Porphyrias: Update on Pathogenesis, Clinical Manifestations, Management

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Disclosures for Herbert L. Bonkovsky

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Employee	Atrium Health Wake Forest Baptist Wake Forest University School of Medicine
Consultant	Recordati Rare Chemicals
Major Stockholder	Oh, how I wish!!
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Scientific Advisory Boards	APEX—American Porphryia Expert Collaborative; Hemochromatosis Research Foundation; Iron Disorders Institute; UPA—United Porphyria Association

Porphyrias--Definition

- Disorders of normal porphyrin and heme synthesis
- Mostly inherited—but with effects of drugs, nutrition, alcohol, other genetic variations
- Major clinical features: acute neuro-visceral attacks or cutaneous photosensitivity
- Symptoms due to effects of ALA or porphyrins
- Most common are AIP, PCT, EPP

Classification of Porphyrias
According to major site of overproduction

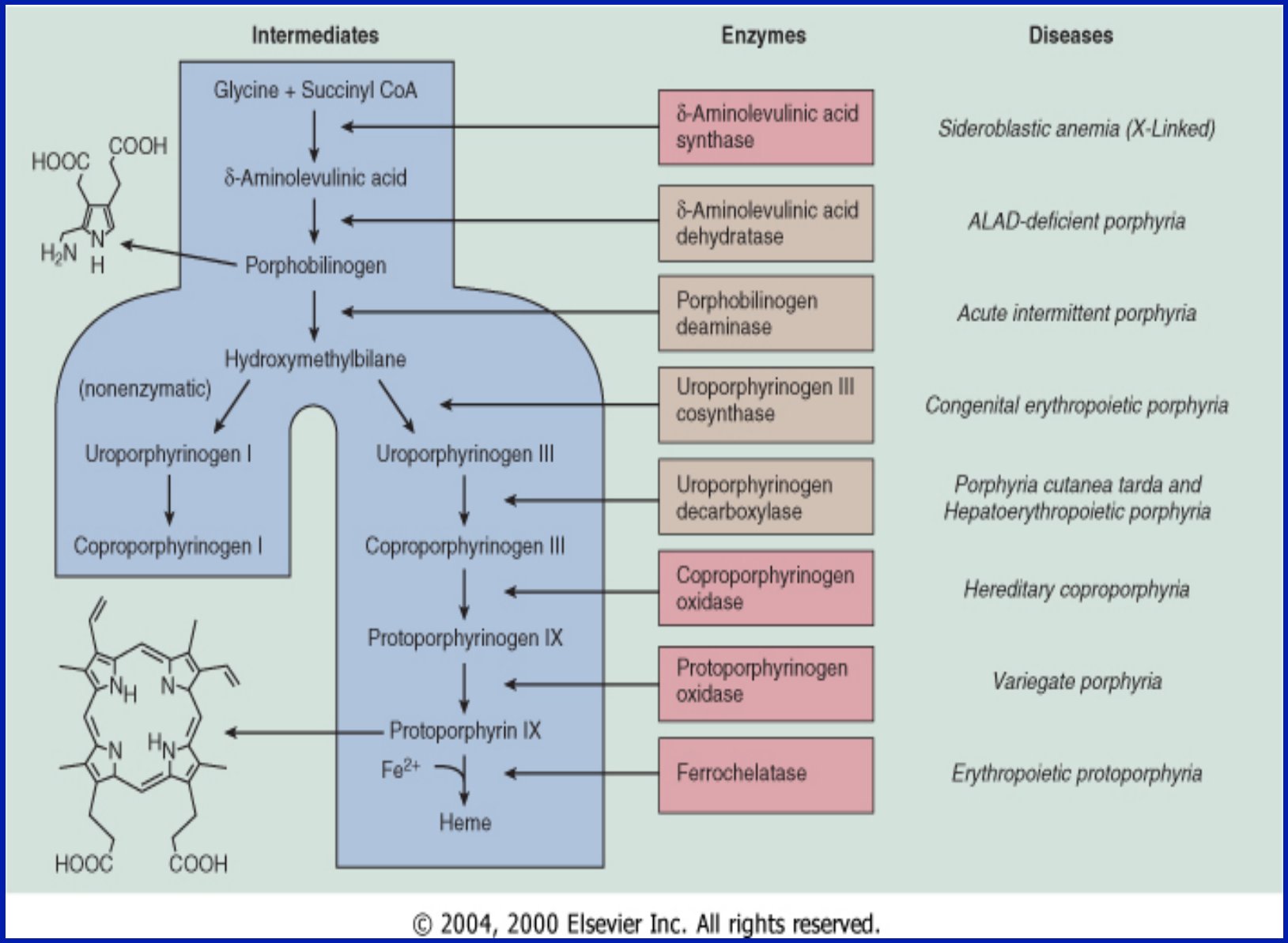
- **Hepatic porphyrias**
  - Acute or inducible porphyrias – 4 types
  - Chronic hepatic porphyrias – PCT, HEP
- **Erythropoietic porphyrias**
  - Congenital erythropoietic porphyria - CEP
  - Erythropoietic protoporphyria - EPP

Classification of Porphyrias
According to major clinical features

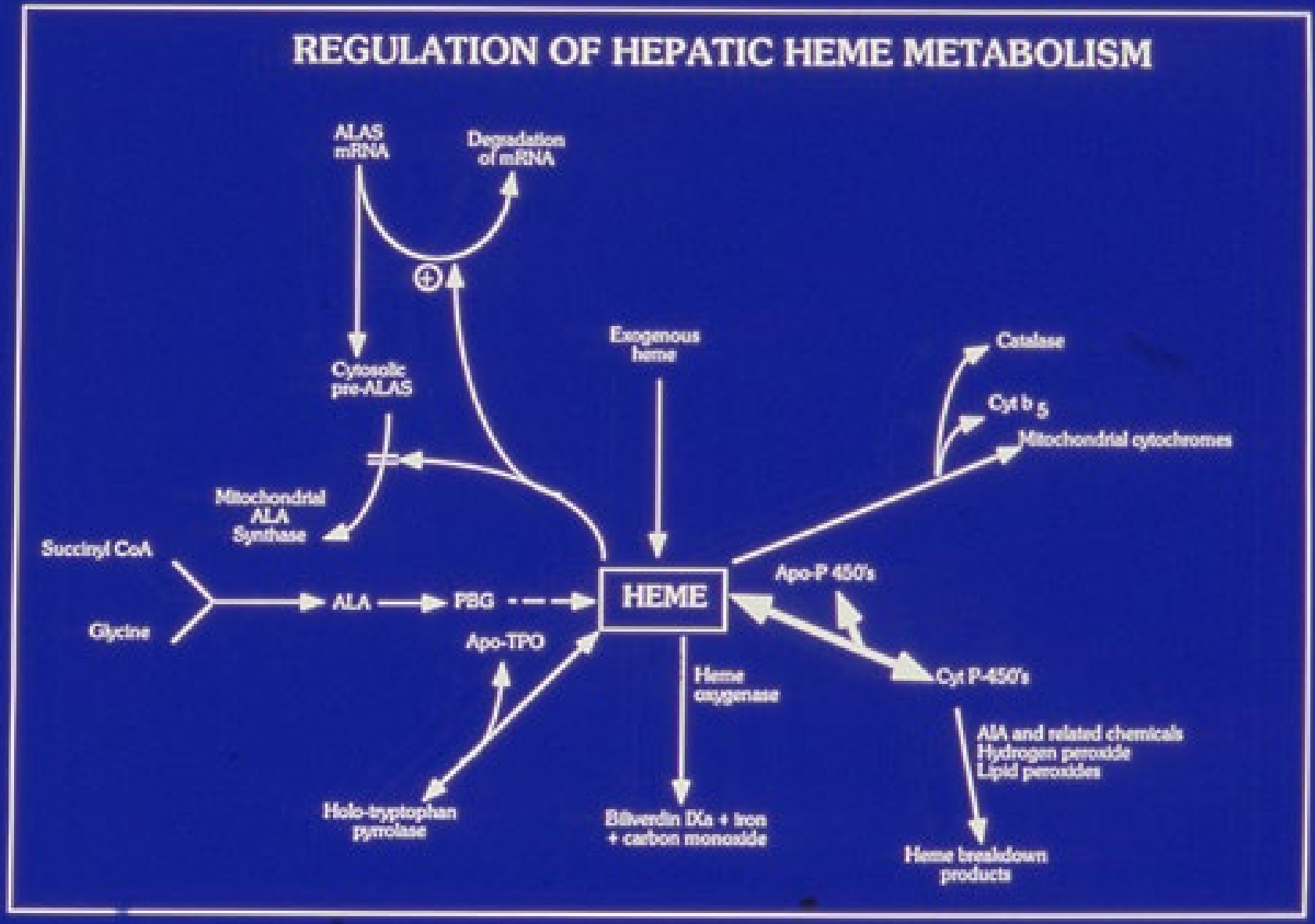
- **Acute porphyrias—neurological features**
  - **Acute Intermittent Porphyria [AIP]**
  - **Hereditary Coproporphyria [HCP]***
  - **Variegate Porphyria [VP]***
  - **Porphyria due to severe deficiency of ALAD [ADP]**
- **Cutaneous porphyrias**
  - **Porphyria Cutanea Tarda [PCT]**
  - **Erythropoietic protoporphyria [EPP]/XLP**
  - **Congenital erythropoietic porphyria [CEP]**
  - **Hepatoerythropoietic porphyria [HEP]**

* May also produce cutaneous lesions

Diseases Associated with Gene Mutations and/or Deficiencies in Enzymes in the Heme Biosynthesis Pathway



Up-to-Date



Bonkovsky HL. "Porphyrin and heme metabolism and the porphyrias", Ch. 14, in D. Zakim and T. Boyer (eds.), Hepatology: A Textbook of Liver Disease, Second Edition, Saunders, Philadelphia, 1990, pp. 378-424.

Acute Intermittent Porphyria
Estimated Prevalence of Disease

- Depends upon country and region: founder effects
  - Sweden 8-10/100,000
  - Finland 2-3 /100,000
  - UK & W Europe 2-5/ 100,000
  - USA 2-5/100,000

  Prevalence of genetic defects much higher, [~65/100,000] implying low penetrance

AIP: Typical case history-1

- 18 yo woman, taking oral contraceptives, generally healthy, develops severe abdominal pain; goes to ED: BP 150/96; PR 110; T 99.5 F; severe pain [10/10]; Abdomen soft; bowel sounds absent; CT of abdomen shows retained stool in colon; no gall stones; normal appendix.
- Patient treated with IV fluids and narcotic analgesics; pain gradually improves over 24-48 h; perhaps admitted for 'observation.'

AIP: Typical case history-2

- Patient does well for 6 months; goes to fraternity party at college; drinks to excess with poor nutritional intake; again develops severe abdominal pain requiring visit to ED. Mild fever and elevated WBC count; undergoes appendectomy despite lack of localizing signs to RLQ; appendix shows 'mild chronic inflammation'.
- Patient receives IV dextrose and analgesics and is improved and discharged after 3 days.

AIP: Typical case history-3

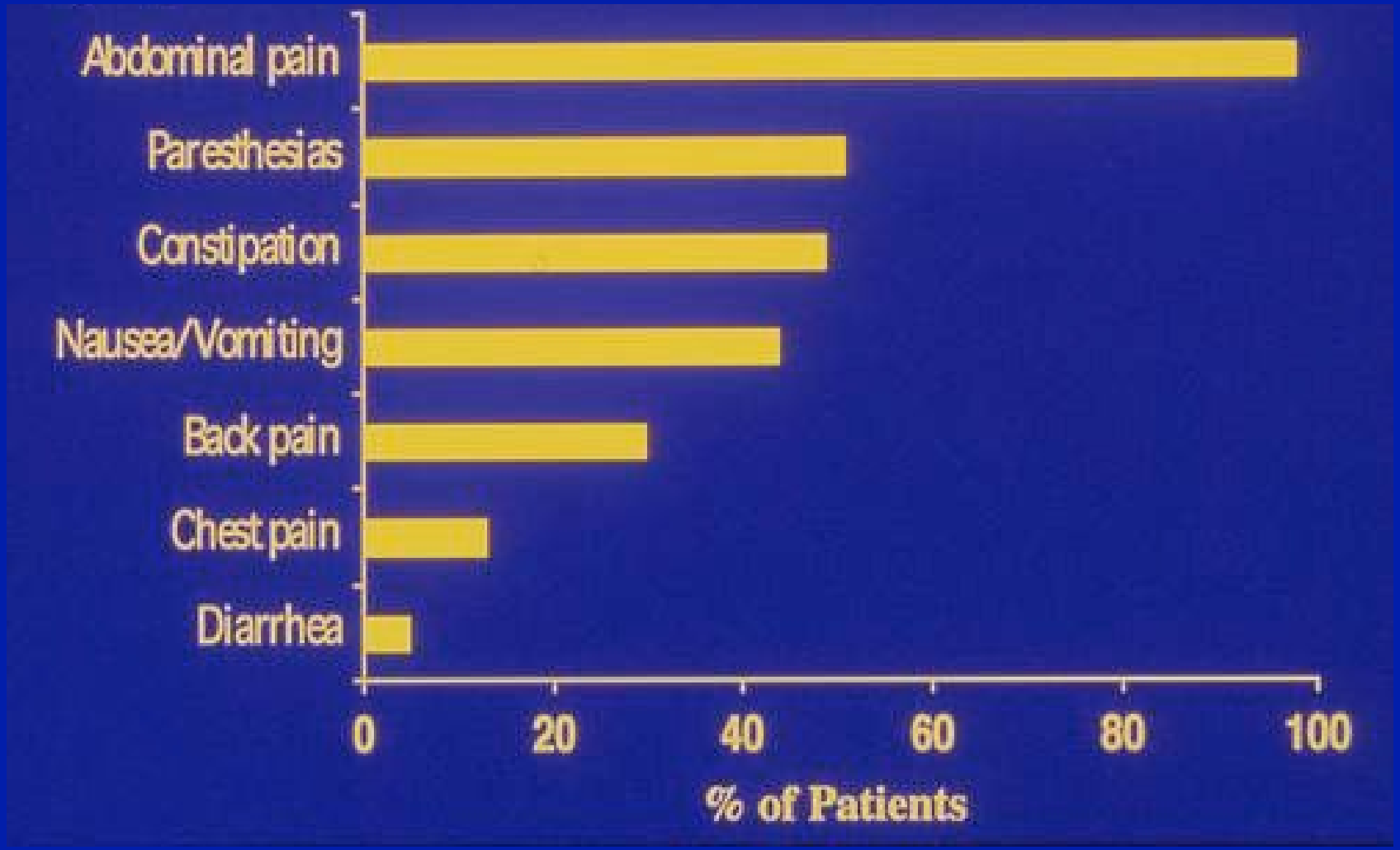
- Patient suffers further acute attacks of abdominal pain with tachycardia and hypertension. Repeat abd US and CT scans show no abnormalities except for retained stool in colon. Patient notes dark reddish-brown urine.
- Astute medical student considers diagnosis of AIP and obtains spot urine for PBG and creatinine. After 10 days, results returned: PBG 60 mg/g creatinine, establishing diagnosis.

Acute Porphyrias
Major Clinical Features

- Due to dysfunction or death of neurons
- Overlapping clinical syndromes
  - Acute attacks – pain crises, autonomic disease
  - Peripheral sensory-motor neuropathy
  - Progression to trunkal, CN, global CNS dysfunction
- Subacute or chronic pain and paresthesias
- (Seizures)

Acute Porphyrias

Symptoms in Patients Needing Hospitalization



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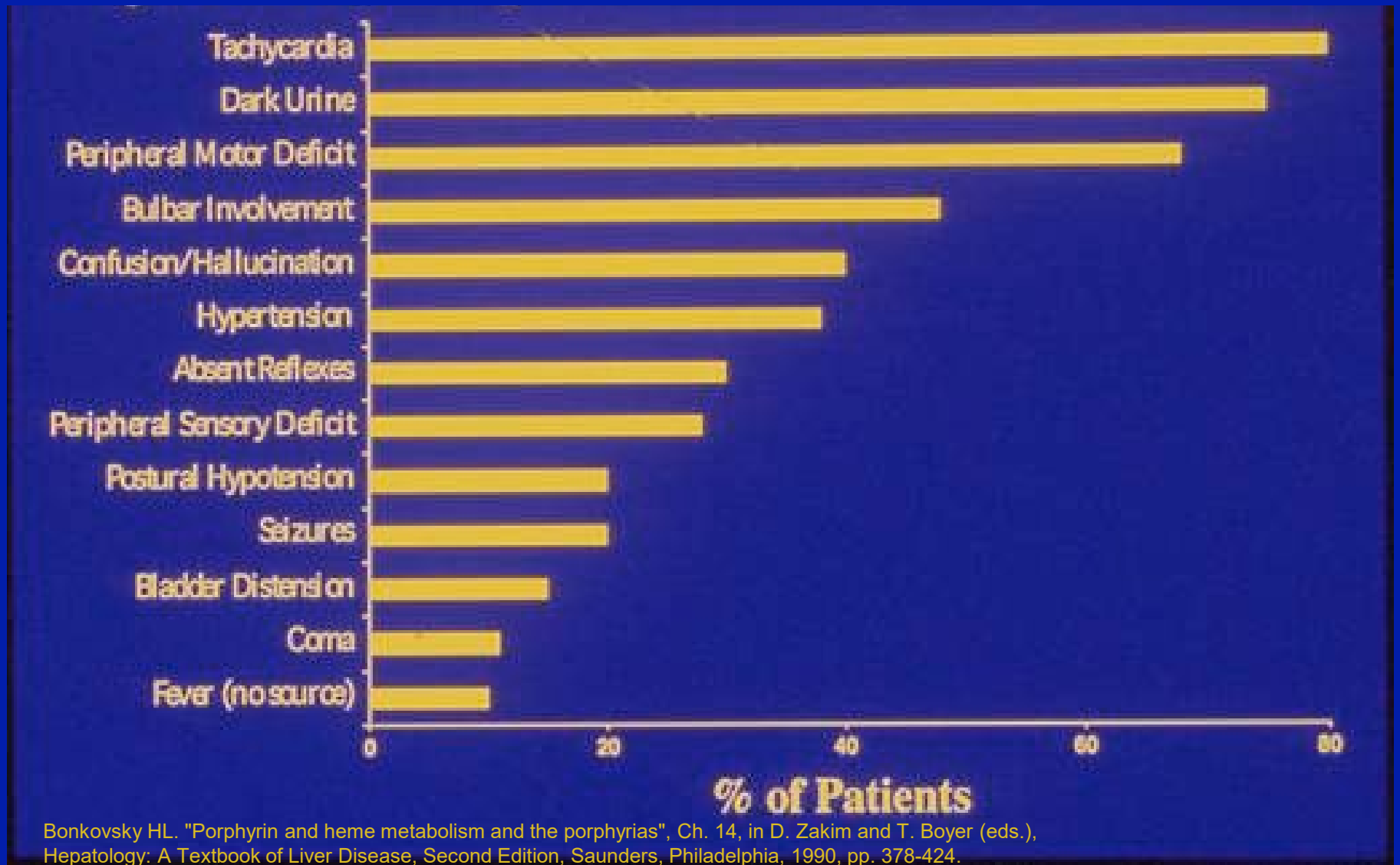
Acute Porphyrias

Signs in Patients Needing Hospitalization



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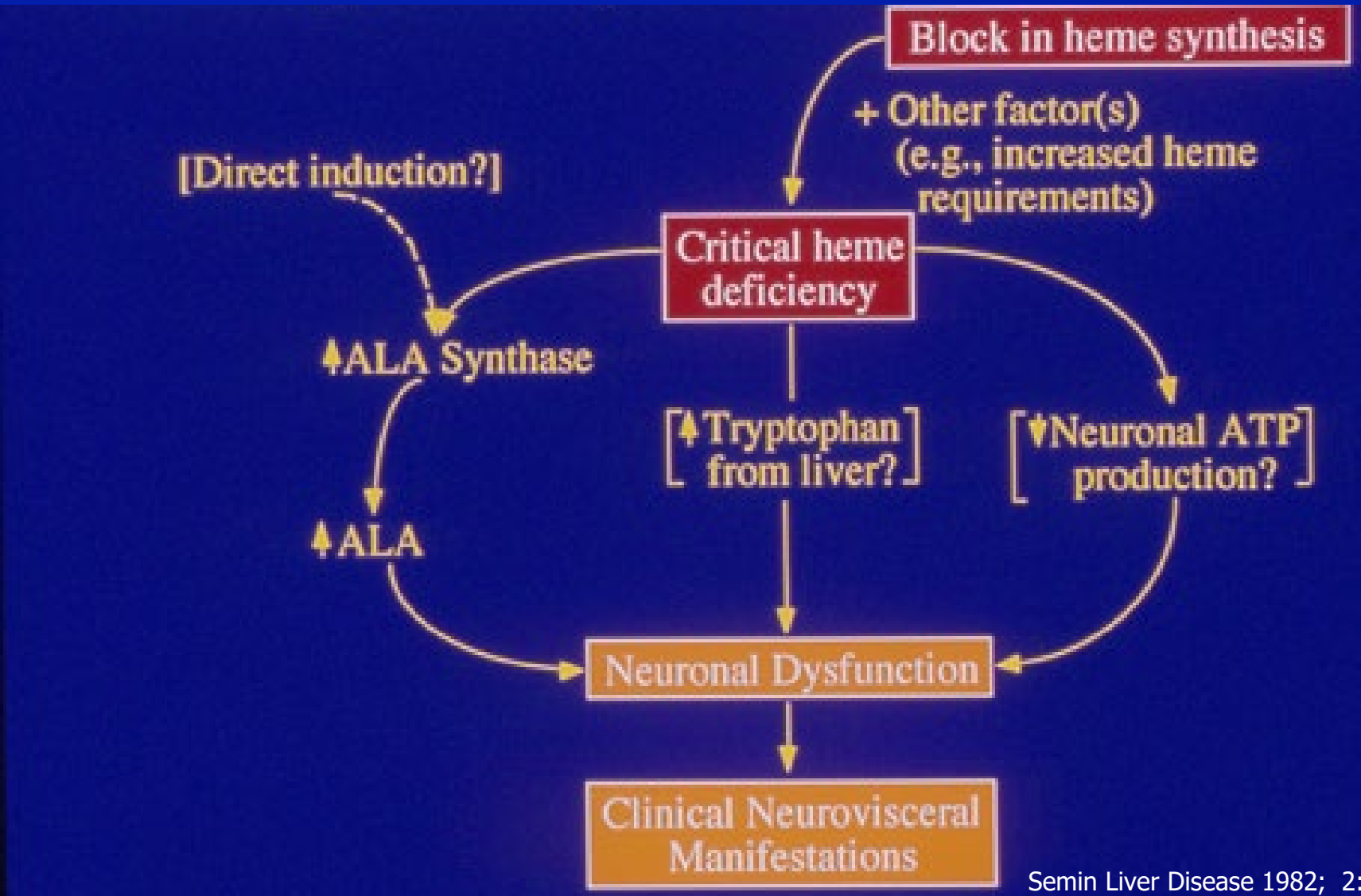
Acute Porphyrias
Precipitating or Aggravating Factors

- **Drugs and chemicals**
  - Alcohol
  - Estrogens
  - Trimethoprim
  - Hydantoins
  - Barbiturates
  - Progestagens
  - Other inducers of hepatic cytochrome(s) P-450 + ALA synthase-1
- **Luteal phase of menstrual cycle**
- **Pregnancy and post-partum period**
- **Infection**
- **Stress / exhaustion**
- **Fasting / starvation**
- **Surgery / anesthesia**

Acute Porphyrias
Pathogenesis of Neurovisceral Features



Semin Liver Disease 1982; 2:108-24
Semin Liver Disease 1998; 18: 43-52

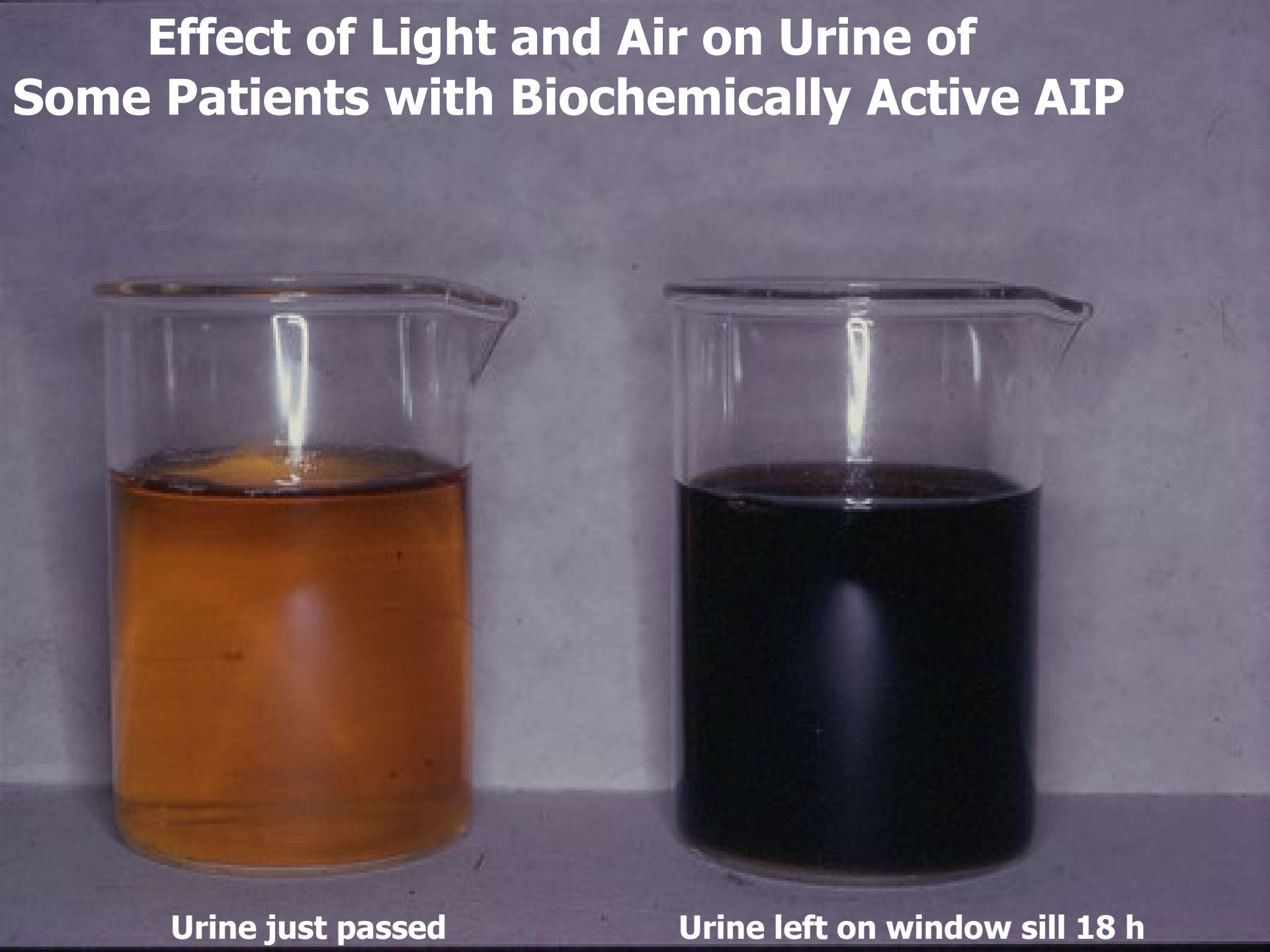
Acute Porphyrias
Laboratory Features during Attacks

- CBC usually normal; Routine liver chems normal
- WBC may be low or high
- NC/NC anemia may occur
- Low serum Na, Mg common
- Glucose tolerance often impaired
- Serum cholesterol, LDL, & serum binding proteins often increased
  - TBG
  - Sex steroid BP's
  - Corticoid BP's
- Urine ALA, PBG, uroporphyrin increased
- Blood volume often decreased

Early Diagnosis of Acute Porphyria

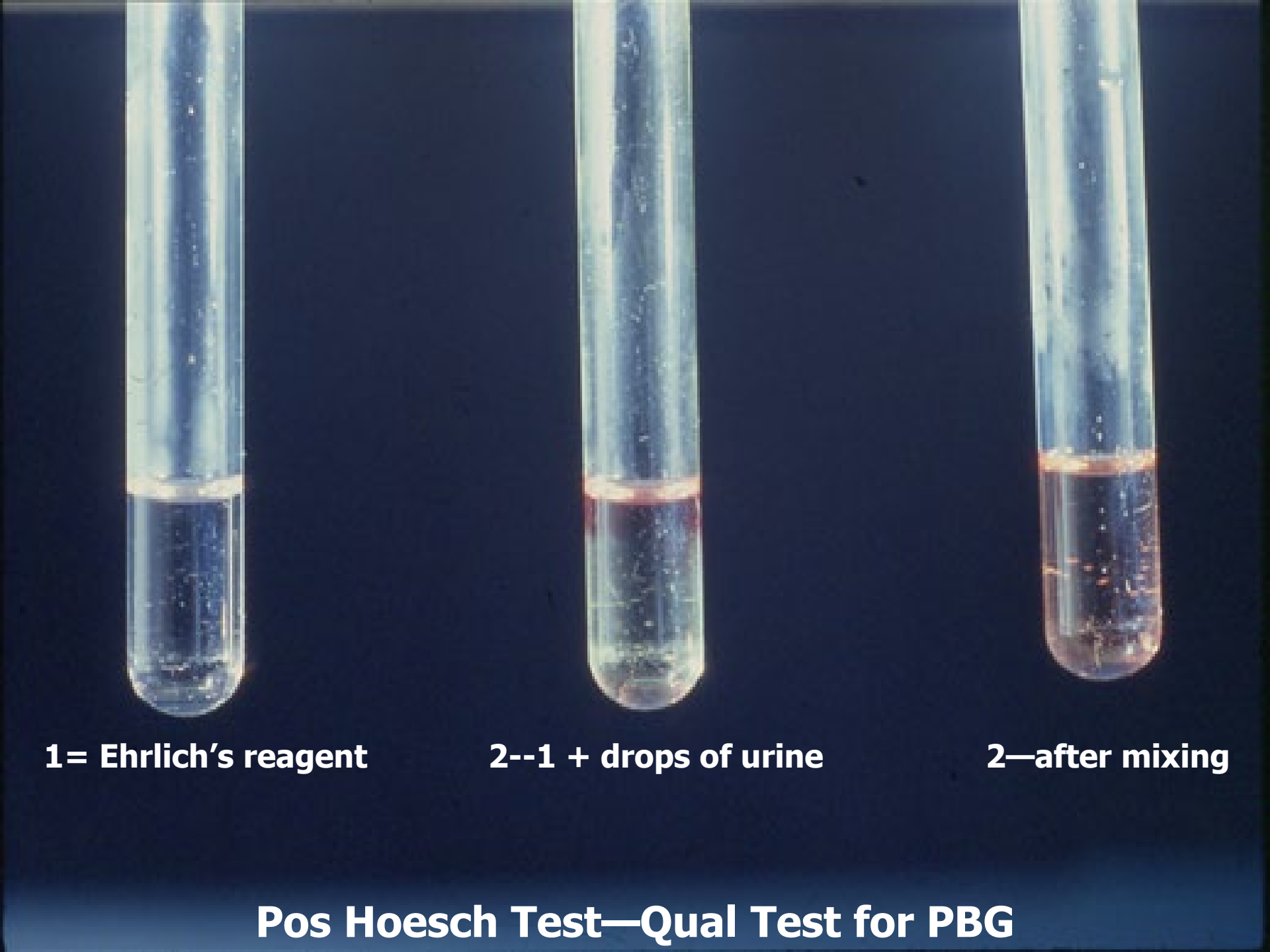
- Consider in all adults with unexplained symptoms, especially women 18-45 y; recurrent abdominal pain; muscle weakness; hyponatremia; dark or reddish urine
- Establish diagnosis rapidly by qual test for PBG in a single-void 'spot' urine [Hoesch, Watson-Schwartz,Trace PBG kit]
- Confirm by Quant PBG & creatinine in a spot urine
- DO NOT order 'porphyrin screen'

Effect of Light and Air on Urine of Some Patients with Biochemically Active AIP



Urine just passed

Urine left on window sill 18 h

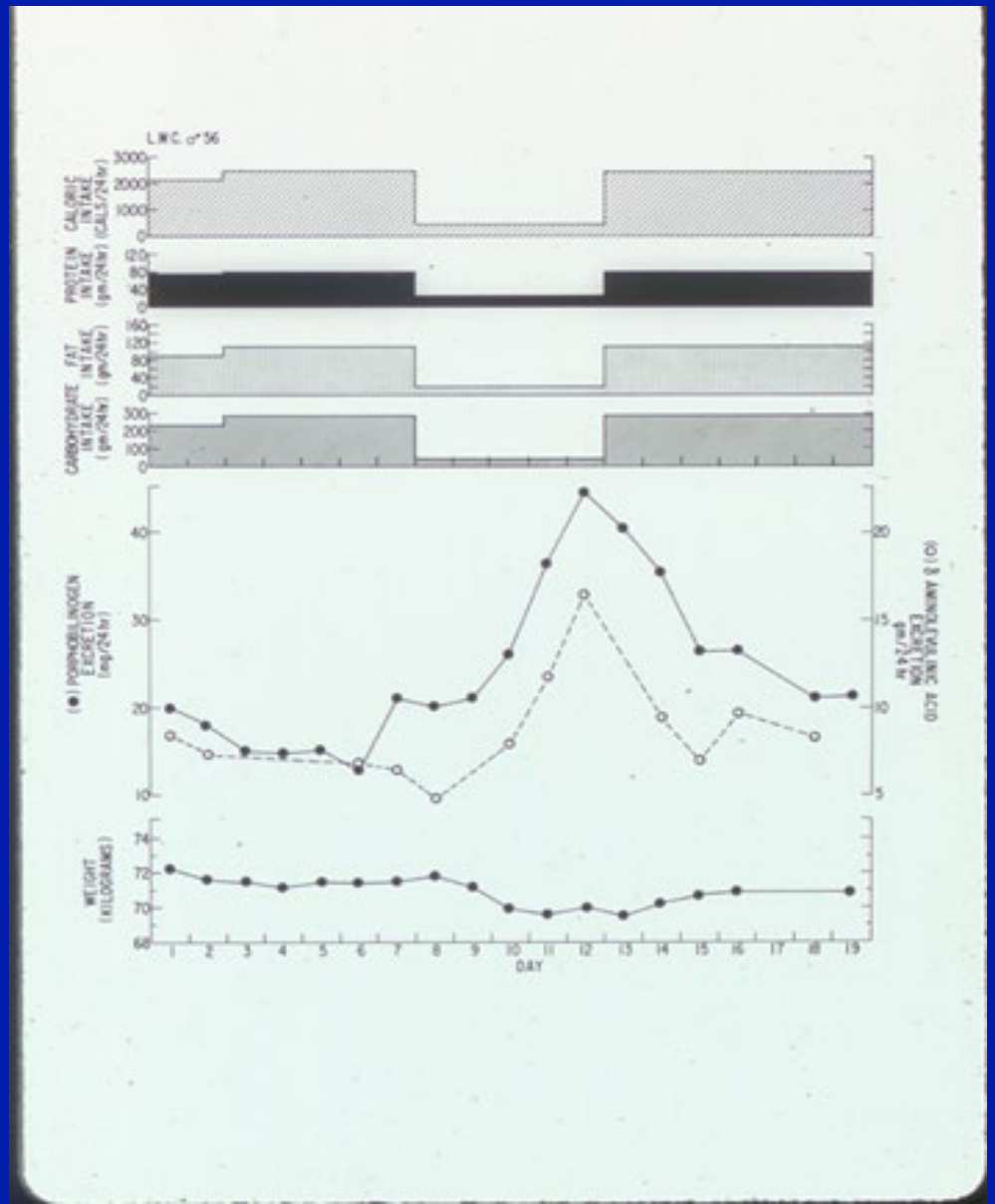


Pos Hoesch Test—Qual Test for PBG

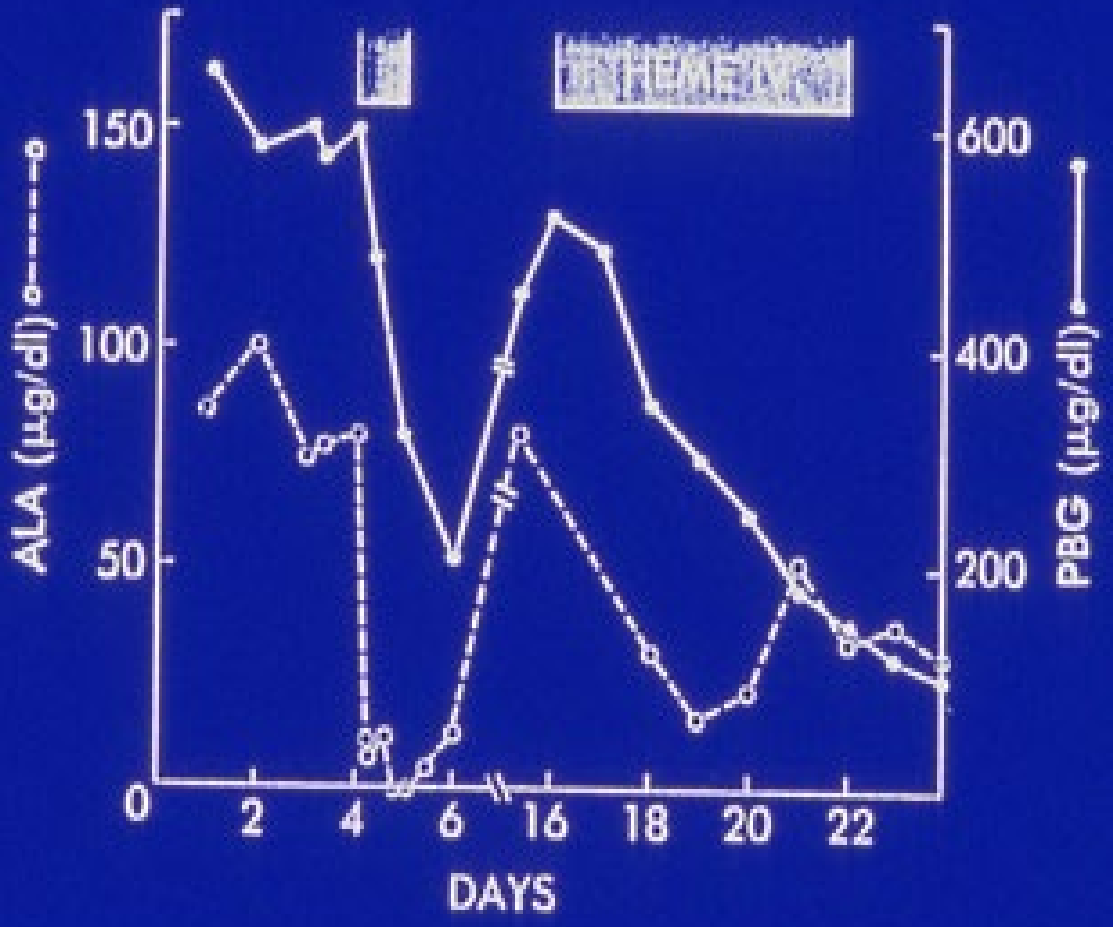
Acute Porphyrias
Management of Acute Attacks

- Primum nil nocere: 1st do no harm
  - Avoid offending drugs, chemicals.
- Maintain nutrition, fluids
  - Watch for hypo-natremia, -magnesemia & treat as necessary
  - At least 300 g/d carbohydrates
- Close watch for CNS involvement
  - Progressive weakness
- For pain - meperidine, morphine, methadone ± thorazine
- For hypertension – propranolol; lisinopril

Effect of Fasting in AIP
Up-regulation of Hepatic ALA Synthase-1



EFFECT OF IV HEME IN FIRST PATIENT WITH AIP TREATED WITH HEME



(Bonkovsky et al, *PNAS* 1971; 68:2725-2729)

Acute Porphyrias
Heme Therapy

- Always effective biochemically if given and prepared properly; best given into hi-flow central vein by PICC or Port.
- Nearly always effective clinically if given early in attack.
- Panhematin in water must be given within 1 hour of preparation.
- Panhematin in albumin can be stored at least 24 hours.
- Usual dose, 3-4 mg heme/kg BW/day.
- Usual course is 3-5 days of IV heme

Am J Gastroent 1991; 86:1050-56
Ann Int Med 2005; 142:439-50
Ann Int Med 2006; 144: 537-8

Acute Porphyrias
Prophylaxis – Prevention of Attacks

- **Avoid porphyrogenic drugs, chemicals**

Alcoholic beverages	Barbiturates
CYP inducers	Hydantoins
Trimethoprim	Progestagens

- **Avoid prolonged fasting, low carbohydrate or protein intake.**
- **Prompt, appropriate treatment of intercurrent illness.**
- **LHRH analogues – for women with frequent cyclical attacks related to menstrual cycle; helps ~ 50%; induces estrogen deficiency.**
- **Periodic infusions of heme—weekly, monthly, etc.; even taken weekly, less costly than givosiran, but also less convenient**
- **Givosiran as prophylaxis for frequent, recurrent attacks [more than 3 in prior year]; very costly**

NEJM 2017; 377: 862-72; J Med Econ 2020; 23: 1441-49

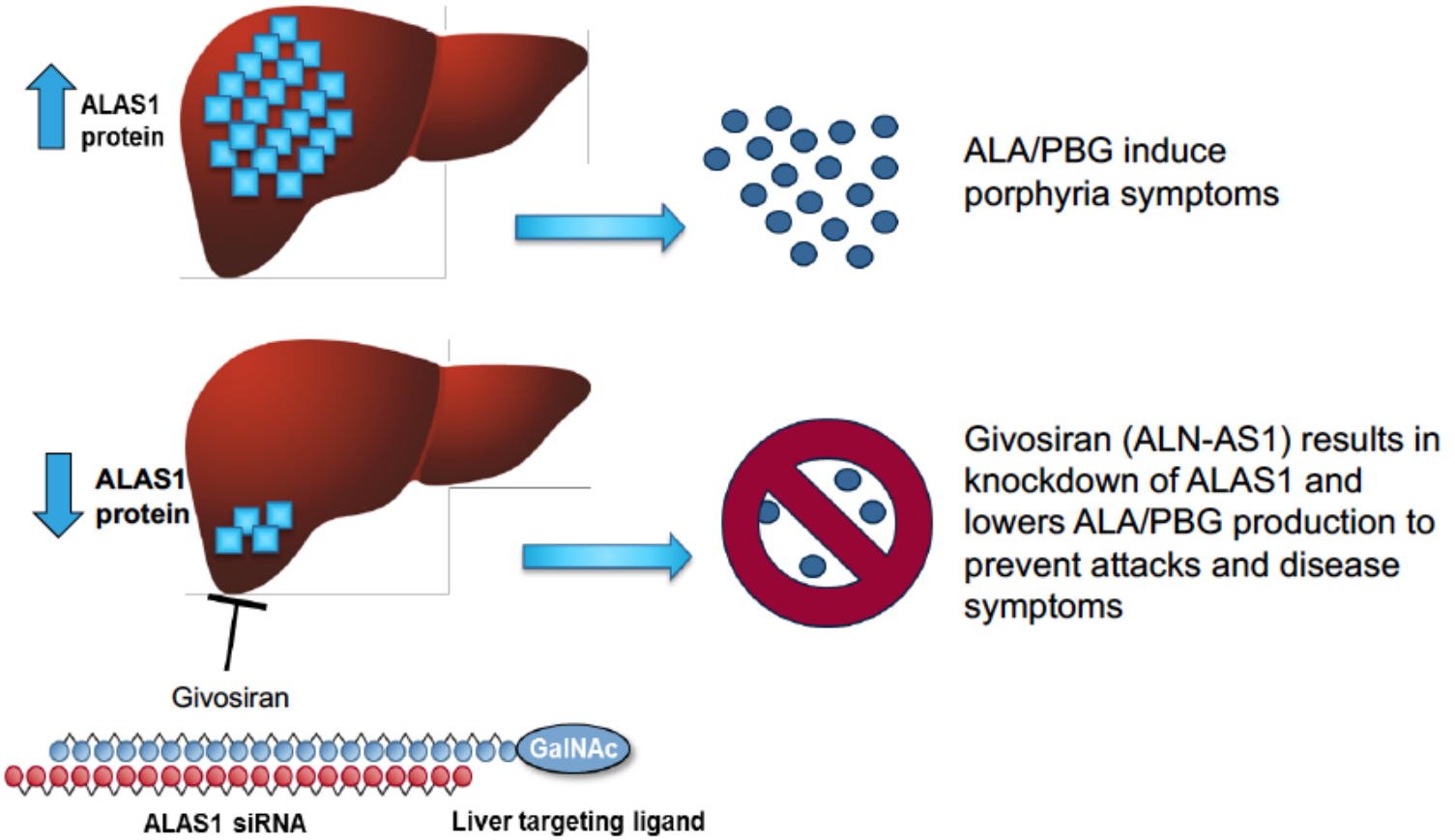
New Therapy for AIP—Prevent Recurrent Attacks

Givosiran—siRNA targeted to hepatocytes via ASGPR
siRNA directed at ALA synthase-1

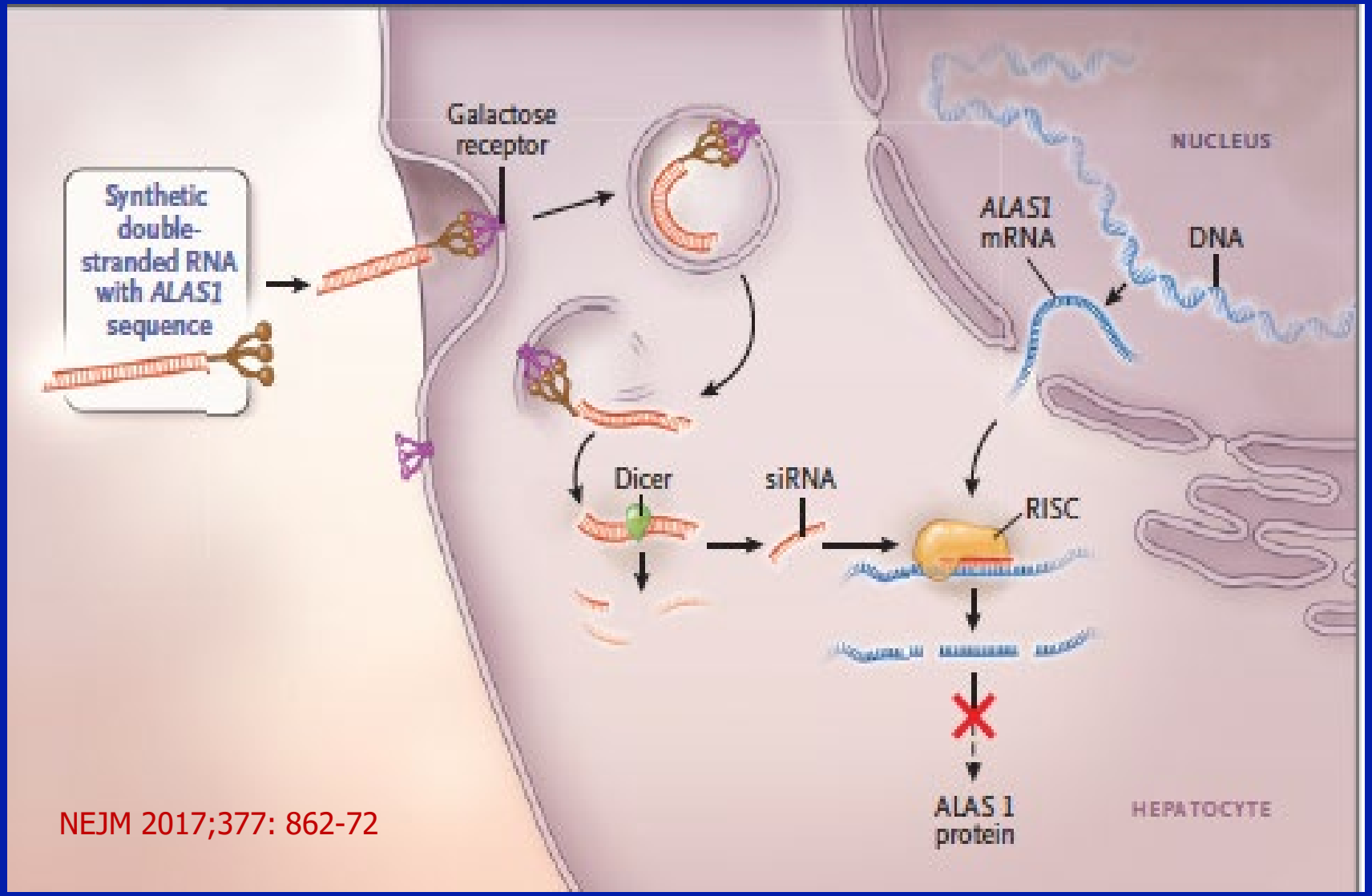
Givosiran: Novel, effective RNAi Therapeutic

Therapeutic Hypothesis

Reduction of Liver ALAS1 Protein to Lower ALA/PBG



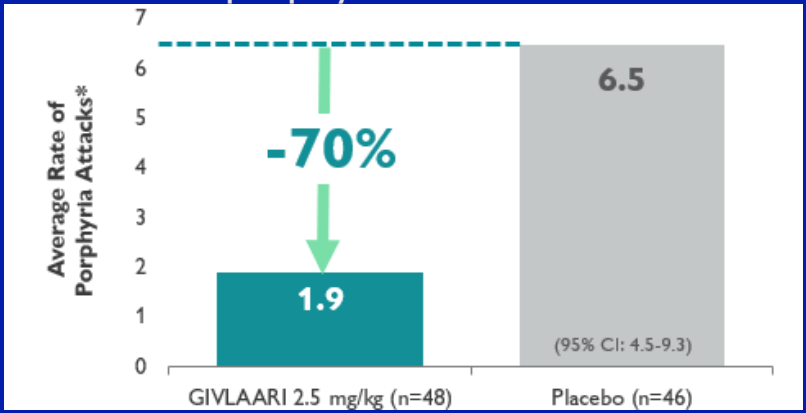
The Mechanism of siRNA Therapy
Givosiran for acute hepatic porphyrias with frequent recurrent attacks



NEJM 2017;377: 862-72

ENVISION 6-month Double-Blind Period: Treatment with Givosiran

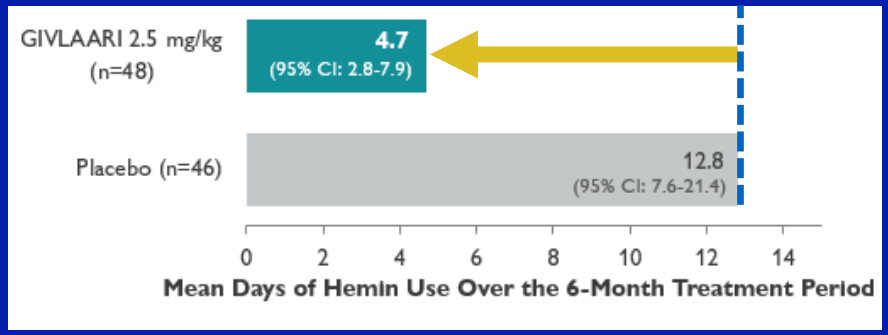
Treatment with givosiran significantly reduced porphyria attacks[1,2]*



- The attack rate ratio of givosiran vs placebo was 0.3 (95% CI: 0.2-0.4); P<0.0001

*Attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home.

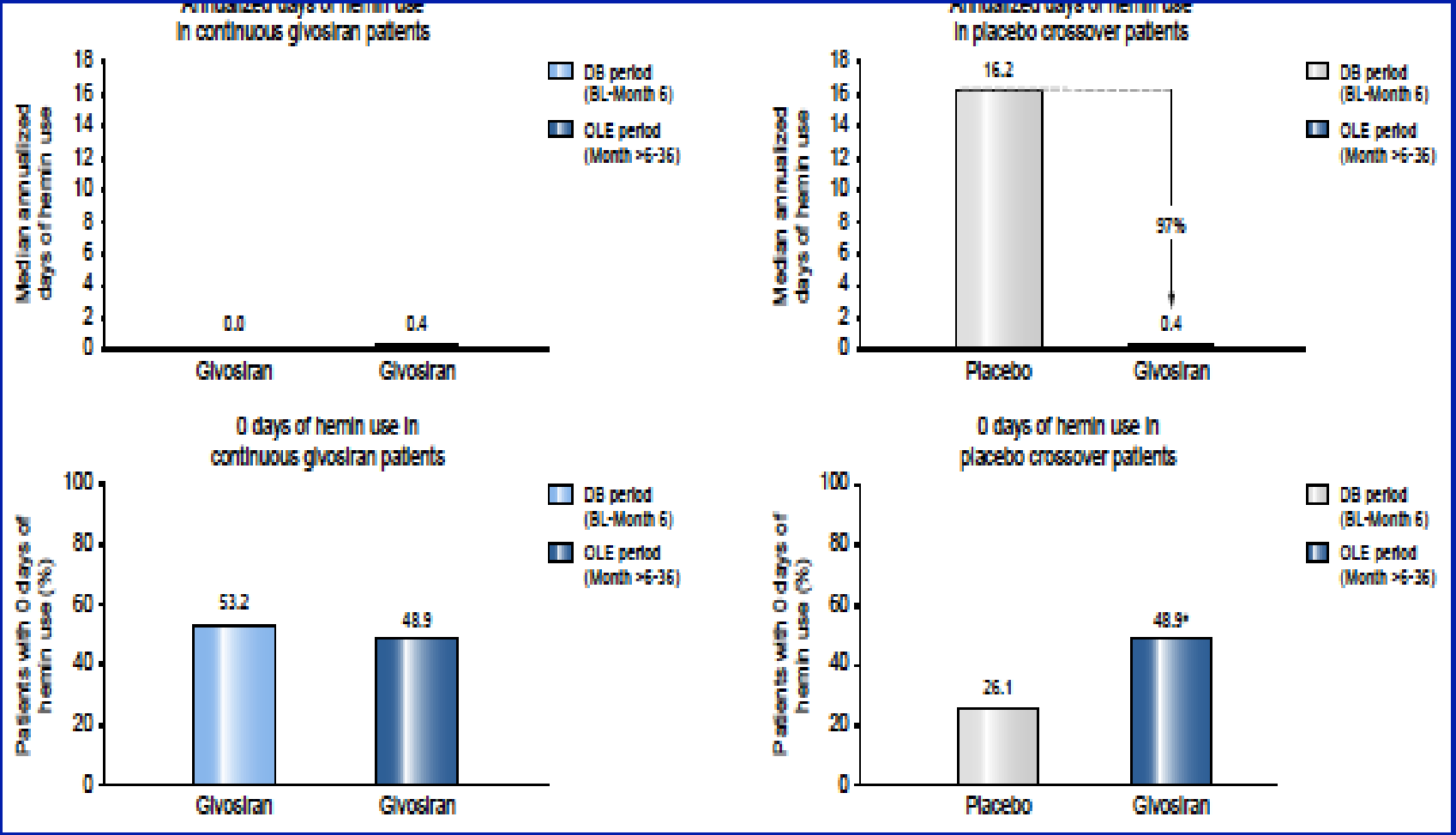
AHP patients treated with givosiran used significantly less hemin[1,2]



- Ratio of hemin use with givosiran vs placebo: 0.3 (95% CI: 0.1-0.5); *P*=0.0002[1]
- **54%** of patients with AIP treated with givosiran had zero days of hemin compared with 23% of patients receiving placebo[1]

N Engl J Med. 2020;382:2289-2301.

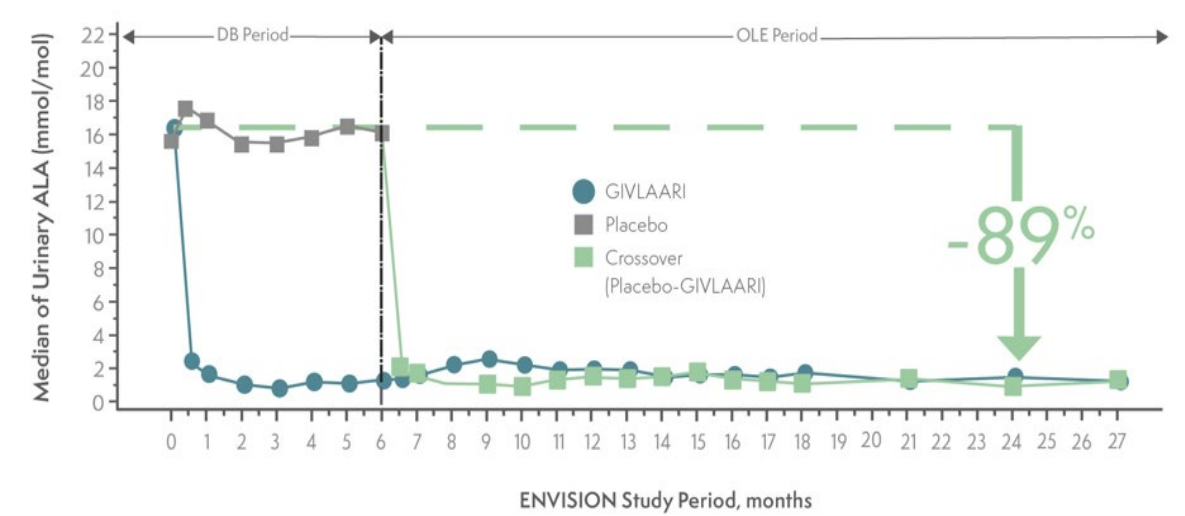
Givosiran markedly reduces acute attacks and need for IV heme for 36 months



J Hepatol 2023; 79:1150-58

Continued treatment with givosiran resulted in sustained reductions of ALA and PBG through month 24[1,2]

ALA levels over time



In patients who crossed over from placebo to givosiran, urinary ALA decreased by 89% from baseline at month 24[2]

- *OLE data for givosiran, 1.25 mg/kg and 2.5 mg/kg groups are pooled.
- **References: 1.** Bonkovksy H et al. Presented at United European Gastroenterology Week 2021. Oral. **2.** Data on file, Alnylam Pharmaceuticals, Inc. **3.** Protocol for: Balwani M et al. *N Engl J Med*. 2020;382:2289-2301. doi:10.1056/NEJMoa1913147

Liver Transplantation for Acute Porphyria

- 10 cases in UK, 2000-2010. 5 with severe neurol features. None with cirrhosis or HCC. 7/10 had mod-severe hepatic siderosis due to chronic heme Rx
- All had complete clin and biochem resolution
- Rate of devel of hepatic artery thrombosis was high—4/10 [40%] vs ~ 3%
- Need has fallen since givosiran approved

Liver Transpl 2011: 18:195

AIP: Natural History and Prognosis
Epidemiology of Cirrhosis and HCC Northern Sweden, 1978-1990

Variable	AIP	Non-AIP	P value	Relative Risk
No.	33	2089		
No. (%) cirrhotic	4 (12%)	11 (0.5%)	<0.0001	19
No. (%) HCC	9 (27%)*	5 (0.2)	<0.0001	114
Men	3	3	=0.0004	78
Women	6	2	<0.0001	147

* 6 with cirrhosis, 3 with advanced bridging fibrosis

J Int Med 1996; 240:195

Recommended Screening of Patients with Acute Porphyria for HCC

- **Beginning at age 50 years:**
- **Check serum alpha fetoprotein every 6 months;**
- **Liver ultrasound every 6 months**
- **Those at higher risk are those with chronic high ALA**

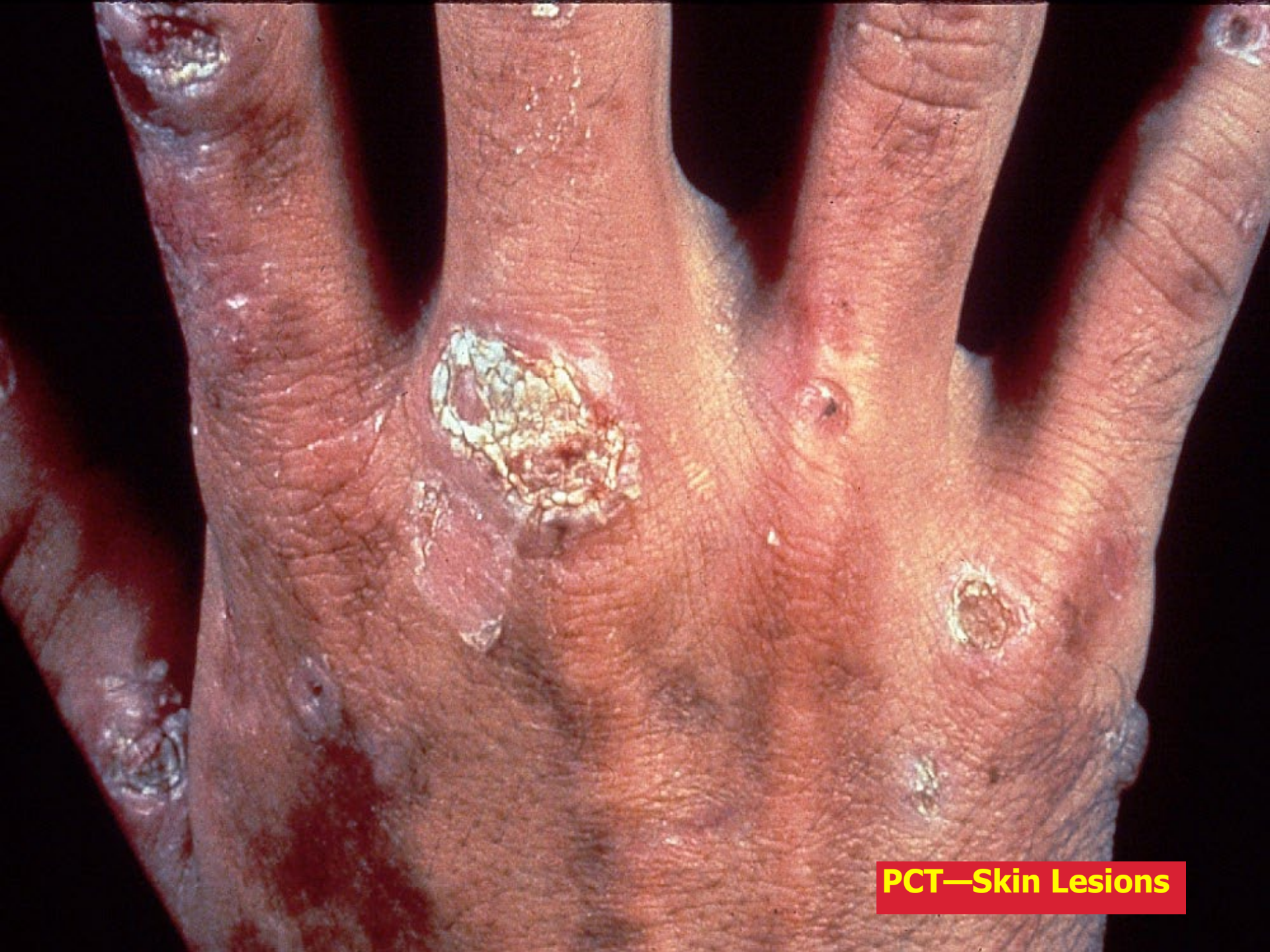
Summary

- Acute hepatic porphyrias—worldwide, pan-ethnic problem
- Low penetrance, but devastating for the patients, mostly women, with recurrent and severe attacks and chronic pain
- Induction of hepatic ALAS1 is key feature in pathogenesis
- Current Rx of choice for acute attacks—IV heme, dextrose, analgesics
- Prophylaxis—RNAi [givosiran] approved in 2019

Porphyria Cutanea Tarda

- Most common type of porphyria - - occurs world-wide
- Blisters, bullae on backs of hands, face, neck
- Liver injury & iron overload usual
  - Remits with iron depletion
  - Relapses with iron re-accumulation
  - Strong association with hepatitis C; treatment of HCV also treats PCT

Liv Intl 2012; 32:880-93
NEJM 2017; 377: 862-72
Dig Dis Sci 2023; 68:2738-46


PCT—Skin Lesions

Classification of PCT

Type	Frequency (%)	Common Name	Site(s) of ↓ Uro-D
I	75-80	Sporadic, acquired	Liver only
II	20-25	Inherited – common form	All cells

Risk Factors for PCT

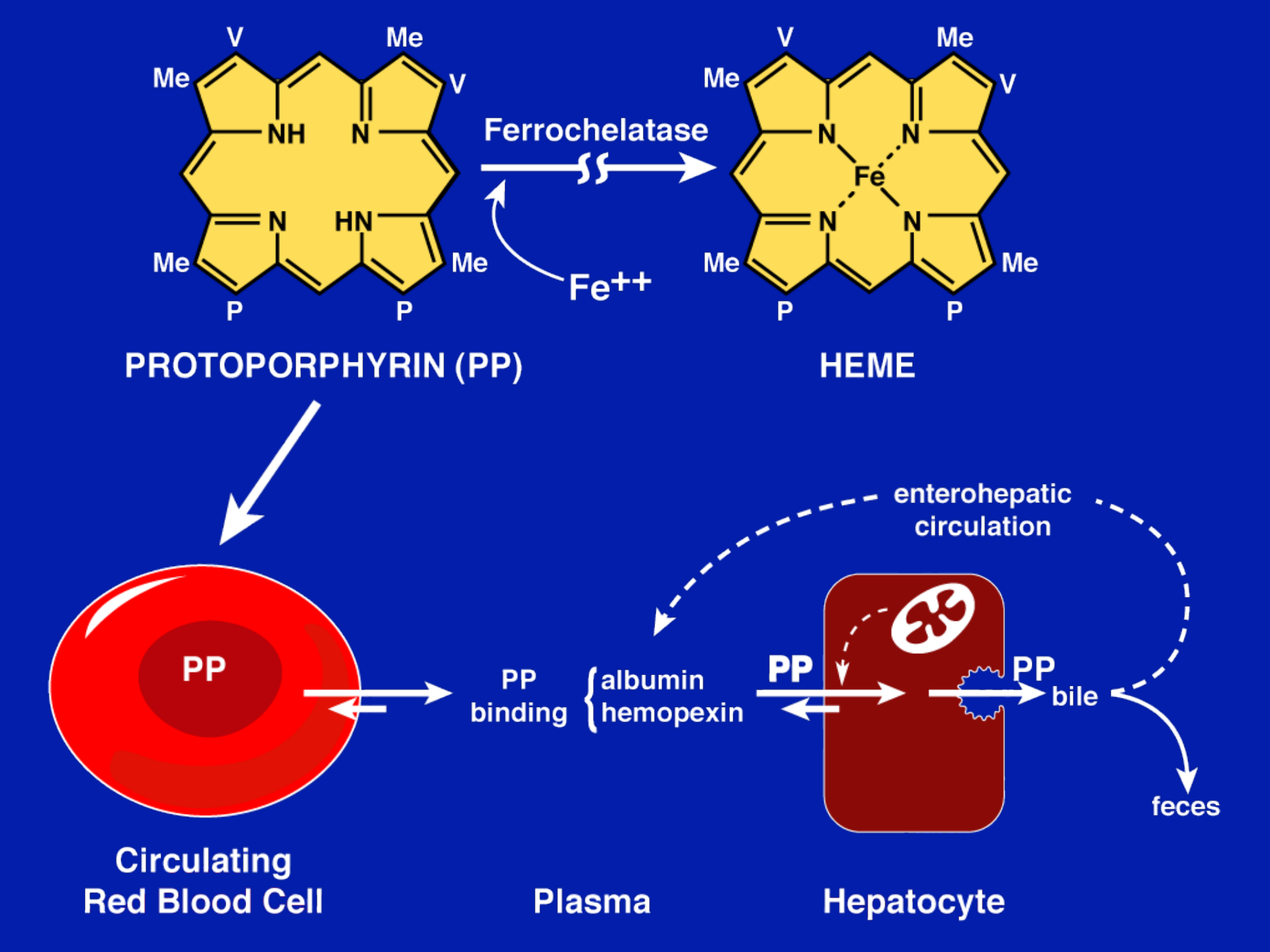
- Toxic chemicals
  - Ethanol
  - HCB, PCB, TCDD, etc.
- Iron—Hereditary or acquired
- Drugs
  - Estrogens
- Chronic liver disease
  - Alcoholic
  - Chronic hepatitis C

PCT - Management

- Avoid precipitating or exacerbating agents
  - Alcohol, iron, estrogens
- Protect skin from light and trauma
  - Treat secondary infections
- Test for *HFE*, HCV, and HIV
- Remove iron - - as for HHC
- Treat HCV, HIV if present
- Anti-malarials - - HCQ 100 mg biw

Erythropoietic Protoporphyria

- Most common form of erythropoietic porphyria
- Initial clinical feature: burning, itching skin after brief sun exposure: solar urticaria
  - Usual onset in infancy
  - Correct diagnosis often delayed until adulthood
- Most serious sequela: Pigmentary cirrhosis, liver failure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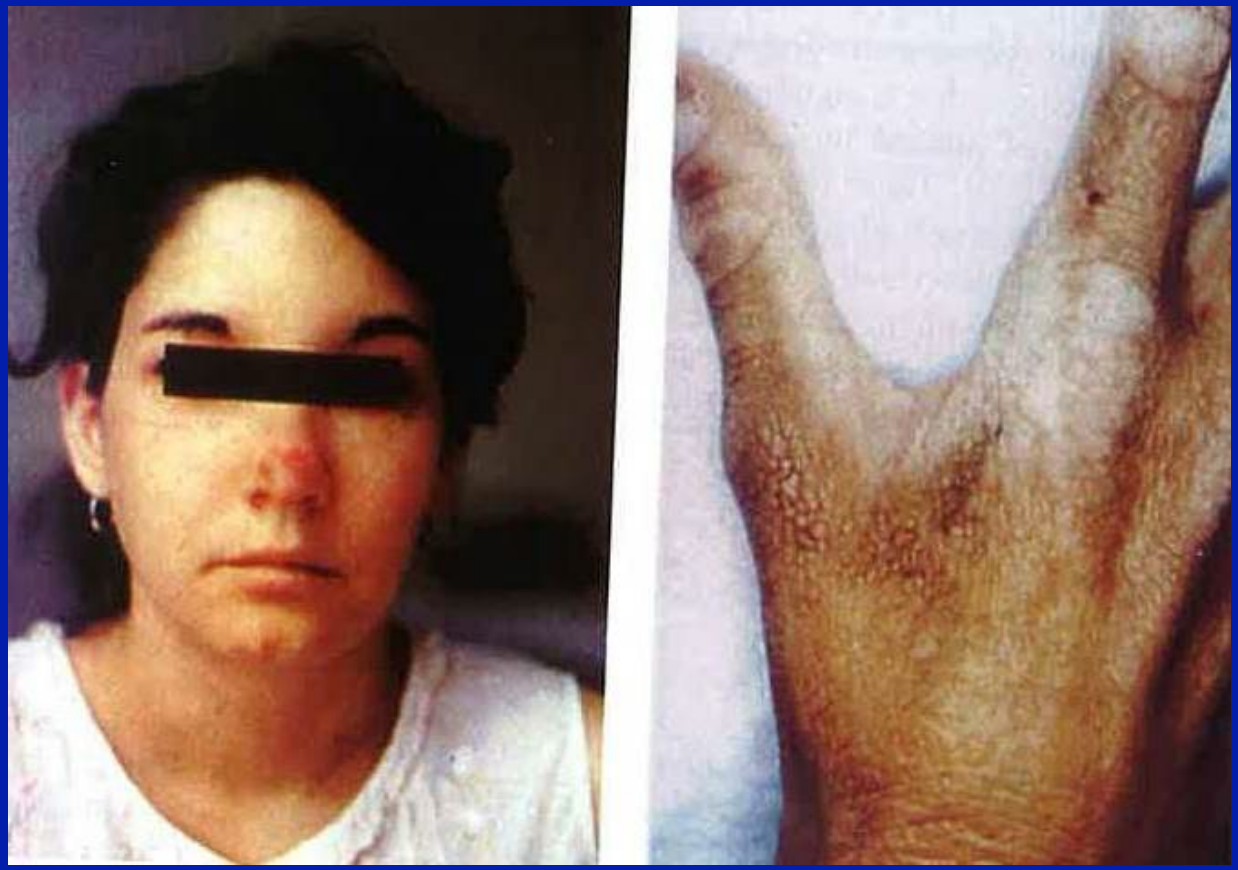
Circulating
Red Blood Cell
Plasma
Hepatocyte



Cutaneous lesions in protoporphyria. L: Acute photosensitivity reaction showing edema of the face and erythema on the bridge of the nose following sun exposure. R: Chronic skin changes on the hand of a patient with protoporphyric liver disease. T here is thickening and lichenification of the dorsum of the hand in areas where there was repeated sun exposure.

EPP - Laboratory Features

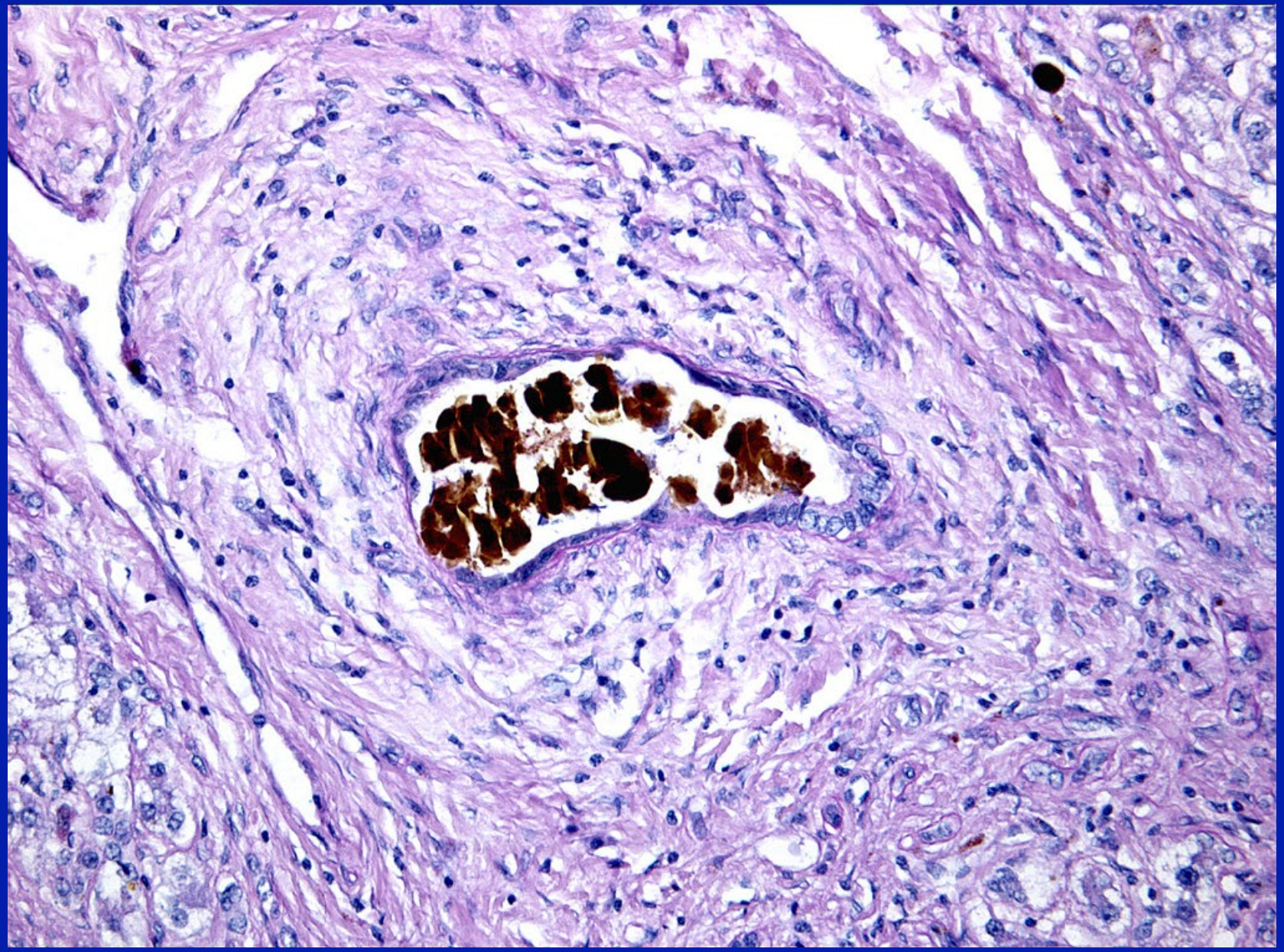
- CBC: Mild anemia
  - often HC/MC
- Serum ferritin often low; Fe lack
- Vit D deficiency common
- Plasma and RBC protoporphyrin elevated
- Fecal PP elevated
- Urinary porphyrins and porphyrin precursors NORMAL
- Bone marrow: ringed sideroblasts

Eur J Clin Invest 1993; 23:130
JAMA Derm 2017; 153: 789-96

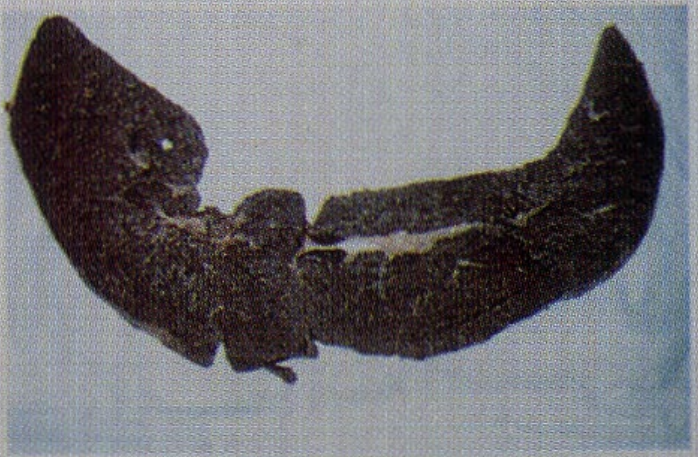
EPP - Hepato-Biliary Features

- PP gallstones common
  - May produce all usual complications
- Precipitation of PP in hepatocytes, canaliculi, intrahepatic BD's may occur
- Intercurrent cholestasis/hepatitis may worsen PP hepatopathy
- Elevations of serum liver enzymes or total bilirubin are cause for concern
  - Worsening often precipitous

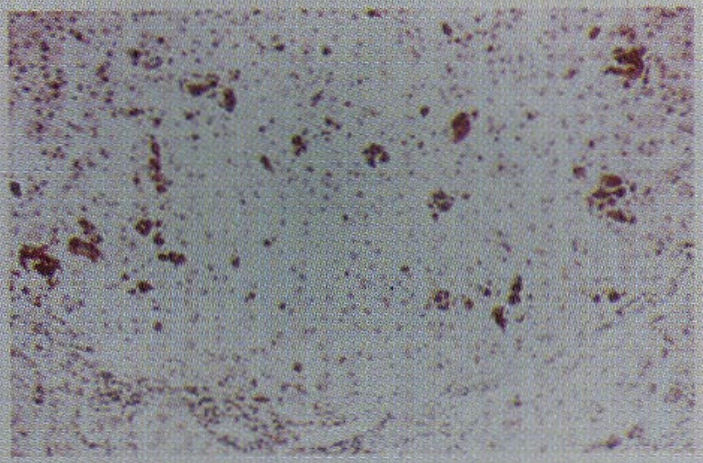
BILE DUCT DAMAGE IN EPP



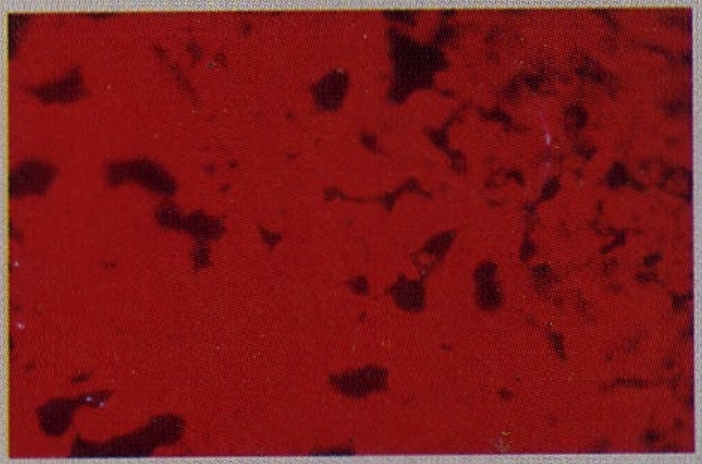
EPP LIVER DISEASE



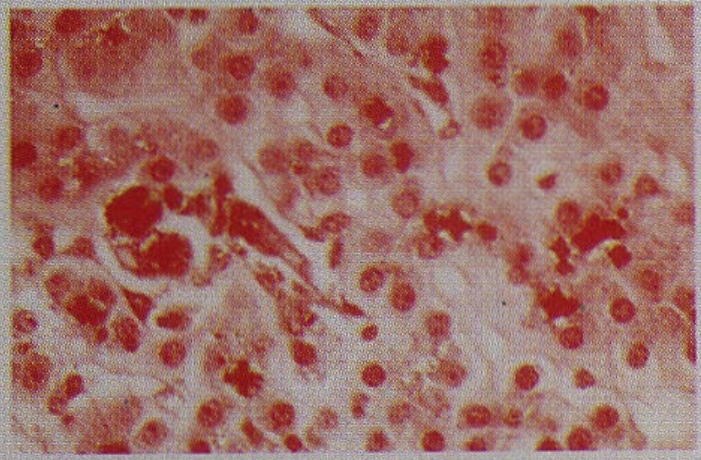
Gross Appearance



Light Microscopy



Fluorescence Microscopy



Polarization Microscopy

EPP - Nature of Metabolic Defect

- **Classical EPP--Inherited 50+% decrease in ferrochelatase (Fech)**
  - **FC gene on chromosome 18 q 21.3**

  More severe Fech deficiency (>75%), photosensitivity, and liver disease associated with a second, defect in the other allele, usually in non-coding sequence (intron 3)

  XLP—gain of function mutations in ALAS2

Nat Genet 2002; 30:27
Hum Genet 2004; 114:256

EPP/XLP - Management - for Skin

- Minimize sun exposure
  Opaque clothing, Zn oxide paste
  Broad-brimmed hats
- Beta-carotene: little benefit
  Yellow skin a problem
- Increase MSH, eumelanin—afamelanotide—approved, but not readily available; dersimelagon [MT-7117]—Ph3 trial in progress
- Decrease PP prodn—bitopertin—Ph 3 trial in progress

EPP - Management - for Liver

- Avoid other hepatotoxins, hepatitis
  - Little or no alcohol
  - Immunize against HAV, HBV, (HCV, etc.)
  - Use drugs sparingly and with great caution
- Aggressive diagnosis and therapy of PP stone disease
- Exchange transfusions most efficient quickly to decrease porphyrin load
- Plasmapheresis and IV heme-albumin for hepatic decompensation
  - Bridge to transplant
- Liver (± Bone Marrow) Transplant
- Bitopertin to decrease PP overproduction

Secondary Porphyrinurias: Most Common Cause of Over-Diagnosis of Porphyria

Mild to moderate increases in urinary porphyrins, usually mainly coproporphyrins, occur in many disorders

--alcohol; drugs
--anemias
--hear failure
--occupational exposures to metals, chemicals.
--liver/biliary diseases
--diabetes mellitus
--blood dyscrasias

These are NOT diagnostic of porphyrias.

Keys to correct diagnosis of acute porphyrias are > 4 x increased plasma or urinary ALA and PBG.

Most common error of providers: ordering the wrong test
--should order spot urine for ALA, PBG, creatinine
--NOT porphyrins


Fe
COOH
COOH

That's all folks!

Questions?

http://rarediseasesnetwork.epi.usf.edu/porphyrias/

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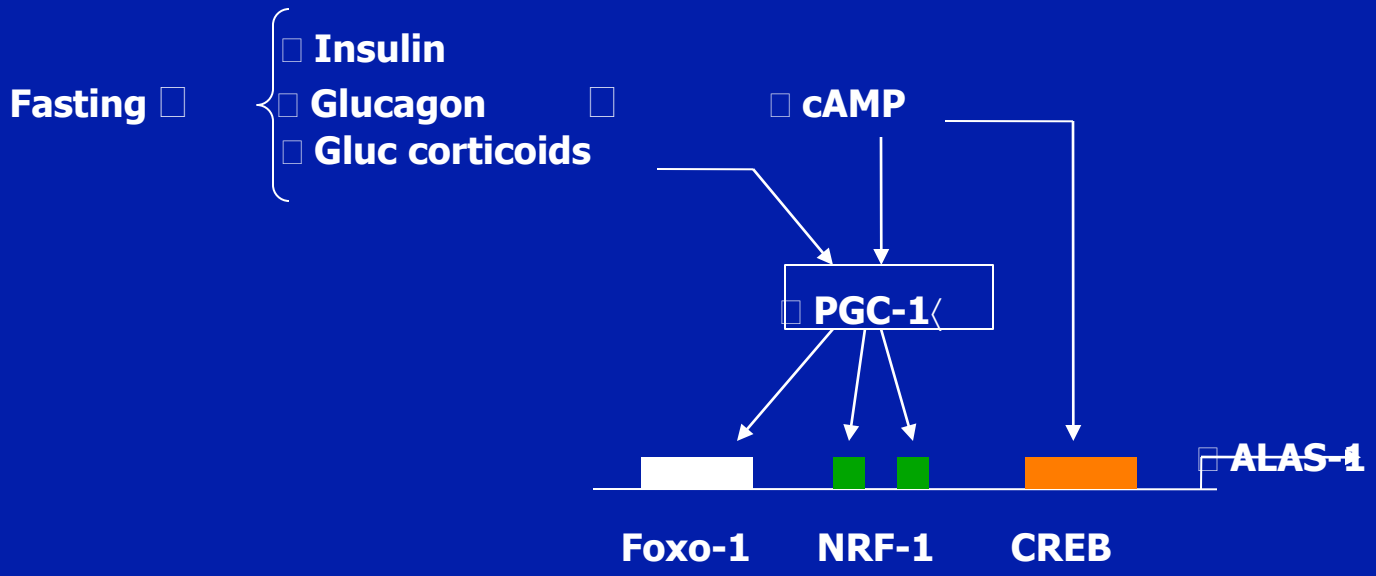
Mechanisms of Up-Regulation & Down-Regulation by "The Glucose Effect"



Glucose has opposite effects:

- **cAMP**
- **PGC-1⟨**
- **ALAS-1**

FOXO-1, transcription factor that activates gluconeogenic genes + ALAS-1
Insulin down-regulates by P-ation via Akt kinase

PGC-1⟨, PPAR© co-activator, induced by cold → UCP → Heat

→ **glucoeogenesis**

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