Porphyria: A Royal Malady or not?

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Leaving Brooklyn

Fuhgeddaboudit

Marty Markowitz
Borough President

Michael R. Bloomberg
Mayor
I Have No Disclosures

Acknowledgement:
The Samuel Goldwyn Company
Summary

- Overview of the Porphyrias
- A Brief History of King George III
- ? Porphyria in the Royal Family ?
- Other Historical (?) incidences of porphyrias
For Starters

- Porphyrus in Greek: Purple
- Porphyrias—a variety of metabolic disorders due to a variety of inherited specific enzyme deficiencies in heme biosynthesis
- A fascinating & very old disease
- First Clinical Description in 1870’s
**HEME – A KEY MOLECULE**

- Structure
- Major sites of heme requirement
  - Liver (cytochromes)
  - Bone marrow (erythropoiesis)
  - Other sites (enzymes)
- Significance !!

Porphyrias: Classified as "hepatic" or "erythroid" - on site of overproduction & accumulation of intermediates
HEME BIOSYNTHESIS
Biosynthesis of Heme

(a) Aminolaevulinic acid (ALA)

- CO₂H
- NH₂

ALAD (Dehydratase) → PBG (Deaminase)

Preuroporphyrinogen

Cosynthase

Uroporphyrinogen decarboxylase

Coproporphyrinogen III

Copro'gen oxidase

Coproporphyrinogen III

(b) Aminolaevulinate

- Doss porphyria

- Acute intermittent porphyria

Preuroporphyrinogen

- Congenital erythropoietic porphyria

Uroporphyrinogen III

- Porphoria cutanea symptomatica

Coproporphyrinogen

- Hereditary coproporphyria

Protoporphyrinogen

- Variegate porphyria

Protoporphyrin

- Erythropoietic protoporphryia

Haem
Heme levels:

a delicate balance of synthesis vs degradation

Regulation of heme biosynthesis:

- **Free Heme** is the major regulator – feedback inhibition
- Free heme pool – Site of regulation varies in liver & erythroid cells
- Heme from these pools is taken up to fulfill various needs, later pools are filled up by new production
Heme Degradation

- **Heme oxygenase (HO)** degrades free heme
- Normally, everything is nicely in balance:

\[
\text{Heme degradation} + \text{Heme utilization} = \text{Heme Synthesis}
\]
How Do Things Go Wrong?

- External factors can influence the balance
  - Heme Oxygenase is induced by endotoxins, chemicals, nutritional deprivation
  - cytochrome inducers – consume free heme
  - starvation: ↑’s denovo synthesis of HO

- These mechanisms degrade free heme pool
- Via the feedback loop more succinnyl CoA & Glycine enter the heme synthesis pathway
  - i.e. the production furnace is stoked up
What If an Enzyme Is Deficient?

**Latent**

ALAS-N → ALA → PBG → Heme

PBGD deficiency

Heme-mediated repression

**Active**

ALAS-N → ALA → PBG → Cytochrome P450

PBGD deficiency

Drugs, chemicals, steroids

Loss of heme repression

Heme → HO-1 → Heme → Heme

Fasting
DISORDERS OF PORPHYRIN METABOLISM
Inherited disorders of heme biosynthesis

Classified as “hepatic” or “erythroid” – depending on site of overproduction & accumulation of intermediates

Classified as “acute” or “nonacute” – depending on clinical features

Most common porphyria: Porphyria Cutanea Tarda (PCT)
Most common acute porphyria: Acute Intermittent Porphyria (AIP)
Most common erythropoietic porphyria: Erythropoietic Protoporphyria (EPP)
Recall: Each porphyria is due to a different enzyme deficiency in the production line of heme.
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<th><strong>ERYTHROPOIETIC</strong></th>
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<td>Predominant neurologic manifestations</td>
<td>Cutaneous photosensitivity</td>
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<td>Acute presentation</td>
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<td>Symptomatic in adults</td>
<td>Birth or early childhood</td>
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<td>Severity depends on environmental &amp; endogenous factors</td>
<td>Depends on specific mutation(s)</td>
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HEPATIC PORPHYRIAS

Acute intermittent porphyria (AIP)
HEPATIC PORPHYRIAS

Acute intermittent porphyria (AIP)

- An acute hepatic porphyria; AD inheritance
- Due to half-normal activity of Porphobilinogen Deaminase
- Synonyms: intermittent acute porphyria, pyrroloporphyria, and Swedish porphyria.
- First case reported in late 1800’s
- Prevalence: 5 in 100,000; occurs in all races, more common in northern European countries such as Sweden, Britain, and Ireland
Clinical manifestations

- Cases usually are heterozygotes; homozygotes rare
- Disease remains latent for a long period
- Symptoms more in women > men ; suggesting hormonal effect
- Symptoms appear after puberty usually, sometimes 3rd / 4th decade
- Symptoms manifest when some precipitating factor is added
- Most carriers never have symptoms so the disease skips generations
Precipitating factors

- Drugs that increase demand for hepatic heme (especially cytochrome P450 enzymes)
- Crash diets (decreased carbohydrate intake)
- Endogenous hormones (progesterone)
- Cigarette smoking (induces cytochrome P450)
- Metabolic stress (infections, surgery, psychological stress)

Inherited deficiency of PBGD is not in itself sufficient to cause clinical expression of AIP
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<th>Probably Porphyrinogenic</th>
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Acute Attacks

- One of the great masqueraders
- Abdominal pain – mc symptom 80 – 85 % cases
  - Pain is neuropathic in origin so tenderness, rebound, etc, absent
- Gastrointestinal symptoms – nausea, vomiting, ileus, constipation
- Dark red urine (upon standing in light, not when fresh or in the dark), dysuria, bladder dysfunction, urinary retention
- Autonomic neuropathy – tachycardia, sweating, tremors, hypertension, postural hypotension
Appearance of Urine

Normal  Porphyria  Port Wine
Freshly Voided  After Standing In Light
Acute Attacks

- Peripheral motor neuropathy – usually proximal beginning in arms; due to axonal degeneration not demyelination
- Sensory neuropathy – paresthesia, dysesthesia often on the trunk
- Cranial neuropathy – most commonly 7th & 10th nerves
- Cortical blindness occasionally – due to vasospasm
- Seizures – maybe a manifestation or due to hyponatremia
- Cardiac arrhythmias
Acute Attacks

- Psychiatric manifestations: anxiety, insomnia, paranoia, depression, disorientation, hallucinations
- Prevalence of AIP may be higher in psychiatric patients than in the general population
- Suggested that schizophrenia is associated with genetic variation at or near the PBGD gene
- Attacks usually develop over hours or days and fade over weeks to months
- Long-term sequelae may include persistent hypertension, renal failure, chronic pain, depression & anxiety
- Rarely bulbar palsy & death
Laboratory Diagnosis

- Put the urine on the window sill
- Urinary PBG excretion during an attack: usually 50–200 mg/24 h [normal, 0–4 mg/24 h]
- Urinary ALA excretion: 20–100 mg/24 h [normal 1-7]

Levels often remain high even after symptoms resolve

- Mutation analysis
Treatment

- General & Supportive measures – pain, vomiting, insomnia, seizures, tremors
- Specific: i.v HEMIN – heme albumin, heme arginate, carbohydrate loading
- Identify precipitating factor & avoid
- Allogenic liver transplant rarely
Now the Fun Part
Born in 1738

Succeeded grandfather to throne in 1760

Married Charlotte of Mecklinburg-Streitz in 1761

15 children (granddaughter Queen Victoria)

1762
Highlights of George III’s Life

- Peace of Paris ended Seven Years War in 1763 making England the World’s greatest colonial power
- Hostilities with American colonies: Lexington/Concord 1775--Yorktown 1781
- Peace of Versailles: 1783
- Regency Crisis 1788-89
Highlights of George III's Life

- Union with Ireland: 1801
- Napoleonic Wars 1803-1815
- Blind, demented 1811
- Regency Act of 1811
- Battle of Trafalgar 1815 ended the threat of Napoleonic invasion of England
  - Admiral Nelson: “Desperate Affairs Require Desperate Measures”
  - Fascinating strategy to study: French/Spanish losses=22 ships. Smaller English force=0
- Died 1820

1803 caricature holding Napoleon
George III’s Illnesses

- January-July 1765, age 26
- October 1788-February 1789, age 50
- February-March 1801, age 62
- January-March 1804, age 66
- October 1810-1820, age 72-82 (death)
  - Punctuated by some remissions early
  - May have been different from earlier illnesses
- Many other minor, brief events

MacAlpine & Hunter, Brit Med J, 1, 1966 65-71
After 1788-89 Attack Recovery

LIKENESS OF WILLIS appeared on one side and a patriotic injunction on the other of a medal that “Doctor Duplicate” distributed to the public when the king, in February, 1789, spontaneously recovered four months after the onset of his chief porphyria attack.
George III’s Attacks

Strangely only two clinical studies have been devoted to it, both by psychiatrists and both American: Ray in the mid-nineteenth century and Guttmacher in the mid-twentieth. From the latter historians have adopted as fact that “His insanity was a form of manic-depression [sic]” (Namier, 1955) or, as in a recent narrative of the regency crisis 1788–9, that “the king’s disorder was undoubtedly psychotic, of a manic-depressive type . . . caused by an underlying conflict . . . exacerbated by violent frustrations, annoyances and emotions” (Trench, 1964).
George III’s Attacks

“The attacks of George the Third are invested with peculiar interest,” wrote Ray (1855). “Five times” was the king struck down by mental disease . . . and twice the recurrence of his disorder gave rise to a degree of political feeling that has seldom been equalled, and to political discussions that settled for ever a vital principle in the British constitution.” No illness had such profound effects on the nation and its institutions as the “madness” of George III, and indeed no other has received so much attention from commentators, biographers, and historians. The royal malady also influenced the history of psychiatry, not least by dragging the “mad-business” into the limelight (Hunter and Macalpine, 1963).
Physical Characteristics of Attacks

- All attacks “were of the same general character”
  - cold, cough, malaise followed by “acute pain in the pit of the stomach shooting to the back and sides”
  - Tachycardia to 144/min
  - Hoarseness
  - Painful weakness & stiffness
  - Paresthesiae (“c/o heat and burning”)
  - Hyperesthesia (“could not bear the touch of clothes or bedding, wig or tie”)
  - Hypalgesia (“scarce sensible of the blisters applied to his legs”)
  - Tremor, dysphagia, visual disturbances
  - Profuse sweating, flushing, oliguria, polyuria, polydipsia

MacAlpine & Hunter, Brit Med J, 1, 1966 65-71
Psychiatric Characteristics

- Agitation
- Talking “with uncommon rapidity and vehemence”
- Sensitivity to light & sound
- Emotional lability
- Uninhibited behavior
- Nocturnal confusion
- Severe insomina
- “Turbulence” & frank delirium
- Delusions & hallucinations (mostly in last illness)

MacAlpine & Hunter, Brit Med J, 1, 1966 65-71
Dr. Thomas Willis, most famous “psychiatrist” of the time “cured” 9 of 10 by his own account

- “He broke in [patients] as horses in a menange”
- Clapped the King in a “winding sheet”
- Restraint chair
- Straitwaistcoat with his legs tied to the bed
- For the medical symptoms: vomits, purges, bleeding, blistering, cupping, leeches, asses milk
Two Diagnoses available when in 1788 the King was considered “mad”:

- “Original Madness”: “solely owing to an internal disorder of the nervous substance” or “Insanity” was considered not amenable to art and spontaneous recovery uncommon
- “Consequential Madness”: delirium secondary to a systemic illness

Dr. Robert Darling Willis to parliament: “...His Majesty’s illness, uniformly, partakes more of the delirium than of insanity.”
Psychiatric “Era of Classification”

- 1891 Professor Emil Kraepelin of Heidelberg observed that patients who had attacks of mental illness from which they recovered usually showed marked mood or emotional disturbance with elation or depression or alternated of these and called these “affective disorders” or manic-depressive psychoses.

- 1931 American Dr. Smith Ely Jelliffe renamed the royal malady “manic-depressive psychosis”. He linked the 1788 attack with the “colonies freeing themselves”.

Later Diagnoses of George III
The 1783 statement of George III to independent America’s first envoy, John Adams:

I wish you, Sir, to believe, that it may be understood in America, that I have done nothing in the late contest but what I thought myself indispensably bound to do by the duty which I owed my people. I will be very frank with you. I was the last to consent to the separation; but the separation having been made, and having become inevitable, I have always said, as I say now, that I would be the first to meet the friendship of the United States as an independent Power. The moment I see such sentiments and language as yours prevail and a disposition to give this country preference, that moment I shall say, let the circumstances of language, religion, and blood have their natural and full effect.
The ‘Mad Business’
Private Madhouses: ‘A Fine Trade’

- Insane poor were left at large or in parish workhouses
- Private madhouses for the wealthier became popular and were doctor-owned
  - Husbands, aided by unscrupulous doctors, had their wives locked up
  - Eventually public opinion resulted in legislation and reform
Bethlem Hospital ("Bedlam")
Bethlem Hospital ("Bedlam")
10. A drawing of 'a portable douche machine' to direct cold water 'upon the head, as well to diminish vascular action, as to repress violence, to overcome obstinacy, and to rouse the patient when indolence or stupor prevails'. The stream of water could be regulated 'to fall on the head of the patient from different heights' according to the needs of the case. (From Sir Alexander Morison's Cases of mental disease, with practical observations on the medical treatment, 1828, pp. 44–5, 163–4).
15. The restraining chair devised by Dr Benjamin Rush, one of America’s great physicians and a signatory to the Declaration of Independence. It was recommended to the royal physicians for George III in 1811 but declined.
22. James Norris, 'an insane American... Rivetted alive in iron & for many years confined in that state by chains 12 inches long to an upright massive bar in a cell in Bethlem'. Drapen from life by C. Arnold at the request of Mr. Edward Wakefield in June 1814 and exhibited to Mr. Rose's Committee the following year. Norris died in February 1815 soon after he was released, from 'a very considerable disease of the lung; a consumption' and became a cause célèbre. His offence had been that he had threatened John Haslam the apothecary and
MacAlpine & Hunter (mother & son psychiatrists) were studying the history of 300 years of psychiatry. They were the first to review actual medical records of the King’s physicians especially Reverend Dr. Francis Willis famous for starting private psychiatric hospitals, later referred to as “The Mad Business” (and a good business it was) until it was eventually discredited.
The physicians had no stethoscope, no knee-jerk hammer, not even a clinical thermometer. Laboratory medicine did not exist but excretions were inspected. Diagnosis was made on what Dr. George Fordyce (1794) called “an estimate of symptoms and appearances”; the doctor listened to the patient’s complaints, inquired into his “animal functions” and general health, felt the pulse, and looked at the tongue.
King’s Physicians Limited

They kept notebooks of their observations:

They were expected to observe protocol however ill or delirious the king was: if they were not addressed first they could ask no questions. Whole visits were spent in fruitless silence, as they reported to the Queen’s Council on 8 January 1812: “His Majesty appears to be very quiet this morning, but not having been addressed we know nothing more of His Majesty’s condition of mind or body than what is obvious in his external appearances.”
recorded, we succeeded in locating four references to discoloured urine: 18 October 1788, Sir George Baker: “urine bilious” (Diary); 6 January 1811, Sir Henry Halford: “The water is of a deeper colour—and leaves a pale blue ring upon the glass near the upper surface” (Willis MSS.), and 14 January 1812, “Bluish 8 and 9 [ounces]” (Royal Archives); 26 August 1819, report of Drs. Baillie and John Willis: “His Majesty has passed . . . bloody water . . . during the last 16 hours,” of which “no tinge” remained the following day (Queen’s Council Papers; Willis MSS.). All these observations were made during paroxysms when the excretion of porphyrins and porphobilin-like chromogens is known to be greatest.
The waistcoat was taken off from His Majesty at noon yesterday, but was put on again soon after two o’clock. It was not taken off till nine this morning. His Majesty has not had more than an hour’s sleep in the night, so good humour’d. But as sickness extends over Sir Robert’s, Dr. Rutherfurd and Sir Henry. He is in a healing state.

Bulfinch—His Majesty passed the night quietly. But with little sleep. His quiet this Morning—

Ramsntr—Per'm in 1. 1st mo. 4. 9. 1788.

4. Entry in Willis Journals for 24 December 1788 (British Museum Add. MSS 41690, folio 18) in the hand of Dr John Willis, showing the contrast between the official bulletin and what actually took place in the sickroom. Sir George Baker and Dr Reynolds attended. ‘The waistcoat was taken off at nine – & blisters dress’d – discharg’d well – very sore – Pulse 96 – perspir’d through the night profusely – but little sleep’. The Prince of Wales was told that the King had been continuously in the strait-waistcoat from 2 o’clock the previous afternoon, had had ‘not more than an hour’s sleep’ and was in the morning ‘as incoherent as ever’. The public bulletin stated ‘His Majesty pass’d the night quietly, but with little sleep – & is quiet this Morning’.
In the 17th Century and before, much attention was paid to urine. Many doctors were “piss-prophets”

Less attention was paid in George III’s times

In order to prove porphyria, one should have a pattern of inheritance and a living descendant with the illness
TRANSLATION OF FIGURE 12
12 July 1613
The King rose very early and with great vigour went riding and stag hunting until 2 in the morning. The season and the day were hot, humid and rainy. He had retention of urine. On his return he passed blood-red urine which was turbid with thick red sediment.

Then he breakfasted. After the meal he passed water again and the urine was turbid and reddish, as if lixiviated, with red sand and not at all white.

He passed his water without any pain whatever.
Shortly after he passed water a third time and it was clear.
At night nephritic pain set in from the left kidney; he vomited much and brought up phlegm which gave him relief.

He passed altogether more than six pints of thin urine clear as water with no trace of sediment as if it had been passed through a filter. The abdomen was blown out with flatus up and down.

13 July. In the morning at about 6 o'clock he felt a little better. At nine he got up and the pain in the kidney and ureter returned. The pain radiated to the bladder and the tip of the glans. Micturition was copious, the urine watery with a burning sensation at the end. He vomited phlegm with relief.

The whole of the preceding night he was feverish. In the morning the pulse was hard, febrile, unequal and missing beats as a result of the pain and restlessness.

NB About two months ago after a large meal of cherries he felt heat when making water, and often passed turbid urine as if lixiviated which was soon followed by clear urine.

NOTA This occurred without any preceding exercise; these symptoms were all nephritic.

NB His Majesty told me that since then he had quite often felt heat when passing water so that he himself feared a stone in the bladder.

He also told me that he quite frequently passed water red like Alicante wine without any pain. But not having seen this myself I cannot pass judgement on it; however most probably the water was red from blood.
Mary Queen of Scots (1542-87): Repeated attacks of vomiting & colic: most severe was at age 24: vomited 60 times, lost her sight and speech, had a series of fits and was unconscious for hours. Within 10 days she up & about. Had many attacks the essential features of which were excruciating pain, vomiting, painful lameness, fits and mental disturbance.
Simplified genealogical table showing members of the Houses of Stuart, Hanover and Prussia mentioned in this study who seem to have suffered from or transmitted porphyria.
Descent of Patients A & B
Patients A & B

- **Patient A:**
  - Pneumonia in her 60’s, urine dark red, elevated coproporphyrin, uroporphyrin & porphobilinogen diagnosed as Variegate Porphyria

- **Patient B:**
  - Recurrent attacks of colic & constipation with, negative GI work-ups: labeled “hysterical.”
  - Sun sensitivity, easy blistering with minor trauma
  - Avoided barbiturates & sulfas which gave her headache, malaise, pain in the limbs
  - Mother had same symptoms, more severe, and with dark red urine during symptoms.
Variegate Porphyria

- More likely to skip generations and have clinically silent carriers
- In re-reviewing the medical notes there were several mentions of skin blistering spontaneously
Some debate about the diagnosis but Porphyria was generally accepted

1994: publication of a newly found cache of 60 letters written by Princes Charlotte, granddaughter of Queen Victoria and great-great granddaughter of George III. Charlotte describes to her Dr. (also Bismarck’s physician) “agonizing abdominal pain, rashes, muscular weakness and the production of red/brown and orange urine”.

Charlotte’s brother was Kaiser Wilhelm II, last emperor of Germany.

Could porphyria have influenced Wilhelm II and the start of World War I?
Peters & Beveridge in *History of Psychiatry* 2010 published “The madness of King George III: a psychiatric re-assessment.”

- They studied original source documents and conclude that most likely George III suffered from manic-depressive and take issue with MacAlpine-Hunter’s 1966 conclusion: “This study allows the certain conclusion that George II’s malady was not ‘mental’ in the accepted sense...this diagnosis clears the House of Hanover of an hereditary taint of madness”

- They felt that MacAlpine-Hunter were biased to find a physical rather than mental explanation
What Do You Think?
Porphyria Cutanea Tarda

- Chronic, not acute attacks
- As name indicates, symptoms are cutaneous
- 60% male, most drink too much ETOH
- Women are often on estrogens
- Most patients > 40 years old
- Most have evidence of iron overload
- LAB: elevated uroporphyrin I
Look at the following photos and holler out what legend Porphyria Cutanea Tarda may have inspired.

There is a prize for the first correct answer.
Does anyone know the story of Vlad the Impaler?

There is another prize

Hint: His father was Vlad II Dracul
“I’m Vlad The Impaler, and I approved this message.”
Thank You For Your Kind Attention