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Today in Chemistry



Wallace Carothers
Invents Nylon
1935

While working at DuPont's research laboratories Wallace and his team discovered Nylon, while trying to find a substitute for silk. Nylon was first used to replace hog's hair as the bristles in toothbrushes.

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Upcoming ACS Webinars™

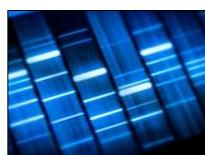
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Thursday May 3, 2012

The Challenges of Scaling a Global Biomaterials Supply Chain

Sharon Feng, [Bayer Material Science](#) and Blake Mosher, [Natural Composites, Inc.](#); moderated by Dr. Judith Giordan, [ecosVc](#).



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Building an Innovative Research Culture: The Case of DNA Sequencing

George Trainor, 2011 Awardee, [ACS Heroes of Chemistry](#).

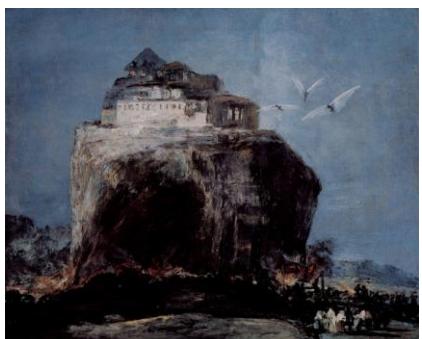
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ACS WEBINARS™
April 26, 2012



Madness of King George



Martin Warren
University of Kent

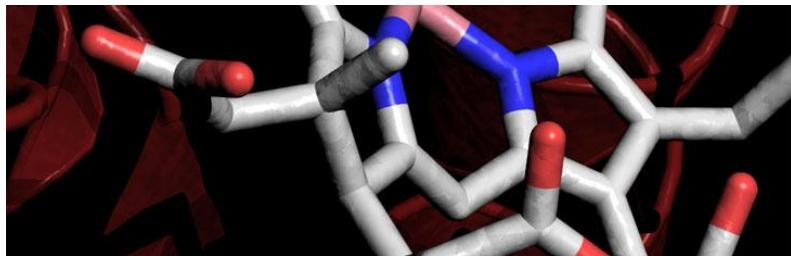


Darren Griffin
University of Kent

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The Madness of King George III

Martin J. Warren
Professor of Biochemistry
University of Kent
ACS Extreme Chemistry Series
26th April 2012



1788 – The Regency Crisis

- England thrown into constitutional crisis
- King George III's mental health deteriorated
- Proposed that the Prince of Wales take over as regent – plan caused political unrest
- This at a time with great radical social and political upheaval in France
- King recovered before regency bill was passed
- Basis of Alan Bennett's play and film
- King suffered lapses in 1801, 1804 and 1810.





The King's symptoms

- Abdominal pain
- constipation
- rapid pulse
- peripheral neuropathy
- insomnia
- temporary mental derangement
- dark urine



Individually, these symptoms can be attributed to a broad range of illnesses – but collectively they are consistent with porphyria, a heme metabolic disorder

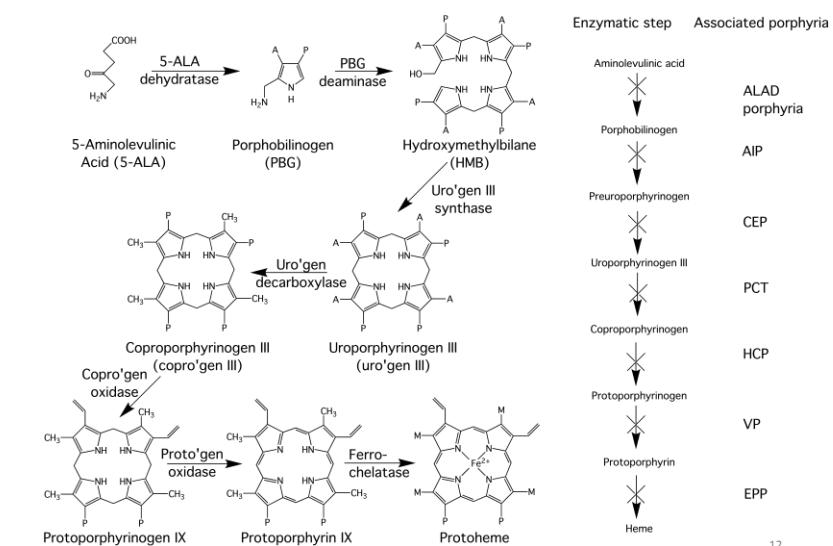
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The cause – porphyria?

- Work of Ida Macalpine and Richard Hunter
- Symptoms consistent with heme metabolic disorder - porphyria
- Provided evidence of hereditary nature of the disorder within Royal families of Europe
- Claimed to have evidence of a clinical diagnosis.



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Causative nature of porphyria symptoms

- Build up of pathway intermediates
- Build up of 5-ALA thought to interfere with autonomic nervous system
- Build up of porphyrins cause photosensitivity and skin lesions
- Color in urine due to excretion of oxidised intermediates – highly fluorescent

(but see Wilfred Arnold for alternative theory - "King George III's urine and indigo blue"
<http://cas.umkc.edu/Chemistry/kacs/King%20%20George%20%20III%20%20urine%20%20and%20%20indigo%20blue/index.html>)

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Re-opening the George III investigation

- Is it possible to obtain some genetic evidence to back the theory that George III suffered with porphyria? Need a biological sample.



A porphyric line from George III via Queen Victoria

Queen Victoria
|
Vicky
|
Charlotte
|
Feodora



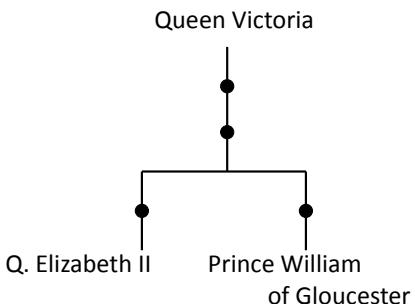
Symptoms:-
periodic illness
sun sensitivity
discoloured urine
peripheral neuropathy
hypersensitivity

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Porphyria in a cousin of the Queen



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Evidence all strongly suggestive of variegate porphyria in George III

- clinical diagnosis
- strong historical evidence
- suggestive DNA evidence
- Taken together these strengthen case for VP as cause of George III's madness
- Also implications for loss of American colonies and decline of European monarchy in general
- **But** - does not explain the late onset or severity of the disease



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Why were George III porphyric attacks so late and so long?

- First major attack when 50 years old
- The methods applied by the royal physicians appeared to prolong the King's illness
- Known that a range of drugs and chemicals induce porphyria by stimulating the heme pathway. Certain metals also induce porphyria
- We wondered whether any of the medication given to the King affected his heme metabolism



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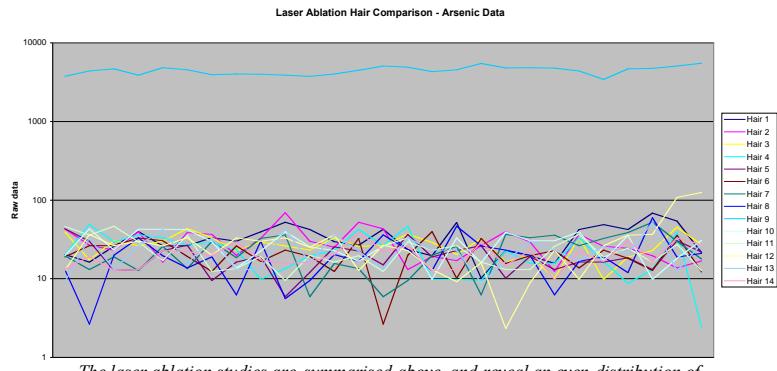
The hair of George III

- Hair was on display in Science museum, as part of the Henry Wellcome collection.
- Given two hair samples – one used for DNA extraction and the other for metal analysis.
- Results revealed elevated As levels



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Metal results in George III hair



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Where did the Arsenic come from?

- Arsenic was a major contamination of many antimony preparations - up to 5% contamination.
- Based on the reported amount of antimony administered to the King, we estimate he was also receiving between 1 and 2.5 mg arsenic/day.



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Conclusion

- The presence of arsenic in a sample of the King's hair provides a plausible explanation for the length and severity of his porphyric attacks; and contamination of the antimonial medications is a probable source of this toxic metal. It is moreover likely that exposure to arsenic would precipitate attacks of porphyria in a genetically predisposed individual.



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Acknowledgements (I)

- John Röhl (Sussex), David Hunt (UCL), George Elder (Cardiff) & Tim Cox (Camb).
- Anna Evans and Caroline Graham
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- John Fothergill (TWI)
- Her Majesty the Queen for her gracious permission to peruse some of the medical records in the Royal Archives
- The BBC
- Funding from The Wellcome Trust, BBSRC, EU, and Queen Mary, University of London.



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Royal Hemophilia

- Queen Victoria is known to be a carrier of hemophilia, the clotting disorder that gives rise to the bleeders
- X-linked disorder - generally only males suffer with the condition and females act as carriers.
- Gene was passed into both the Royal families of Russia and Spain, with disastrous consequences.
- Shown to be caused by mutation in F9 gene (hemophilia B - Christmas disease) - Rogaev *et al* Genotype Analysis Identifies the Cause of the Royal Disease www.scienceexpress.org / 8 October 2009.
- The origin of the haemophilia gene is not known



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Hemophilia – the other Royal disorder

- If there is no evidence of hemophilia in the Royal family prior to Queen Victoria – where did she it get from? Which answer do you think is correct:
 - 1. Spontaneous mutation
 - 2. Her father was not her father
 - 3. She was a changling
 - 4. She was not a carrier



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