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We will start momentarily at 2pm ET



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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™

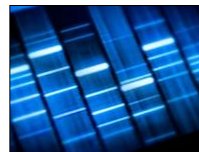
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Thursday May 3, 2012

### 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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**Extreme Chemistry**

Intersection of Science, Ethics and Society

WITH Prof. DARREN GRIFFIN

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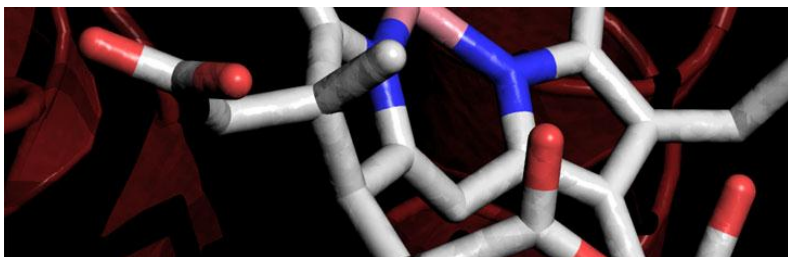
April 26, 2012

**Madness of King George**Martin Warren  
University of KentDarren 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  
26<sup>th</sup> 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



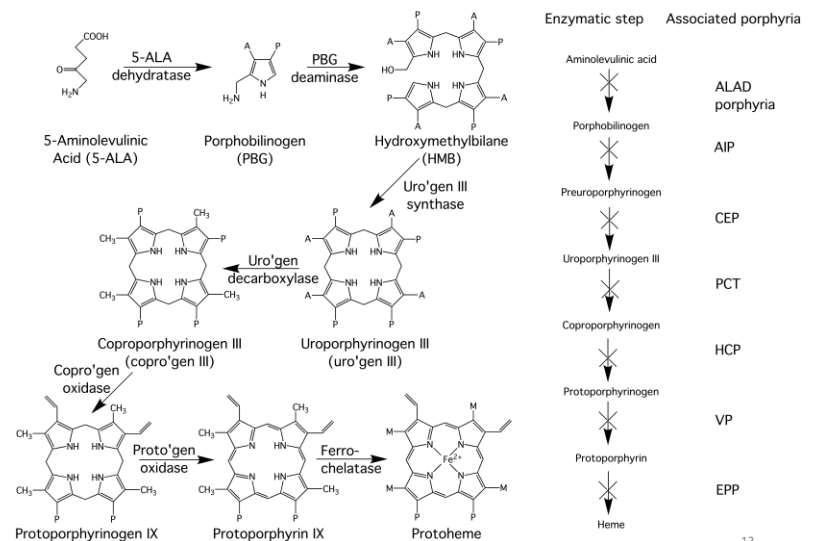
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## The cause – porphyria?

- 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/kcacs/King%20George%20III%20urine%20and%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.



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## A porphyric line from George III via Queen Victoria

Queen Victoria

|

Vicky

|

Charlotte

|

Feodora



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



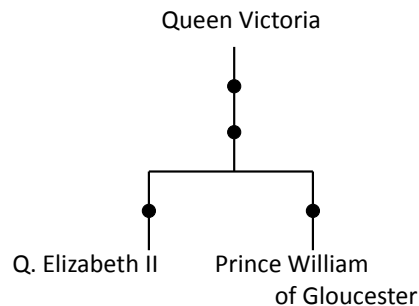
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## Porphyria in a cousin of the Queen



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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?

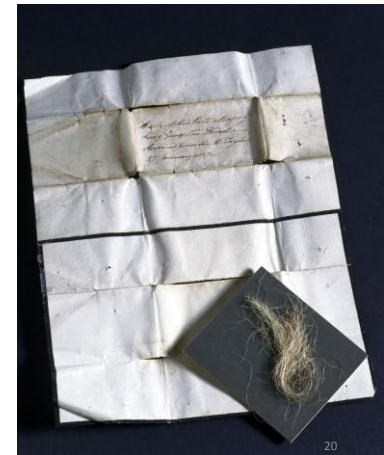
- First major attack when 50 years old
- The methods applied by the royal physicians appeared to prolong the King's illness
- Known that a range of drugs and chemicals induce porphyria by stimulating the heme pathway. Certain metals also induce porphyria
- We wondered whether any of the medication given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



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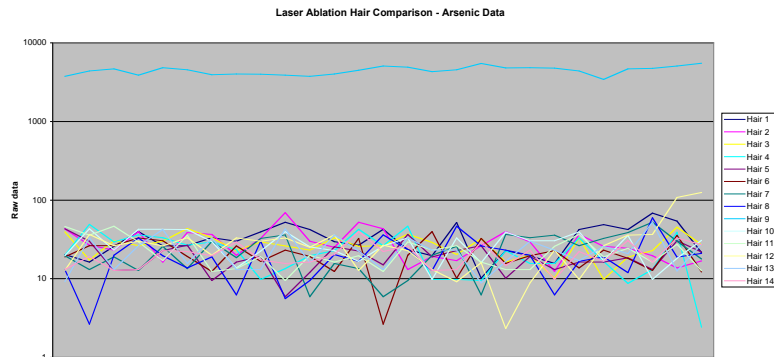
## The hair of George III

- 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



*The laser ablation studies are summarised above, and reveal an even distribution of arsenic along the hair strand. The results obtained for a series of contemporary healthy adult volunteers are also depicted and clearly illustrate the abnormally high quantities of arsenic in the sample from George III. Our findings suggest that the arsenic was incorporated within the structure of the hair during life.*



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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
- Dr Janice Haines, Prof Watlin (Perth)
- 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.sciencexpress.org](http://www.sciencexpress.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 get it 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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April 26, 2012



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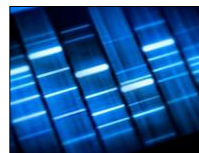
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