King George III and porphyria: an elemental hypothesis and investigation

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In 1969 it was proposed that the episodic madness suffered by King George III (1738–1820) resulted from an acute hereditary porphyria, variegate porphyria, caused by deficiency of protoporphyrinogen oxidase. The diagnosis was based on the historical archive and a contentious claim that living members of the House of Hanover were affected with the condition. A re-examination of the medical evidence and the appearance of new historical material have suggested that porphyria did indeed exist in the Royal Houses of Europe. We report the analysis of hair obtained from George III. Although no genomic DNA could be obtained, metal analysis revealed high concentrations of arsenic. Since arsenic interferes with haem metabolism, it might have contributed to the King's unusually severe and prolonged bouts of illness. We have identified sources of arsenic in the context of the medication George III received from physicians.

Introduction

King George III (1738–1820), who was monarch from 1760 until his death, was one of the longest serving British sovereigns. During his reign, Britain achieved oceanic mastery, the defeat of Napoleonic France, and expansion of its empire to a level similar to a superpower. Despite these achievements, his reign is best remembered for the humiliating loss of the American colonies and his well-documented bouts of madness. While on the throne, the king had five major episodes of a long illness in which physical abnormalities were associated with profound mental derangement. The best-documented episode was from October, 1788, to February, 1789, when the king was aged 50 years; this illness occasioned the constitutional review known as the Regency crisis.[1,2] The king's periods of mental incapacity were originally thought to be due to psychiatric illness[3,4] but a detailed study of the accompanying physical manifestations of disease led to the suggestion that the monarch suffered from acute attacks of porphyria[1,4,5]—a severe metabolic disturbance caused by genetic defects of haem biosynthesis.[6]

The porphyria theory was proposed by two German-born British psychiatrists, the mother-and-son team of Ida Macalpine and Richard Hunter.[5] Their detailed investigation of the king's illness identified numerous clinical features of porphyria, including lameness, hoarseness, acute abdominal and limb pain, a racing pulse, insomnia, temporary mental disturbance, and the excretion of discoloured urine. Initially, acute intermittent porphyria was suggested,[5] but after a follow-up study, which included many forebears, descendants, and collaterial relatives of George III, the diagnosis was refined to variegate porphyria (figure 1).[4]

Later, a cache of letters from Princess Charlotte (1860–1919), sister of the last Kaiser, was discovered.[7] In these letters, Charlotte, a descendant of George III, described many of the symptoms that Macalpine and Hunter had noted, including bouts of abdominal pain, lameness, and passage of red urine.[8] Moreover, further archival research showed that many of these symptoms were also recorded by Charlotte's mother, Victoria ("Vicky") the Princess Royal (1840–1901), and Charlotte's daughter, Princess Feodora (1879–1945).[8] The probable source of the condition would have been Queen Victoria (1819–1901), whose father, Edward Duke of Kent (1767–1820), was a son of George III and was judged by Macalpine and Hunter to have been affected.[1,4] Recently, it was disclosed that Prince William of Gloucester (1941–72), a direct descendant of Queen Victoria, had been diagnosed with variegate porphyria independently in 1968.[8]

Protoporphyrinogen oxidase (PPOX), which catalyses the penultimate step in the haem biosynthetic pathway, is deficient in variegate porphyria. The enzymatic defect leads to over-production of protoporphyrinogen and the excretion of excess porphyrin precursors and protoporphyrin IX.[6] We believe that, taken together, the evidence for acute episodes of porphyria as the cause of George III's malady is strong, although there is little information available to identify the initiating factors or to account for the unusual persistence, severity, and late onset of the attacks. One possibility is exposure to environmental factors, such as heavy metals, including lead and mercury. These metals are potent inhibitors of the enzymes of haem formation and thus could precipitate or exacerbate acute porphyria by further disturbance of the biosynthetic pathway. Accordingly, we investigated possible exposure to such metals by analysis of a sample of hair from the king.

Methods of metal analysis

The hair was provided by courtesy of the Wellcome Trust collection and the Science Museum (London, UK). The hair, which had been obtained at the King's death, formed part of an authenticated collection after it was purchased by a representative of Sir Henry Wellcome at Steven's auction house in 1928. The lock of hair was subsequently loaned by the Wellcome Trust to the Science Museum, where it has been on display. Attempts to extract DNA for molecular analysis to detect the PPOX gene had been unsuccessful.[8] The hair, which

had been kept without addition of any visible preservative in a black-edged envelope, was washed in a solution of ethanol and water (1:10) and agitated for 10–15 min to remove any surface contamination, before analysis with two different procedures. The first procedure involved pressure dissolution of the hair in mineral acid and examination of the resulting solution by inductively coupled plasma mass spectrometry (ICP-MS) to quantify the metal content. The second procedure involved laser ablation along the length of the hair at 2-μm intervals; the ablated material was then analysed with ICP-MS. The relative abundance of metals present in the hair was assessed by reference to the raw data obtained from control hair samples. The control samples were obtained directly from adult male and female volunteers and were assessed in the same way as the king's sample.

Results and discussion

Metal analysis revealed concentrations of mercury in the normal range, but slightly raised concentrations of lead, consistent with the widespread contemporary use of lead in plumbing, water management schemes, cooking utensils, and glassware (table). An unexpectedly high concentration of arsenic (17 parts per million [ppm]), compatible with systemic toxicity, was also detected. Control hair samples had concentrations of arsenic between 0·05 ppm and 0·25 ppm (table). Values greater than 1 ppm in hair are thought to indicate possible arsenic poisoning.[9]

Arsenic trioxide has been used as an insecticide in preservation, and it is important to remove potential surface contamination before dissolution and analysis. In this study we used a mixture of alcohol and water to wash the hair samples. It is not possible to unequivocally determine whether the arsenic was present on the hair or incorporated within it, although the laser ablation tests, which indicate the distribution of the metal within the hair structure, can assist. Externally applied arsenic should appear as peaks of high intensity using this procedure, whereas arsenic deposited within the hair during life would have an even distribution. In the sample from George III, arsenic was distributed evenly along the hair strand (figure 2), suggesting that the arsenic was incorporated within the structure of the hair during life. Provided that external contamination is excluded, the arsenic content in hair is a reliable index of long-term exposure to the metal: the amount of arsenic detected in the sample is in a range that indicates systemic toxicity rather than gross external contamination.[9]

Arsenic, like heavy metals, induces disturbances of haem biosynthesis, and haem precursors appear in the urine after exposure to arsenic. In its trivalent state, it reacts with sulphydryl groups and inactivates several enzymes of the haem pathway.[10,11] Although there is no established proof that arsenic alone provokes acute attacks, exposure to arsenic and lead in "moonshine" whisky has been reported to precipitate variegate porphyria[12] and excretion of porphyrin metabolites correlates with the degree of chronic arsenic exposure in animals and man.[10,13] If George III did indeed inherit the inborn error of metabolism that causes porphyria, he would be sensitised to the effects of arsenic and other heavy metals. Indeed, amounts of toxic metal insufficient to induce frank poisoning would, in all probability, exacerbate porphyric attacks in a susceptible individual. Excess lead was present in the hair sample and might, as

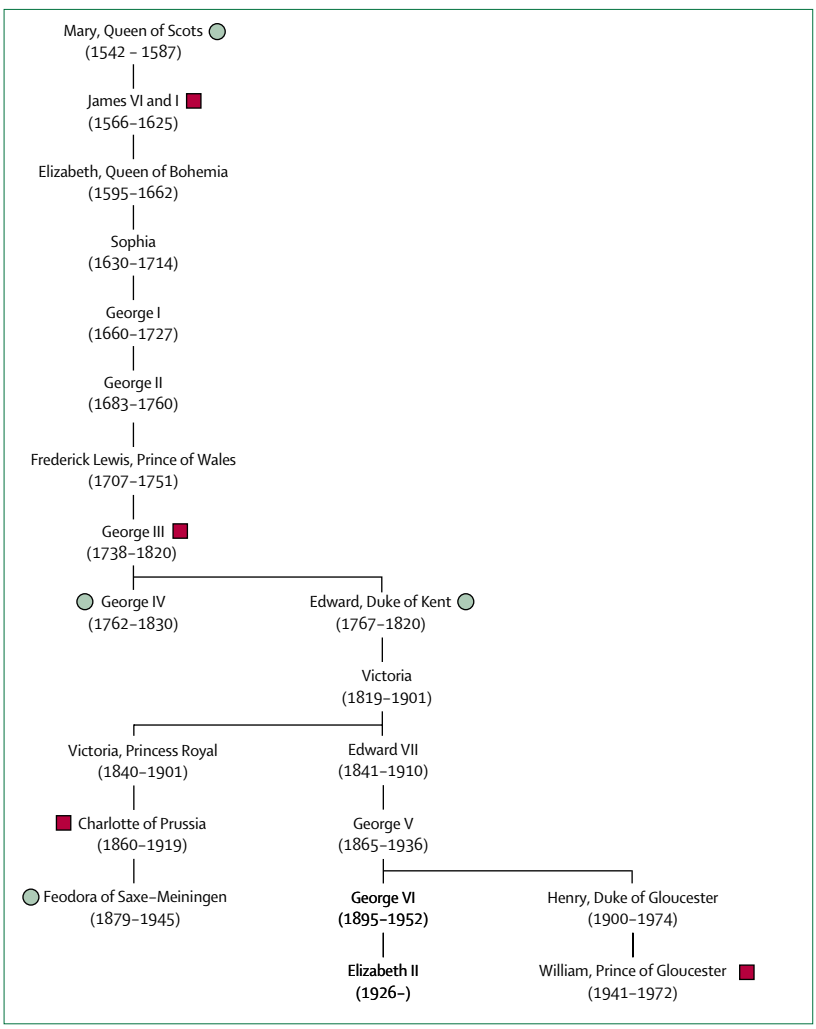

Figure 1: **Simplified royal pedigree including the Houses of Stuart, Hanover, and Windsor**
Individuals with manifestations compatible with porphyria are marked with a green symbol; those who also reported red or discoloured urine[2,5,8] are marked in red. Acute porphyrias are autosomal dominant traits that show highly variable clinical expression and thus might not appear in every generation.

	Concentration		
	Mercury (ppm)	Lead (ppm)	Arsenic (ppm)
Control volunteer	0·95	<0·2	<0·7
King George III	2·5	6·5	17·0

Table: **Concentrations of mercury, lead, and arsenic in hair samples**

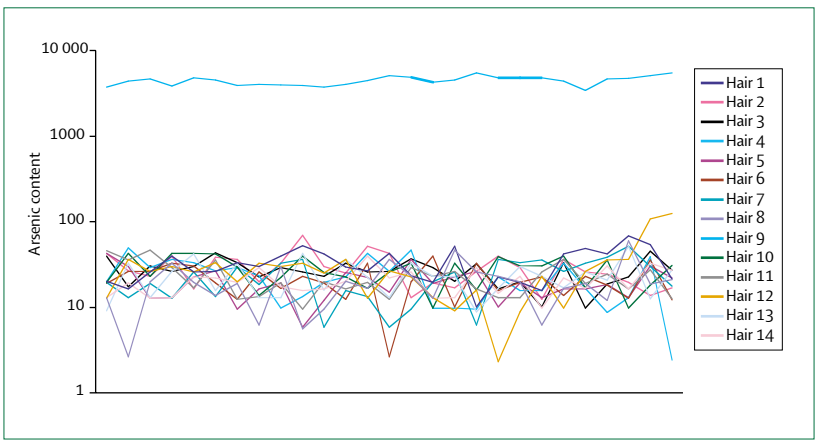

Figure 2: **Relative arsenic content measured by ICP-mass spectrometry along the length of hair strands after laser ablation**
Over its entire length, the hair of George III (sample 9) shows an arsenic content two orders of magnitude greater than that of the 13 samples from healthy controls.

we originally suspected, have contributed to his illness, but the toxic metal most abundant in our findings was arsenic.

The question then arises as to the source of the arsenic. Arsenic became popular as a medicine in the 18th century and, with the introduction of Fowler's solution in 1785, arsenical preparations were used widely as a tonic or for syphilis and skin complaints until the middle of the 20th century. Willis, the medically qualified keeper of a provincial madhouse who was appointed with overall responsibility for the treatment of the King during the regency crisis, was known to use new medicines such as the antimony-based febrifuge, James' powder and emetic tartar (potassium antimony tartrate). The Royal physicians' clinical notes make for disturbing reading, since the medication was clearly administered by force or deception. Henry Halford reported that "This has been a day of considerable excitement throughout the whole of it—His Majesty's medicine was given him by force at seven o'clock and this has certainly contributed to increase his irritation and irascibility which has prevailed ever since" (Reports of the King's physicians, 1811). The medication prescribed to the King included laudanum, zinc, iron, and copper salts (Reports of the King's physicians, 1811). However, the principal compound administered to the King during his illnesses was emetic tartar. Indeed, Robert Fulke Greville, the King's equerry, noted with concern the amount of emetic tartar administered against the King's will by the Royal physicians and their strong faith in its effects.[14] For example, on November 29, 1788 the King was prescribed 2 grains (120 mg) of emetic tartar every 6 h.[15]

Arsenic and antimony frequently co-exist in nature and antimonial preparations may have served as a source for the more persistent and toxic elemental arsenic that was identified in the King's hair. Significantly, reports in the 19th century suggested that arsenic contamination of antimony-based medicines (as much as 5%) caused several deaths.[16] The emetic dose of tartar emetic is described as 30–60 mg (half to one grain). Two grains of emetic tartar given to the King every 6 h corresponds to about 45 mg of antimony. If this medicine was contaminated to the extent of 2–5% by arsenic, as reported,[16] the single dose would have contained 0·9–2·25 mg (3·6–9 mg arsenic per day). Regular ingestion of such quantities would cause chronic arsenical poisoning. The minimum acute lethal dose of arsenic is 60–80 mg. A single dose, however, requires many weeks for complete excretion, and chronic poisoning readily develops.[17]

The presence of arsenic in a sample of the King's hair provides a plausible explanation for the length and severity of his attacks of illness; and contamination of his antimonial medications is the probable source of the arsenic. We propose that exposure to arsenic would exacerbate attacks of porphyria in a genetically predisposed individual. King James I/VI, a direct ancestor of George III, was also thought to have porphyria (figure 1); his Huguenot physician, Sir Theodore de Mayerne, recorded that the King's urine turned "the colour of Alicante wine".[4] Notably, Theodore de Mayerne was banned from teaching in Paris because of his use of chemically-based drugs—especially antimonials![18] Thus, James I might also have suffered from the same metabolic disturbance exacerbated, as is acute porphyria today, by the prescription of medications in common use.[6]

Contributors
T M Cox wrote the manuscript jointly with M J Warren and suggested the analysis of metal content of archival samples; he assisted M J Warren in the valuation of historical material in the Royal Archives, Windsor, and in the library at Lambeth Palace, London, UK. M J Warren wrote the manuscript jointly with T M Cox, procured the King's hair sample from the Wellcome Collection, initiated the active collaboration with scientists at Harwell for the metal analysis, and assisted T M Cox in the valuation of historical material in the Royal Archives and in the library at Lambeth Palace. R J Watling contributed to the experimental design and analysis of hair samples reported as belonging to King George III and carried out laser ablation inductively coupled plasma mass spectrometry at the School of Applied Chemistry in Curtin University, Perth, Australia. He also extracted these data, and interpreted and collated the results. J Haines designed and assisted in the execution of experiments that measured the metal content of the various hair samples. She interpreted the results, wrote the section in the paper on the metal analysis, and initiated the collaboration with J Watling on the laser ablation studies. S Lofthouse and N Jack assisted in the design of the experiments and in the calculation and interpretation of data obtained with the initial set of hair samples.

Conflict of interest statement
We declare that we have no conflict of interest.

Acknowledgments
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