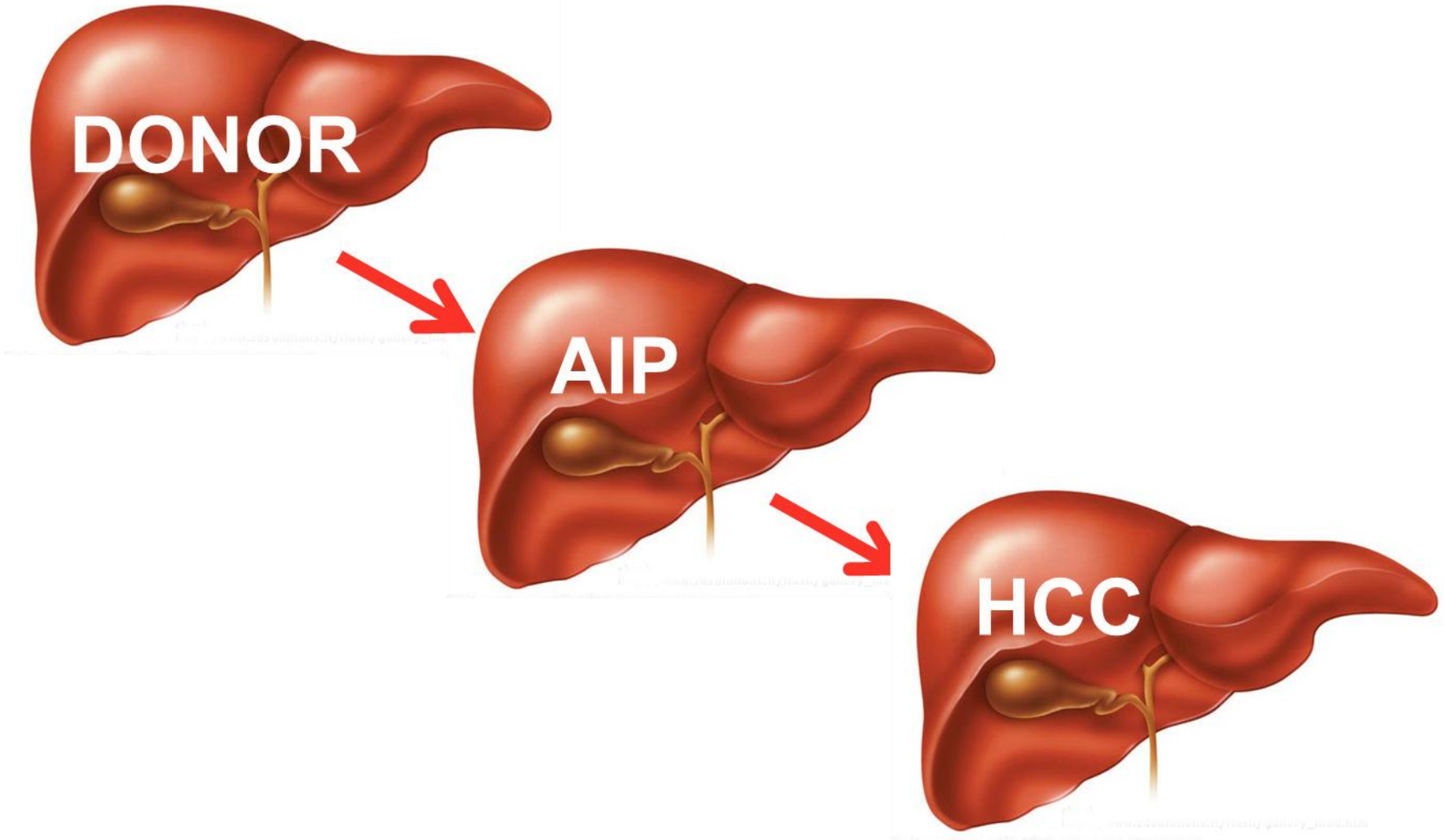
Domino transplant for AIP



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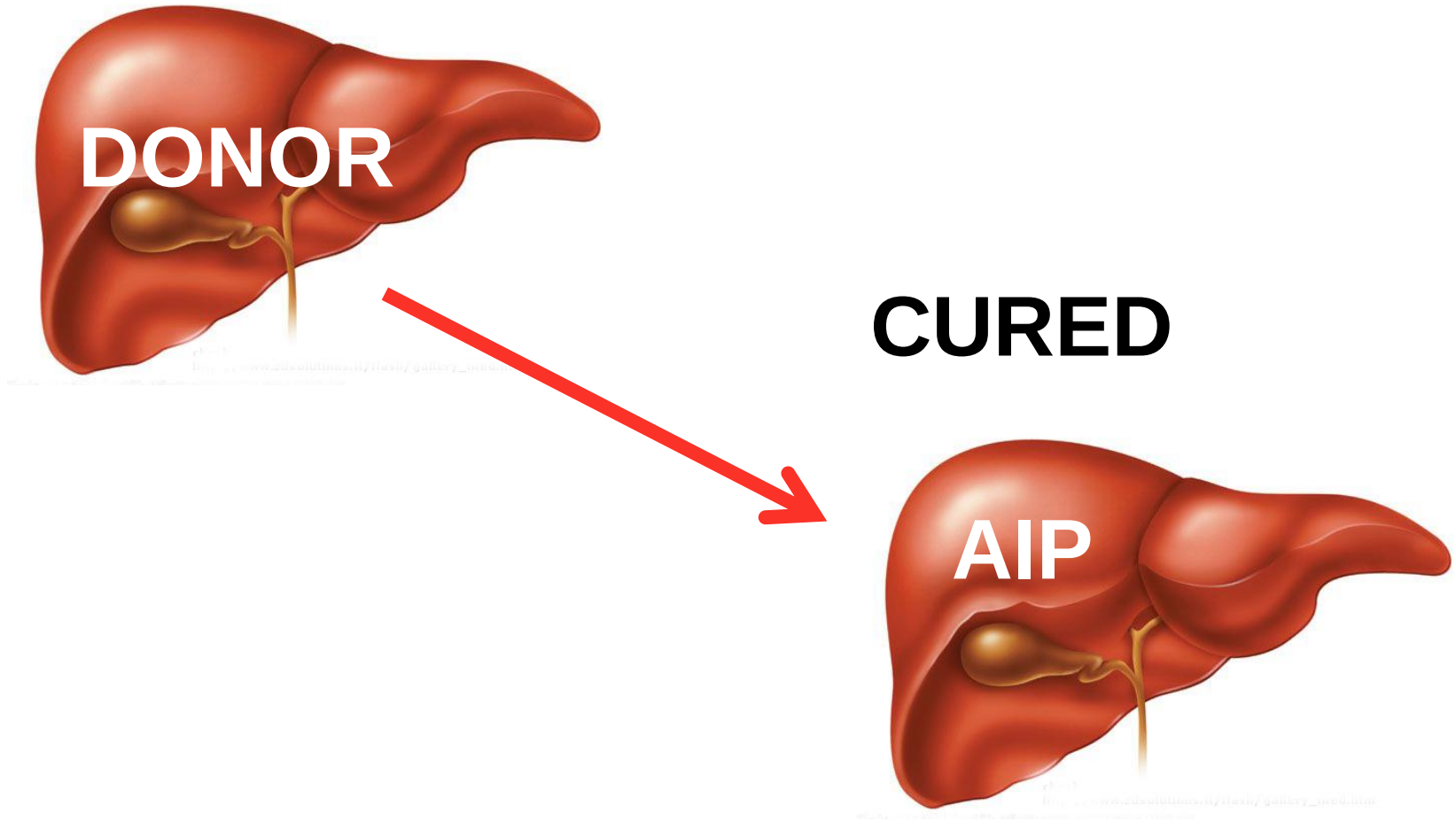
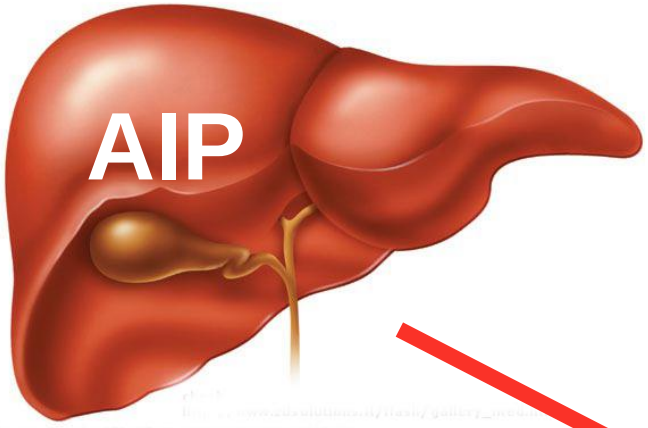
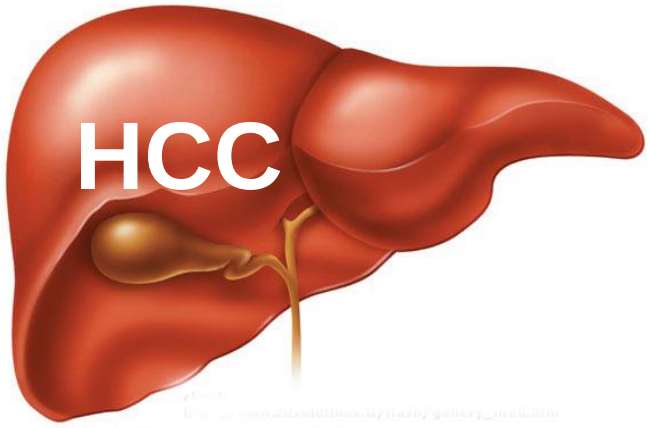
Domino transplant for AIP



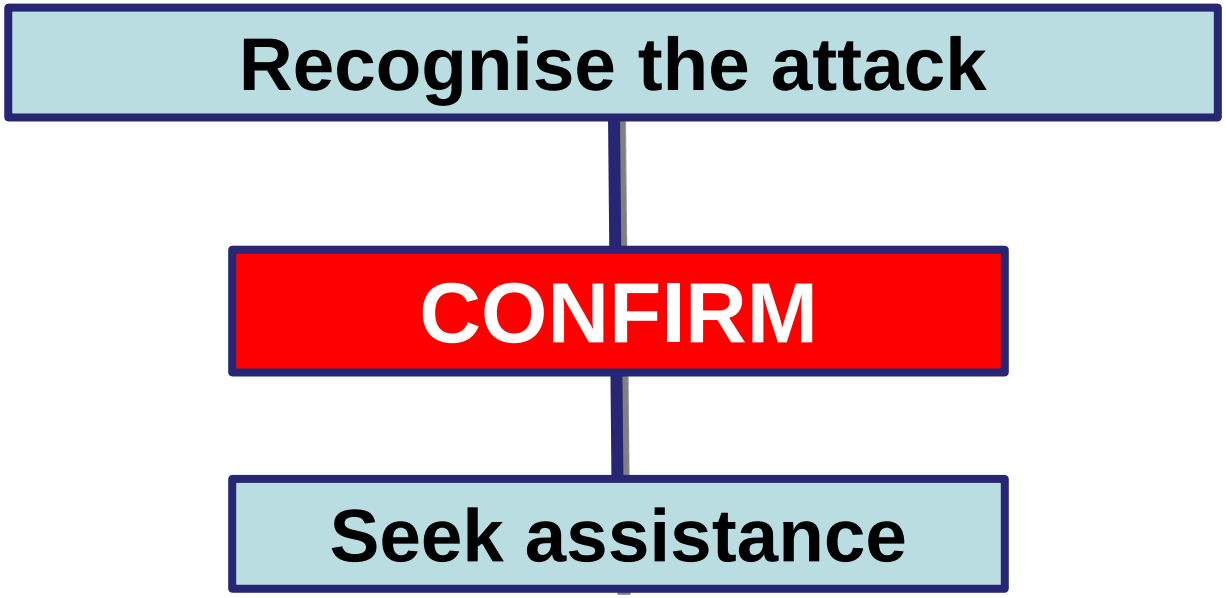
Domino transplant for AIP



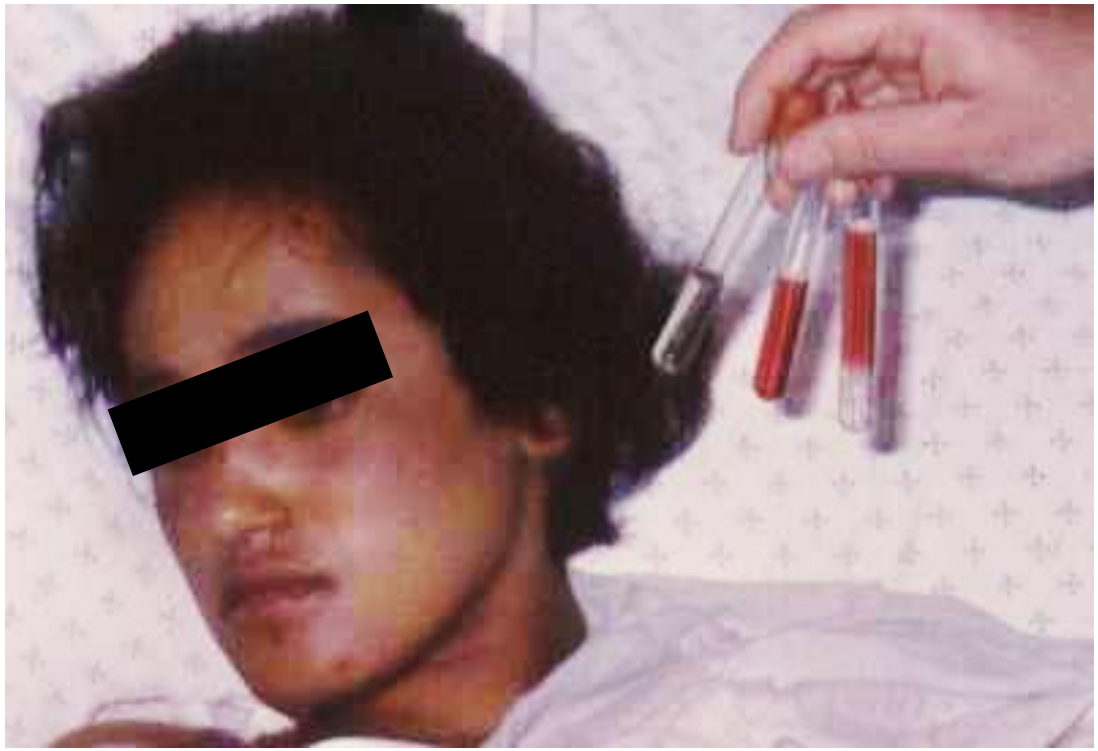
SEVERELY SYMPTOMATIC PORPHYRIA



Steps in management



Confirm the presence of an acute attack

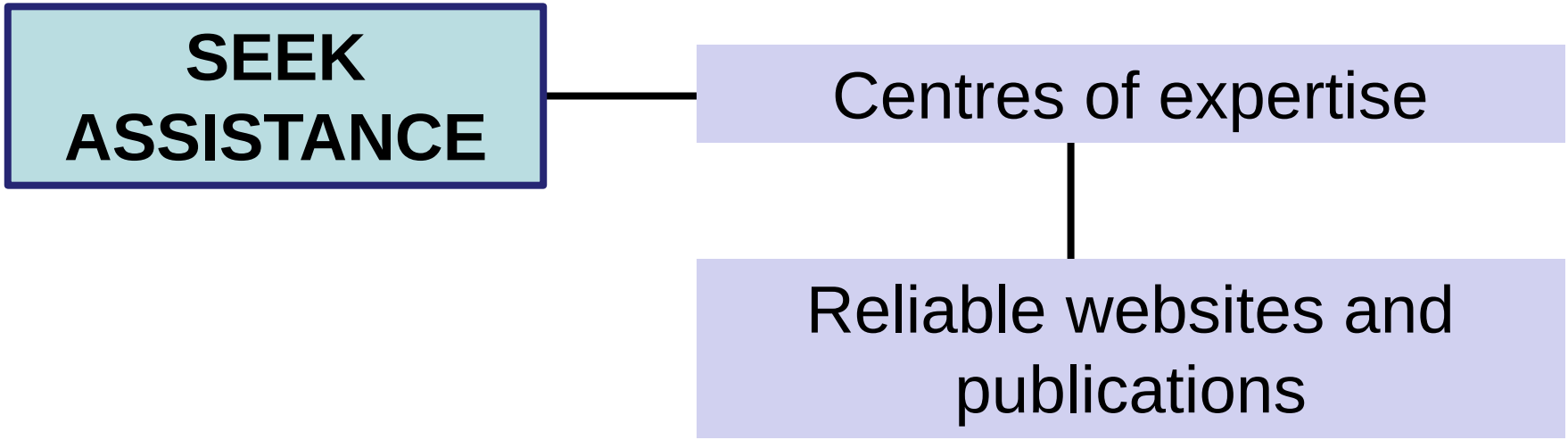


ALA, PBG in the urine

).

http://www.porphyria-europe.org/02-for-healthcare/carte-europe.asp

Managing the acute attack



Expert assistance

European Porphyria Network

- http://www.porphyria-europe.org/

Porphyria South Africa

- http://www.porphyria.uct.ac.za/

Incidence

Country	Population (millions)	Incidence (new cases per year per million inhabitants)		
		AIP	VP	EPP
Finland	5.4	0.13 (0.02–0.45)	0.06 (0.002–0.35)	NCI
France	62.2	0.12 (0.07–0.18)	0.12 (0.08–0.19)	0.06 (0.03–0.11)
Irish Republic	4.2	NCI	0.16 (0.03–0.57)	0.08 (0.002–0.44)
Northern Italy	27	0.11 (0.05–0.21)	–	–
Italy	58.1	–	0.06 (0.03–0.11)	0.07 (0.04–0.12)
Netherlands	16.7	0.18 (0.08–0.34)	0.06 (0.01–0.24)	0.18 (0.08–0.37)
Norway	4.7	0.14 (0.02–0.51)	0.07 (0.002–0.39)	0.36 (0.11–0.83)
Poland	38.5	0.16 (0.08–0.27)	0.01[a] (<0.001–0..05)	0.03 (0.003–0.09)
Spain	40.5	0.14 (0.08–0.22)	0.04 (0.01–0.10)	0.03 (0.01–0.07)
Sweden	9.1	0.51 (0.28–0.86)	0.11 (0.02–0.32)	0.18 (0.06–0.43)
Switzerland	7.6	0.22 (0.07–0.51)	0.26 (0.10–0.57)	0.35 (0.15–0.69)
UK	61.1	0.16 (0.11–0.23)	0.08 (0.04–0.13)	0.33 (0.24–0.39)
All countries	308.05	0.13[b] (0.11–0.16)	0.08 (0.06–0.10)	0.12 (0.10–0.15)

Elder G, Harper P, Badminton M et al. (2012). Journal Of Inherited Metabolic Disease

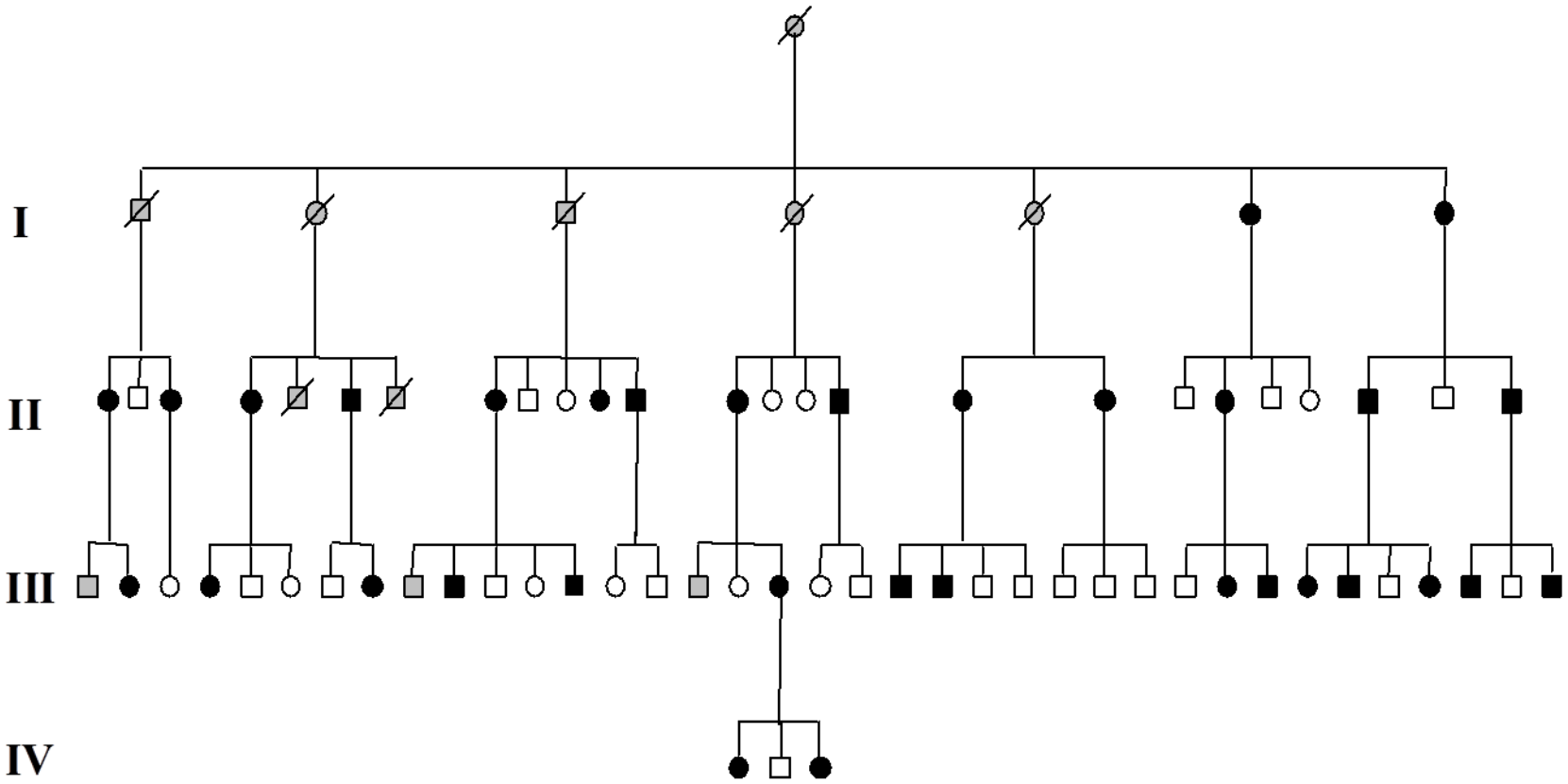
Prevalence

J Inherit Metab Dis

Table 4 The calculated prevalence of patients with current or past symptoms of AIP, VP or EPP in European countries

Country	Population (millions)	Prevalence (cases per million inhabitants) (calculated from incidence)			Total cases in each country (calculated from prevalence)		
		AIP	VP	EPP	AIP	VP	EPP
Finland	5.35	5.9 (0.9–20.3)	2.4 (0.08–14.0)	–	32 (6–109)	13 (1–75)	–
France	62.2	5.5 (3.2–8.1)	4.8 (3.2–7.6)	4.6 (2.3–8.5)	342 (119–504)	299 (199–473)	286 (143–529)
Irish Republic	4.2	–	6.4 (1.2–22.8)	6.2 (0.2–33.9)		27 (5–96)	26 (1–142)
Northern Italy	27	5.0 (2.3–9.5)	–	–	135 (62–257)		
Italy	58.1	–	2.4 (1.2–4.4)	5.4 (3.1–9.2)		139 (70–256)	314 (180–535)
Netherlands	16.7	8.1 (3.6–15.3)	2.4 (0.4–9.6)	13.9 (6.2–28.5)	135 (60–256)	40 (7–160)	232 (104–476)
Norway	4.7	6.3 (0.9–23.0)	2.8 (0.1–15.6)	27.7 (8.5–63.9)	30 (4–108)	13 (1–73)	130 (40–300)
Poland	38.5	7.2 (3.6–12.2)	0.40[a] (<0.1–2.0)	1.5 (0.2–6.9)	277 (139–470)	15[a] (1–77)	58 (8–266)
Spain	40.5	6.3 (3.6–9.9)	1.6 (0.4–4.0)	2.3 (0.8–5.4)	255 (146–401)	65 (16–162)	93 (32–219)
Sweden	9.1	23.0 (12.6–38.7)	4.4 (0.8–12.8)	13.9 (4.6–33.1)	209 (115–352)	40 (7–117)	127 (42–301)
Switzerland	7.6	9.9 (3.2–23.0)	10.4 (4.0–22.8)	27.0 (11.6–53.1)	75 (24–175)	79 (30–173)	205 (88–404)
UK	61.1	7.2 (5.0–10.4)	3.2 (1.6–5.2)	25.4 (18.5–30.0)	440 (306–635)	196 (98–318)	1552 (1130–1833)
All countries	308.05	5.9[b] (5.0–7.2)	3.2 (2.4–4.0)	9.2 (7.7–11.6)			

Elder G, Harper P, Badminton M et al. (2012). Journal Of Inherited Metabolic Disease

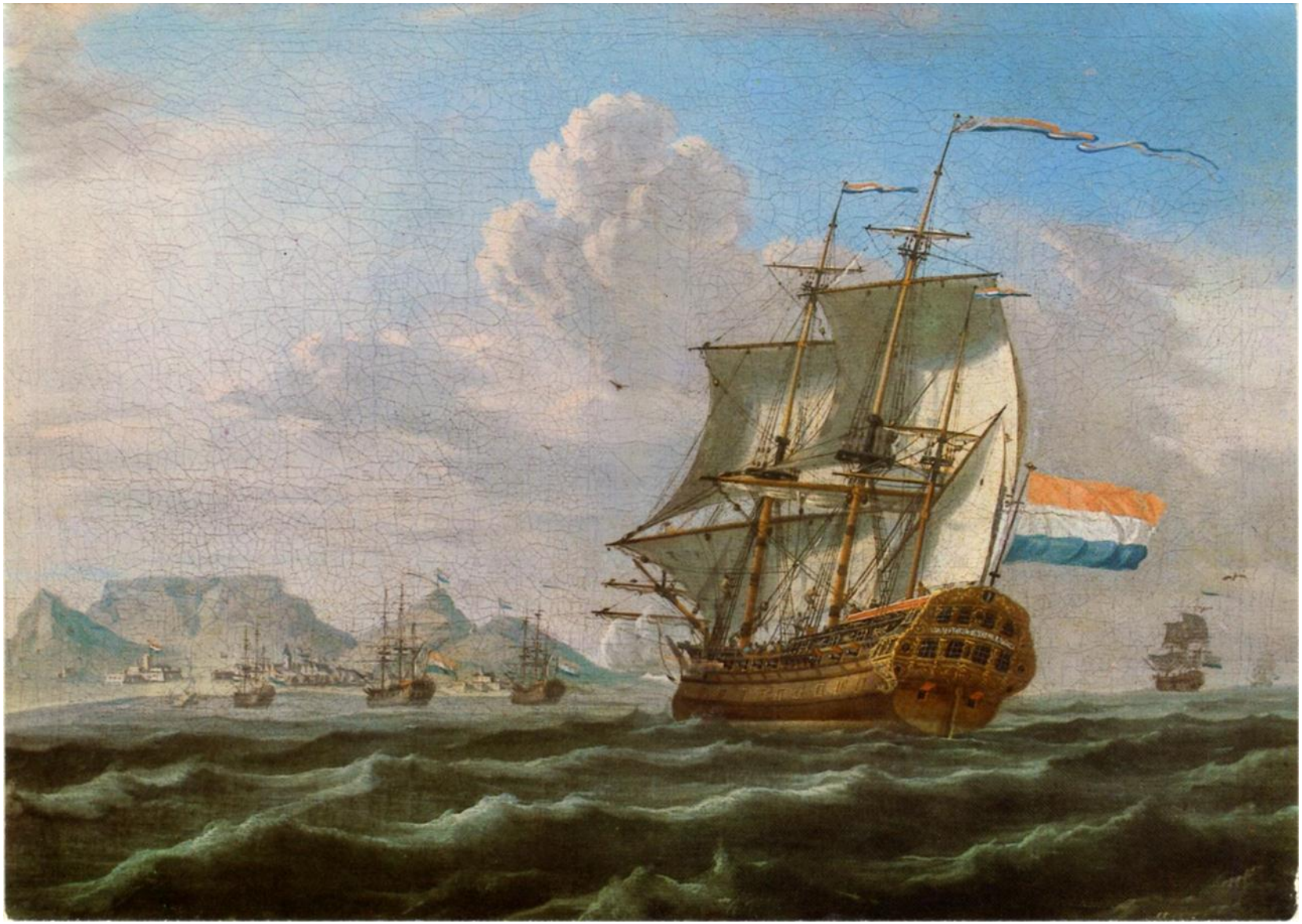


Turkey: Porphyria burden (95% CI)

	AIP	VP
New cases per year	8-12	5-8
Prevalence	347-485	185-300

Turkey: Porphyria burden (95% CI)

- 13-20 new cases/year
- 531-793 cases nationally



http://upload.wikimedia.org/wikipedia/commons/6/66/Anonymous_The_Noord-Nieuwland_in_Table_Bay,_1762.jpg

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http://www.talismancoins.com/catalog/Jan_Van_Riebeck_Arrival.jpg

The spread of VP

Durban, South Africa

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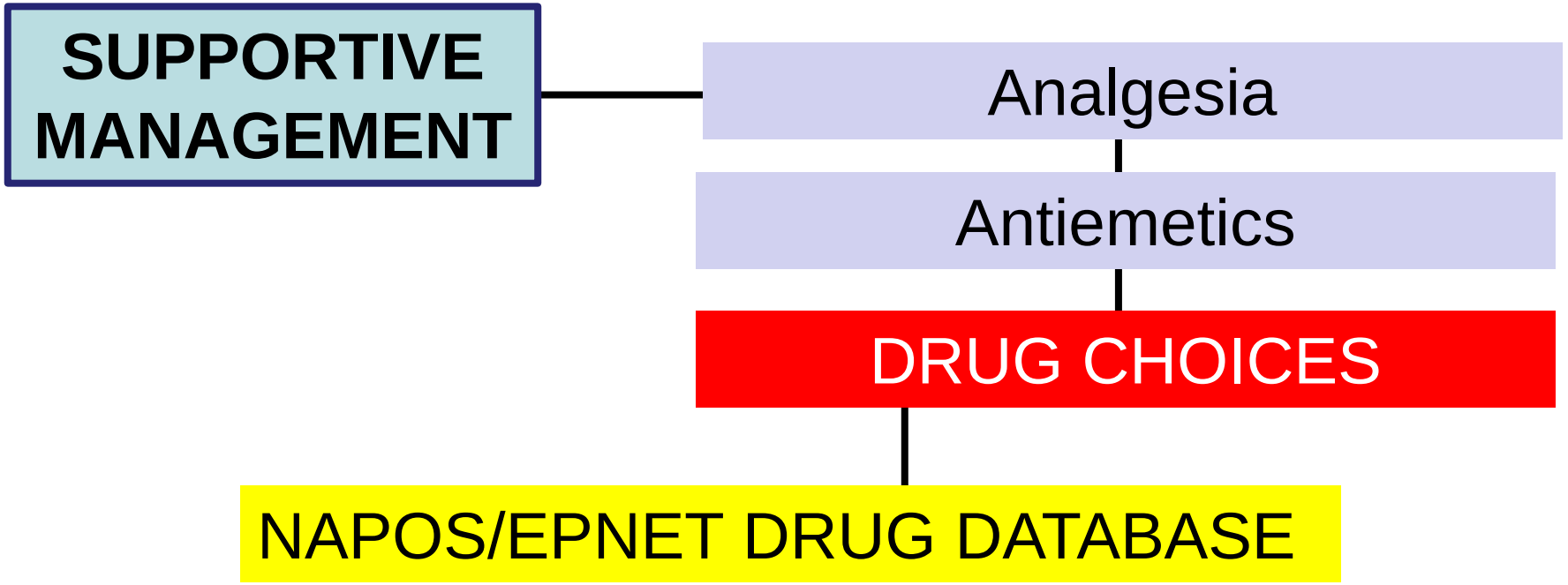
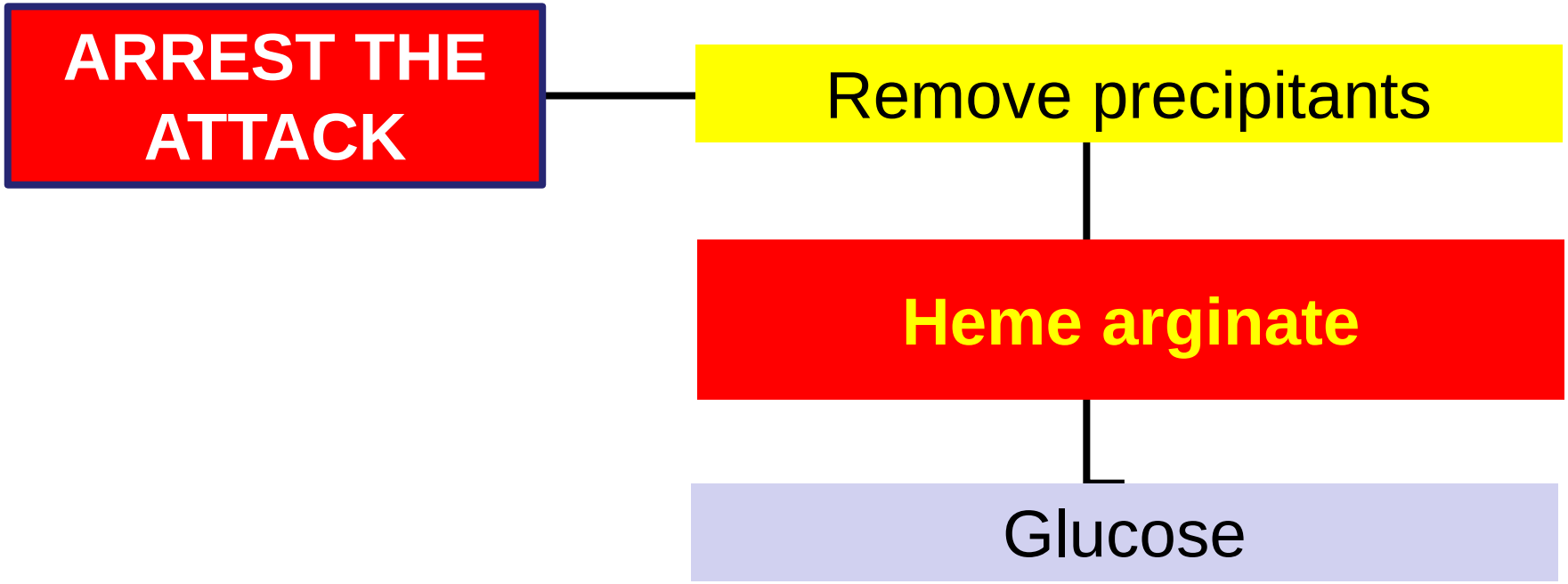
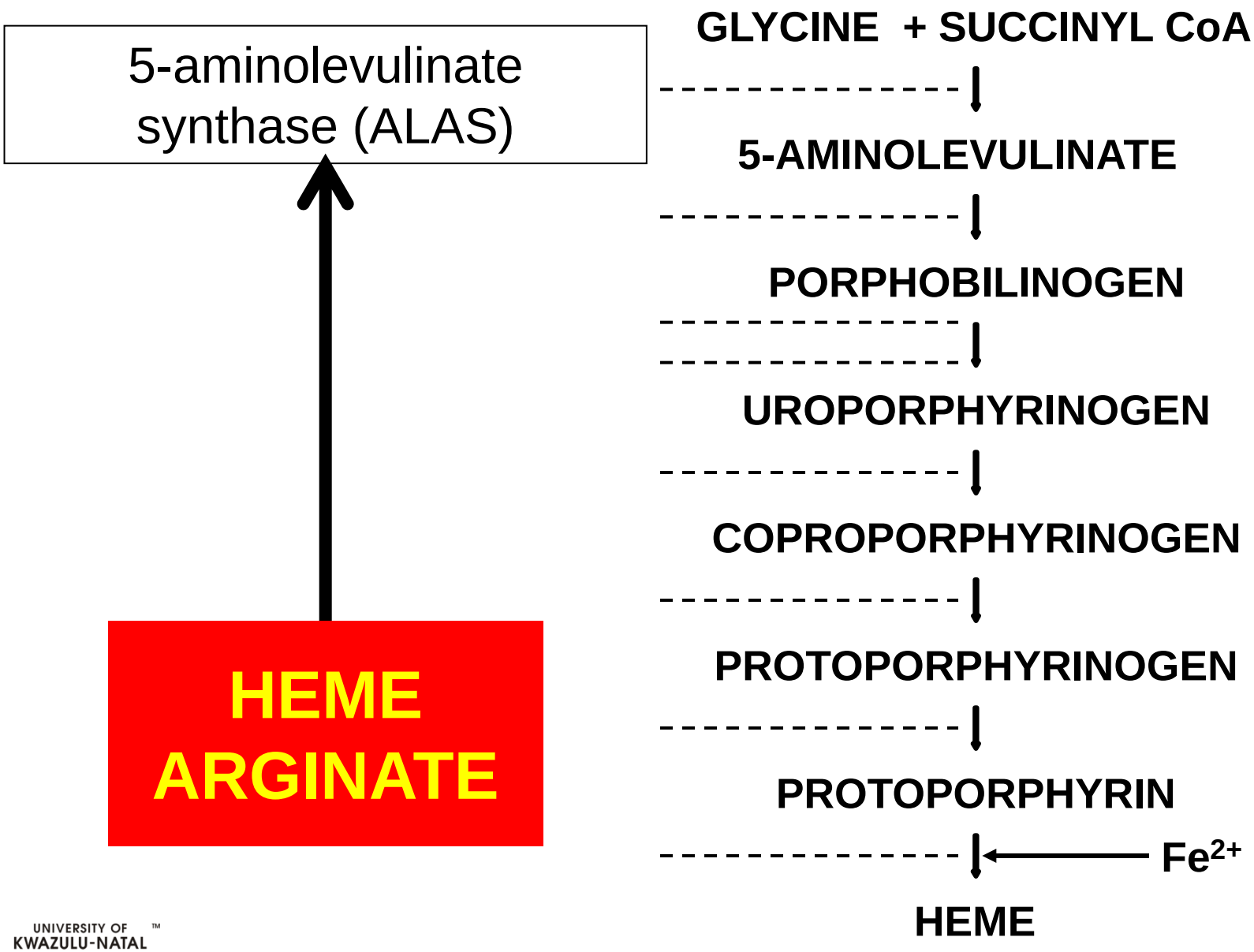
Managing the acute attack



Managing the acute attack

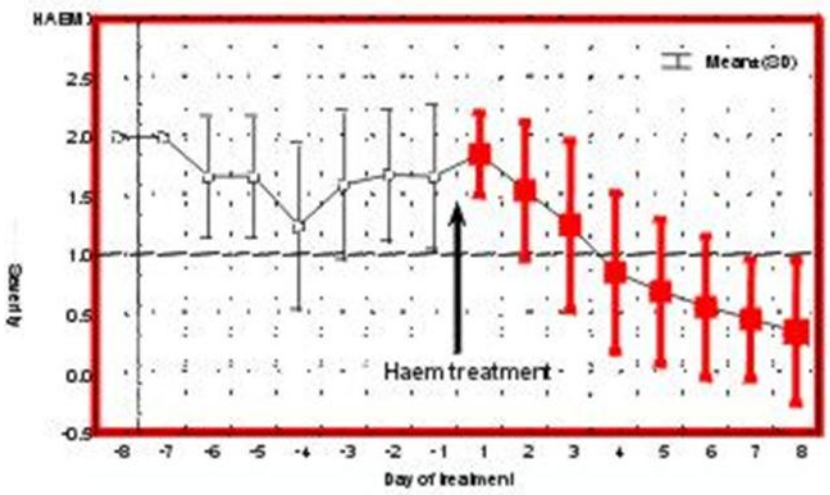




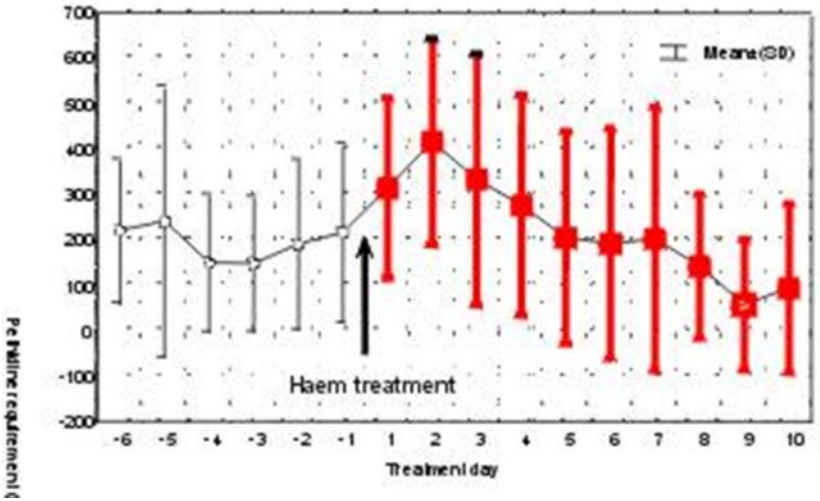
Heme arginate

Efficacy of heme arginate

Pain score



Opiate requirement



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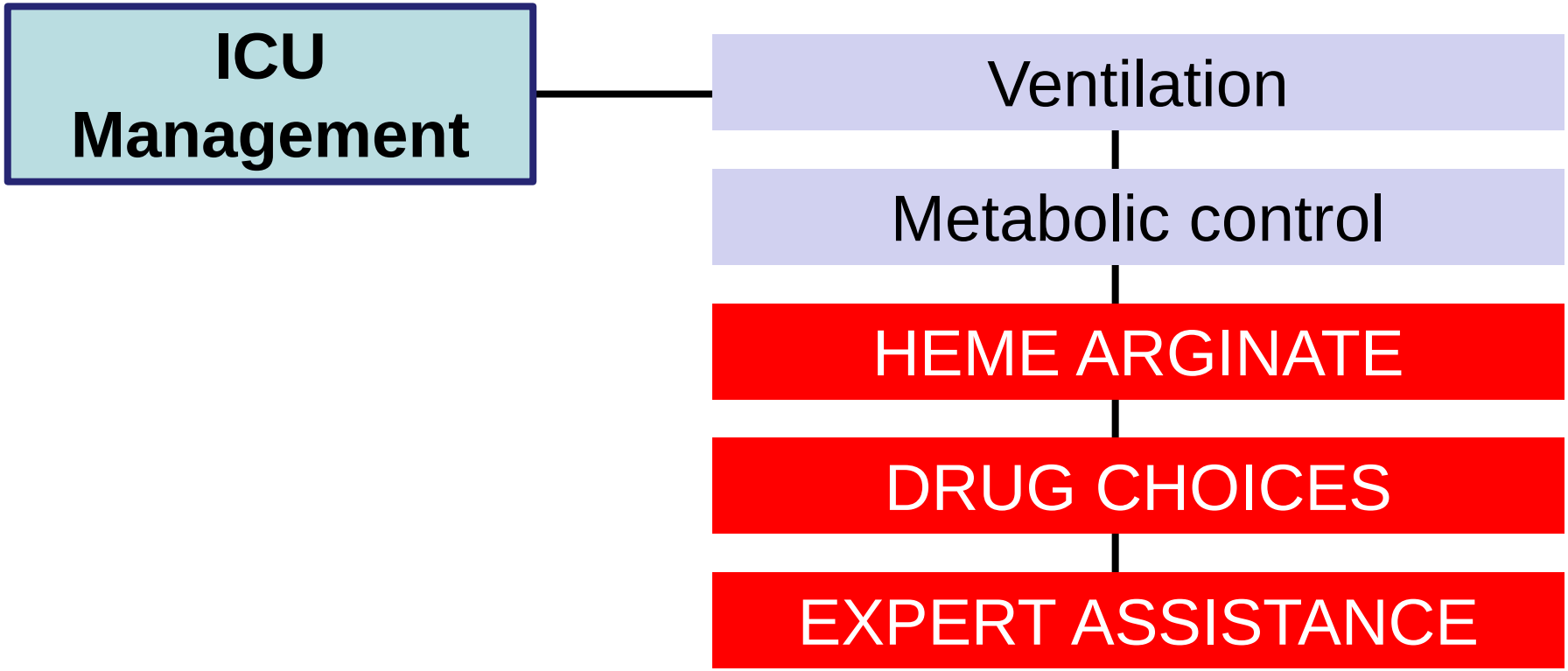
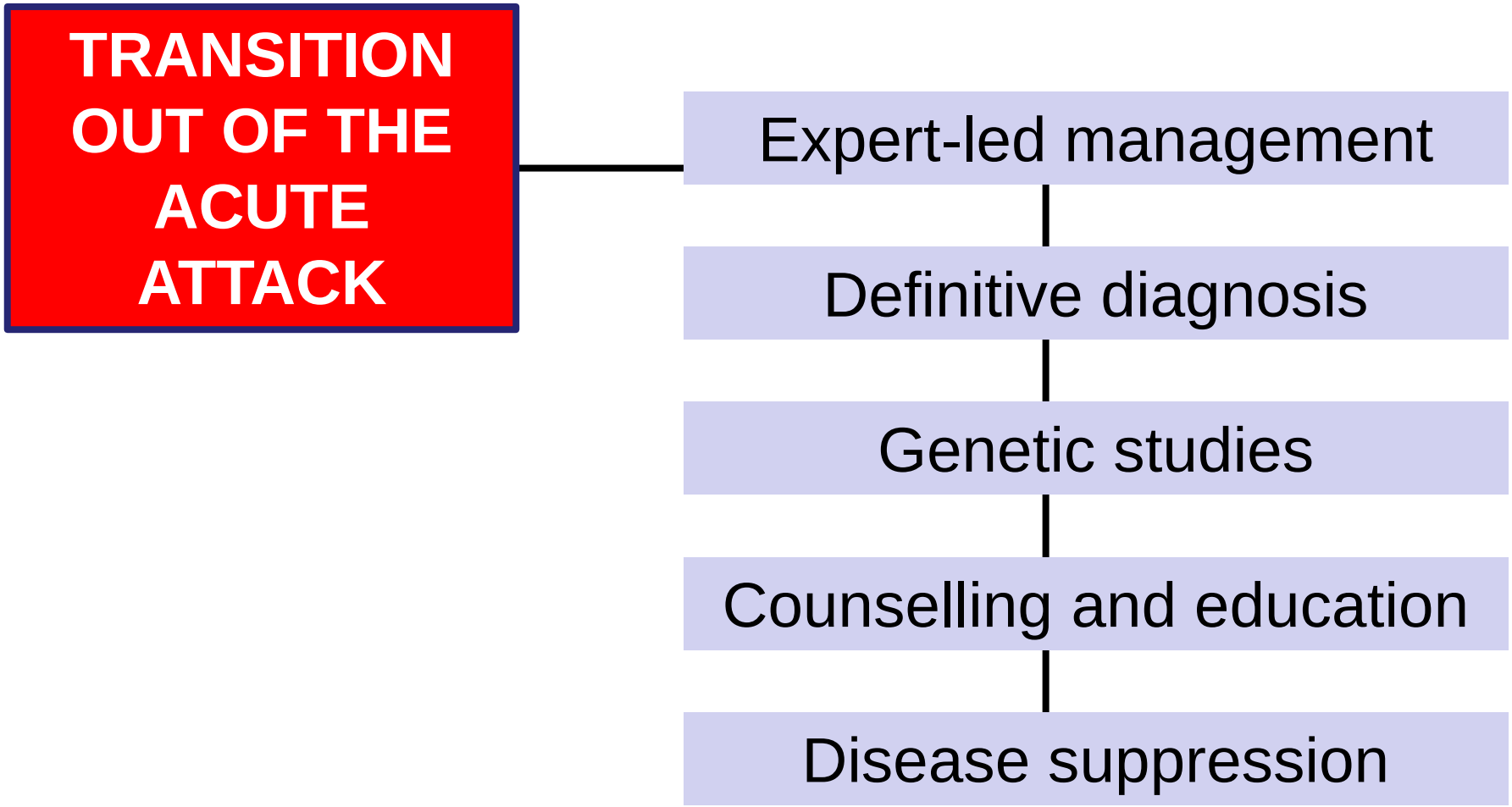
Managing the acute attack



Preparing for a lifetime of uneventful porphyria



Innovative therapies under study

- Enzyme replacement
  - Recombinant hydroxymethlbilane synthas
- Hepatocyte transfer
  - Restores activity
- RNA interference
  - RNAi targeting ALAS-1

HOMOZYGOUS PORPHYRIAS

Recessive presentations of porphyria

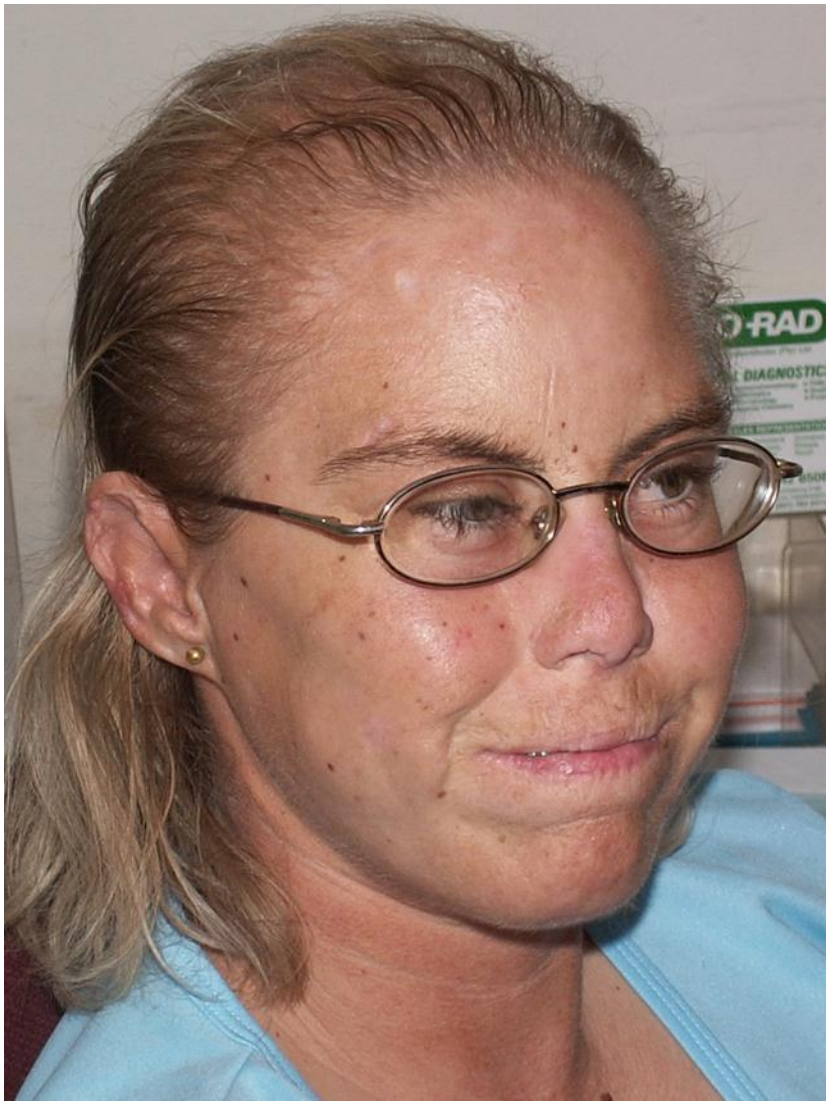
AUTOS0MAL RECESSIVE

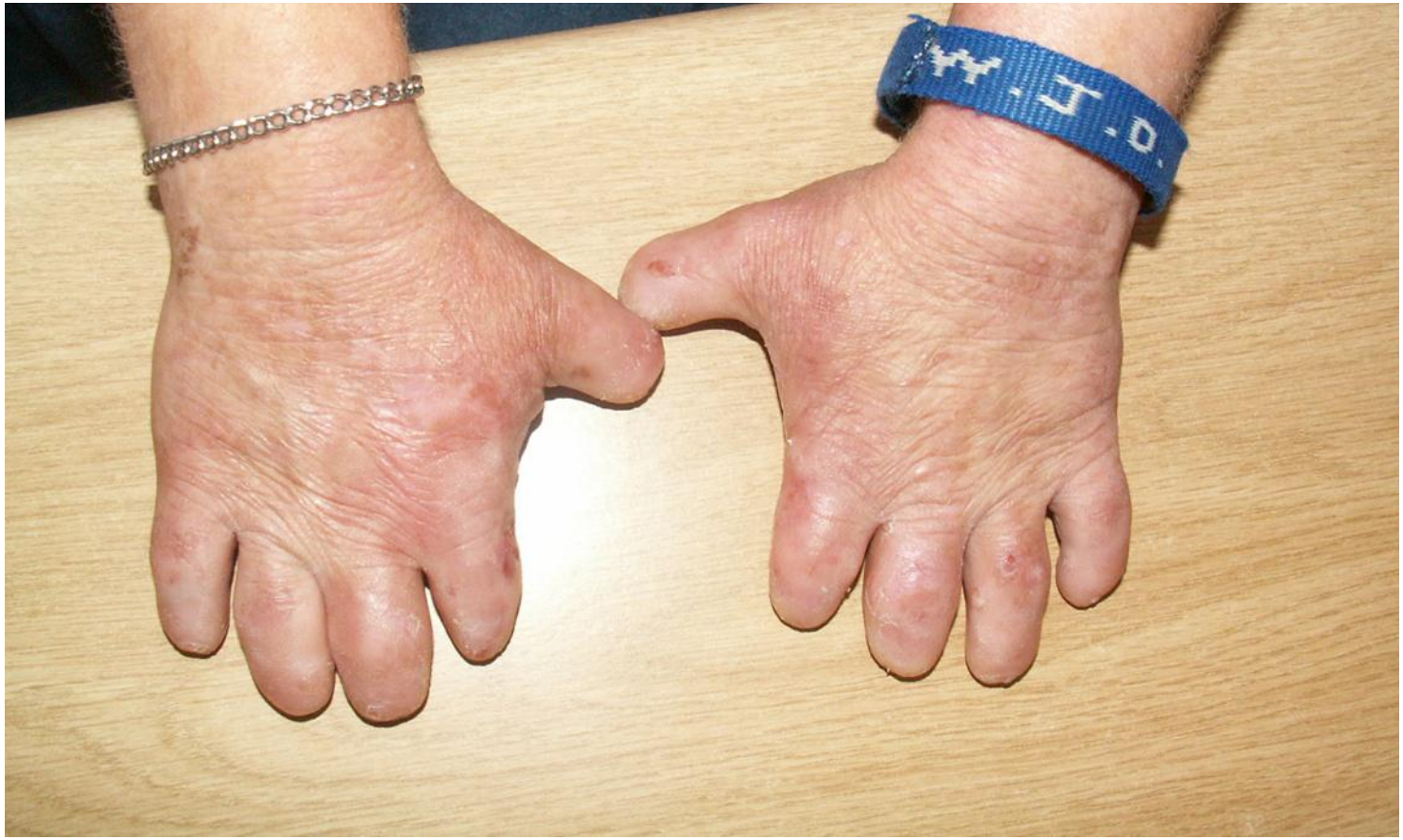
- ALA dehydratase porphyria
- Congenital erythropoietic porphyria
- Erythropoietic protoporphyria

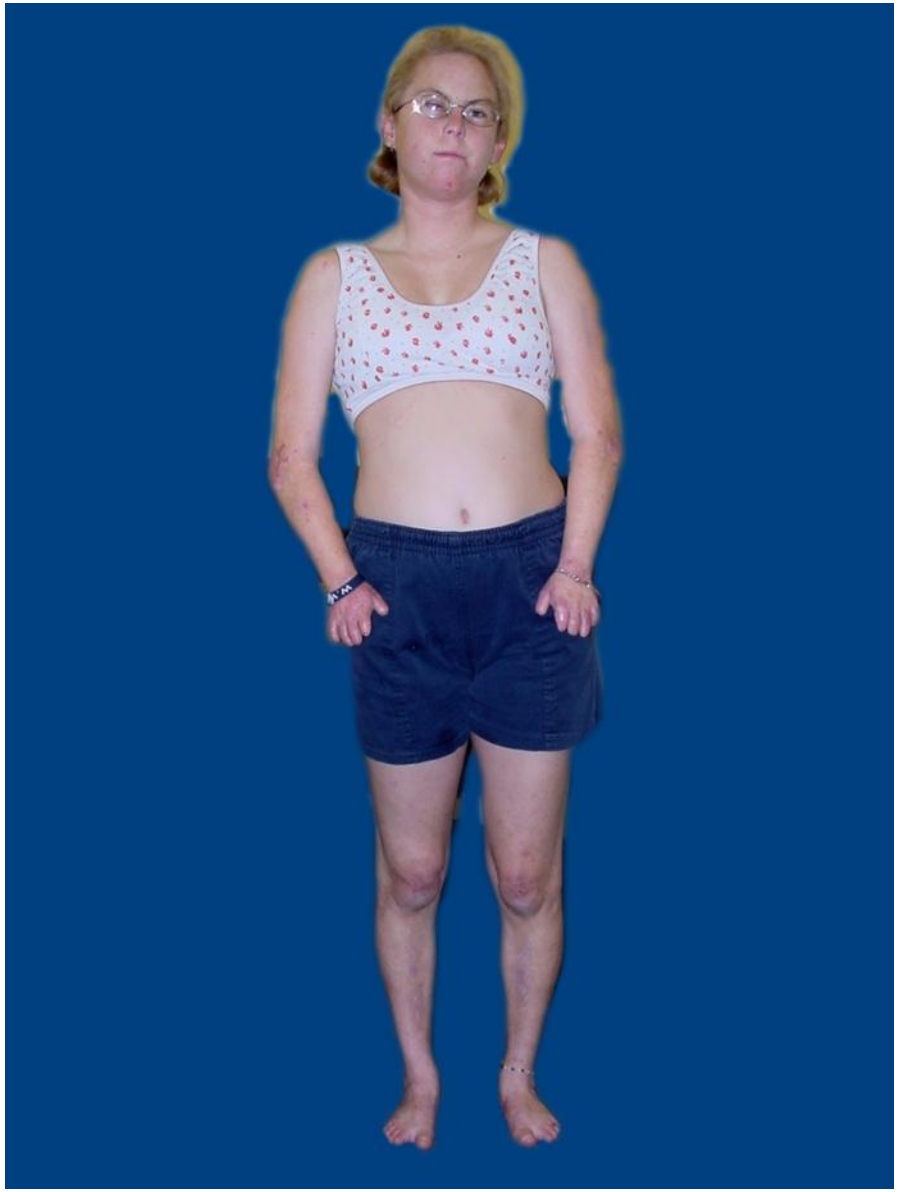
AUTOSOMAL DOMINANT

(presenting with homozygosity)

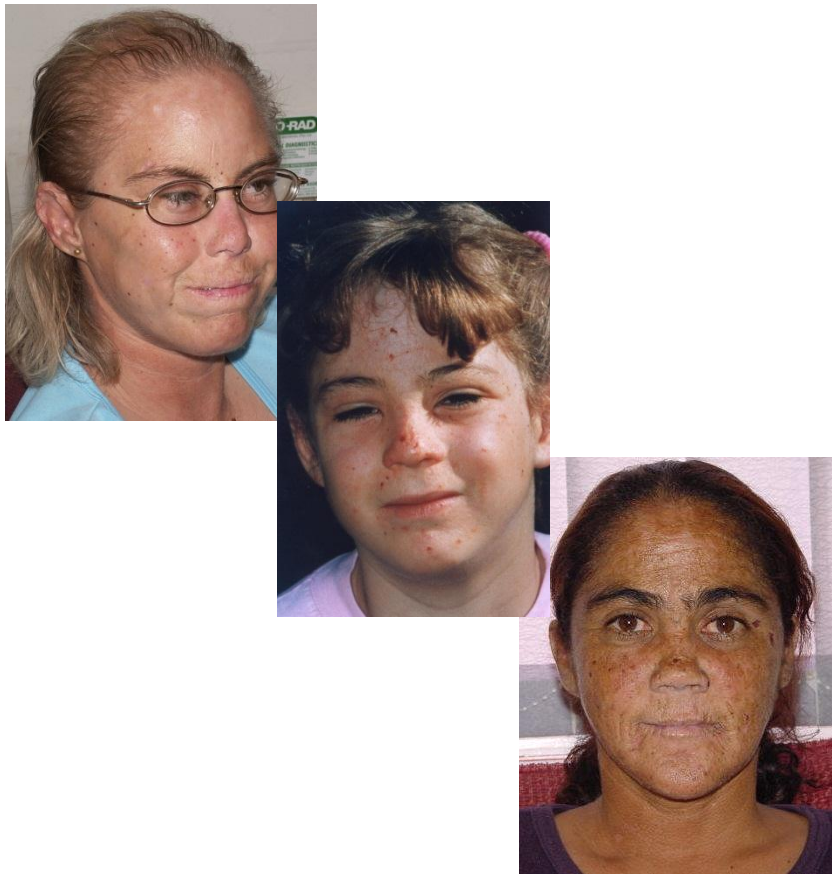
- Acute intermittent porphyria
- Porphyria cutanea tarda
- Hereditary coproporphyria
- Variegate porphyria


RAD





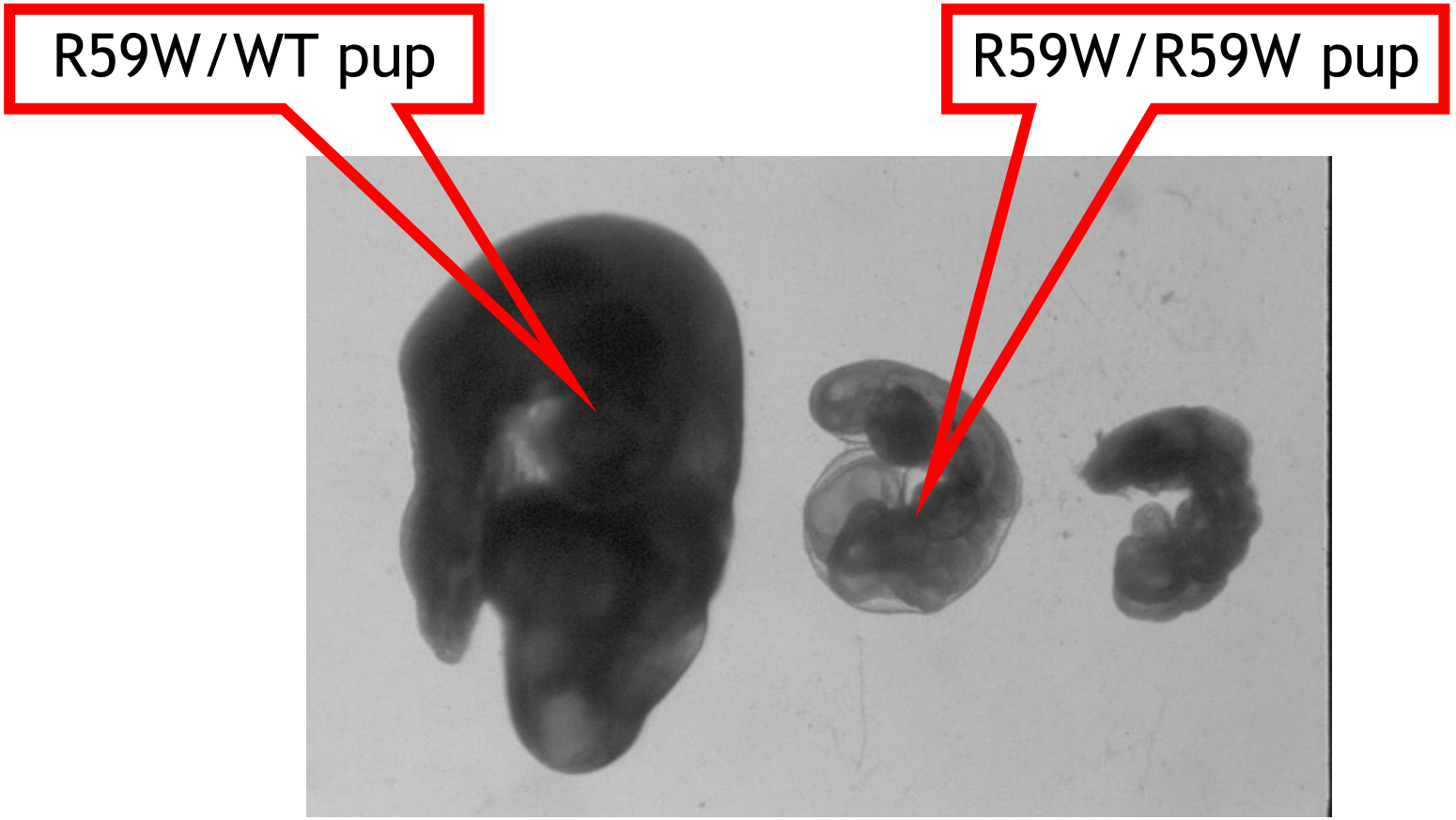
“Homozygous” VP



I	R59W	RI68C
II	R59W	Y348C
III	R59W	R138P

Meissner et al *Nature Genet* 1996
Corrigall et al *Mol Genet Metab* 2000
Palmer et al *Br J Dermatol* 2001

Homozygosity for a potent mutation is lethal



THANK YOU