Porphyrins and Lead

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Objectives

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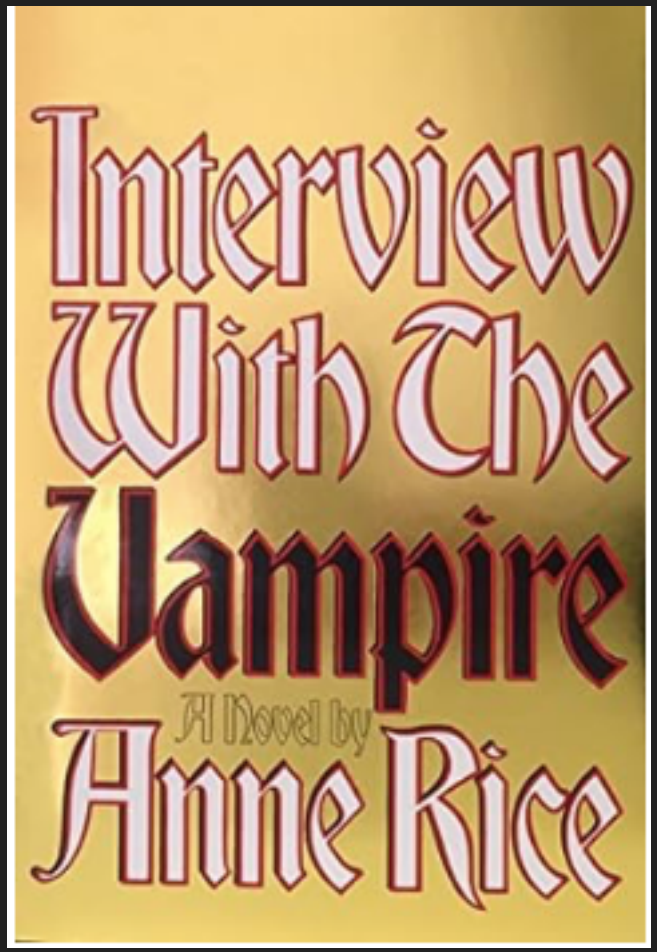
1. **Define porphyria**
2. **Discuss various porphyrias**
3. **Identify lab findings observed in individuals with lead poisoning**


Something to think about . . .


Interview
With The
Vampire
A Novel by
Anne Rice

Vampire Myths ???

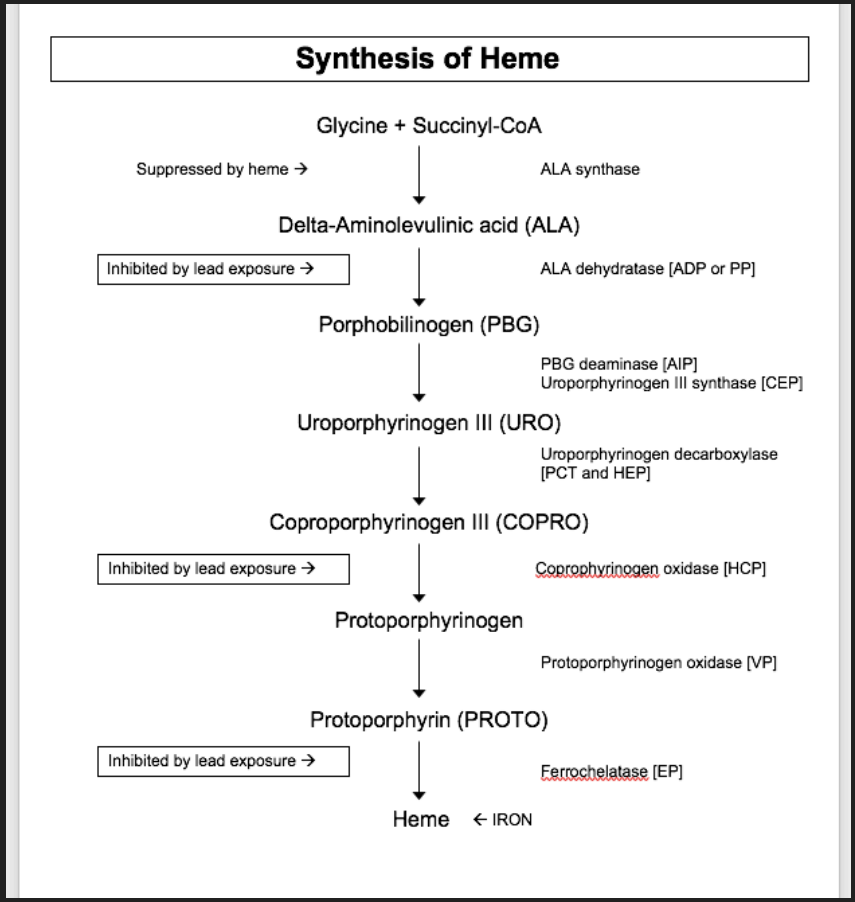
Vampire Myths ???

Porphyrins

- Intermediate compound in heme production
- Iron is chelated within porphyrins to form heme

- Analyzed to aid in diagnosis of **porphyrias**
  - Porphyria → **result of disturbance in heme synthesis**
  - Identify presence of specific porphyrin

Synthesis of Heme



Heme Synthesis

- Negative feedback
- Regulation
  - Excess heme inhibits ALA synthase
  - Deficit of heme stimulates ALA synthase
- **Rate limiting step → ALA synthase**

Porphyrias

- Overproduction of heme precursors
  - Accumulation of porphyrins:
    - BM → Erythropoietic porphyrias
    - Liver → Hepatic porphyrias
- Inherited or acquired
- Enzyme deficiency identified at every step of heme synthesis except ALA synthase

Diagnosis

- Based on:
  - Clinical features
  - Porphyrins/precursors present in blood, feces, or urine
  - Cutaneous is easier to diagnose → photosensitivity is presenting symptom
  - Neurological porphyrias difficult to diagnose

Excess of early precursors

- **ALA (aminolevulinic acid)**
- **PBG (porphobilinogen)**

- Neuropsychiatric symptoms
  - Abdominal pain, vomiting, constipation
  - Tachycardia
  - Hypertension
  - Fever, leukocytosis
  - Psychiatric symptoms

ADP

ALA Dehydratase Deficiency Porphyria (Also called PP → plumboporphyria)

- **ALA dehydratase deficiency**
- Inherited & extremely rare
- Lab findings:
  - **↑ALA urine**
- Similar lab findings in lead poisoning
  - Sulfahydral reagent

AIP
Acute Intermittent Porphyria

- **PBG deaminase deficiency**
- Inherited

- Lab findings:
  - **↑ ALA urine**
  - **↑ PBG urine**
  - Hyponatremia
  - Red/dark brown urine

Excess of late precursors

- **URO (uroporphyrinogen)**
- **COPRO (coproporphyrinogen)**
- **PROTO (protoporphyrinogen)**

- Cutaneous symptoms & photosensitivity

PCT
Porphyria Cutanea Tarda

- Most common porphyria
- **Deficiency in uroporphyrinogen decarboxylase**

- Clinical manifestations appear in adulthood
  - Cutaneous blisters, skin light-sensitive, abnormal hair growth

PCT

- Lab results:
  - **↑urine URO**
  - **↑ plasma URO**
  - ↑ serum iron and ferritin
  - Liver damage → ↑ liver enzymes

EP
Erythropoietic porphyria

- 2nd most common porphyria
- **Deficiency of ferrochelatase**

- Clinical symptoms:
  - Photosensitivity (starting in infancy)
    - Burning, itching, pain in skin when exposed to sunlight
  - Severe liver disease

EP

- Lab findings:
  - **Normal urine porphyrins**
  - **↑ PROTO (RBCs, plasma, stool)**

HEP
Hepatoerythropoietic porphyria

- **Deficiency in uroporphyrinogen decarboxylase**
- Clinical manifestations similar to CEP:
  - Photosensitivity starting in childhood, excess facial hair, scarring of hands and face
  - Leads to liver disease

HEP

- Lab findings:
  - **↑urine URO and COPRO**
  - **↑ ZPP (erythrocyte zinc protoporphyrin)**
  - Red/brown urine

CEP
Congenital erythropoietic porphyria
Gunther's Disease

- **Deficiency of uroporphyrinogen III cosynthase**
- Symptoms appear shortly after birth
  - Red – brown urine (see in diaper)
  - Cutaneous photosensitivity, infected lesions, scarring
  - Teeth fluoresce red under UV light
  - Excessive hair

CEP

- Lab findings:
  - ↑ **urine URO and COPRO**
  - ↑ **fecal URO**

Legend of the Werewolf

- Photosensitivity → lesions → infected and scarred → disfigured
- Abnormal hair growth in exposed areas
- Avoid daylight

Excess of both precursors

- Neurocutaneous symptoms
  - Both neurological & cutaneous

HCP Hereditary Coproporphyria

- **Deficiency of coproporphyrinogen oxidase**

- Lab findings:
  - **↑ COPRO III, ALA, PBG in urine**
  - **↑ COPRO III in stool**

VP

Variegate Porphyria

- **Deficiency of protoporphyrinogen oxidase**
- Lab findings:
  - **↑ COPRO III, ALA, PBG in urine**
  - **↑ COPRO III and PROTO in stool**

Treatment

- Avoid sunlight
- Use sun-blocking agents
- Oral beta-carotene
- Reduce heme load
  - Phlebotomy
- Intravenous hematin

Diagnosis

- Urine has red or port wine color after exposure
- Teeth may stain red
- Screen for presence of porphyrins in urine, stool, or blood
  - If positive → id by HPLC and quantitate


...Now the symptoms make sense!

Lead

Lead poisoning

- ~90% absorbed lead taken up by RBC → inhibits heme synthesis

- Enzymes inhibited by lead:
  - ALA dehydratase
  - Coproporphyrinogen oxidase
  - Ferrochelatase

Lead poisoning

- CDC recommends analysis of **whole blood** because 90% lead in RBCs
  - Test ZPP level as screening test
  - Test lead level
    - Lead level >10 µg/dl is unsafe level

- ZPP → zinc protoporphyrin
  - Chelation of zinc with protoporphyrin
  - Inc in iron insufficiency
  - Hematofluorometer

Lead poisoning

- Lab findings:
  - ↑ urine ALA, COPRO, or PROTO
  - **N** urine PBG
  - ↑ erythrocyte ZPP (FEP)
  - **Blood lead levels**

Lead poisoning

- Sources of lead: lead based paint, lead pipes, etc.
- Lead exposure in infants hampers mental development
- Lead in adults – remove from exposure; monitor

CDC action levels for lead exposure

<10 µg/dl	No lead poisoning
15 µg/dl	Increase monitoring
20 µg/dl	Evaluate carefully
45 µg/dl	Chelation therapy
70 µg/dl	Medical emergency

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