

Channelling the Emperor: what really killed Napoleon?

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SUMMARY

Arsenic was present in Napoleon's hair before he arrived on Saint Helena and the findings at necropsy are consistent only with the diagnosis of ulcerating, regionally invasive, gastric carcinoma. The question of whether Napoleon died of, or merely with, arsenic poisoning is illuminated by developments in the treatment of promyelocytic leukaemia. Arsenic trioxide induces remission in many, but treatment can be complicated by QT prolongation, *torsades de pointes* and sudden death. At clinically relevant concentrations, arsenic blocks both I_{K_r} and I_{K_s} channels and, at the same time, activates I_{K-ATP} channels. The balance of these forces is easily disrupted, and QT prolongation is worsened by hypokalaemia. Napoleon was chronically treated with tartar emetic for gastrointestinal symptoms, and the day before he died he was given a huge dose of calomel (mercurous chloride) as a purgative. Both treatments would have caused potassium wastage. In addition, the Emperor was being treated with a decoction containing 'bark'—presumably 'Jesuit's bark'. The quinine in Jesuit's bark is another cause of QT prolongation. It is likely that the immediate cause of the Emperor's death was *torsades de pointes*, brought on by chronic exposure to arsenic and a medication error.

INTRODUCTION

Those with an opinion about the cause of Napoleon's death rely largely on the results of hair testing. Over thirty different samples, mostly of reasonable provenance, have been analysed in the past decade. Some of the hair samples were obtained during Napoleon's first exile, in Elba, years before he arrived on Saint Helena. Others, such as those saved by Madam Noverraz, the wife of Napoleon's valet, were obtained within six hours of death. All studies have revealed raised concentrations of arsenic, and in the most recent investigation, instrumental neutron activation analysis disclosed not only arsenic but also antimony in above-normal concentrations.¹ These observations, coupled with written accounts of the symptoms and signs exhibited by the Emperor, have led to near universal agreement that arsenic poisoning was the cause of death.

CONFLICTING THEORIES

Evidence for intentional poisoning comes from the Emperor's own hand. He wrote in his will, 'I die before my time, murdered by the English oligarchy and its hired assassin'. Those who accept the poisoning theory have proposed Count Montholon, one of the Emperor's retainers

(Napoleon left a bequest of two million francs for Montholon), as the most likely candidate. For proponents of the poisoning theory, the only question remaining is who put Montholon up to it.

Others maintain that exposure was environmental. Many sources of environmental contamination have been proposed but there is compelling evidence that Napoleon was poisoned by his own wallpaper; it was painted with 'Scheele's green' pigment, a mixture of copper arsenides.² Certain moulds, some likely to have been present in Napoleon's wall coverings, can volatilize arsenical salts, and 'poisoning by wallpaper' was well-recognized as long ago as the 1890s. X-ray fluorescence measurements of a wallpaper sample removed from the drawing room of Longwood House (the room where Napoleon died) show arsenic in substantial concentrations. Whether or not Napoleon's dwelling in Elba was similarly adorned with Scheele's green pigment is not known.¹

Other explanations are possible. Those favouring the poisoning theory tend to downplay the fact that a thorough necropsy was performed.³ Napoleon had requested necropsy because of the belief that he, like his father before, had stomach cancer and that his children might be at risk. Five English physicians were present as observers but the necropsy was performed by Francesco Antommarchi, who had been acting as Napoleon's personal physician.⁴ The division of labour was not a matter of protocol. Antommarchi was the only physician on Saint Helena trained for the task; he had been an anatomical prosector at

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the Santa Maria Nuova hospital, Florence, and a pupil of the famed anatomist Paolo Mascagni.

Though some physicians present at the necropsy subsequently expressed divergent opinions about the cause of death, none disputed the anatomic abnormalities demonstrated by Antommarchi, which were consistent only with an ulcerating, invasive, gastric carcinoma with local extension and distant metastasis.

Because the Emperor had wished his hair to be distributed among the members of his family, Antommarchi caused Napoleon's head to be shaved just before beginning the dissection,⁴ and many of these samples have survived for further analysis. The latest studies show that arsenic and antimony must have been present in the hair before his arrival on Saint Helena. The question, then, is whether Napoleon died 'of' arsenic poisoning or 'with' arsenic poisoning.

CARDIAC ION CHANNELS

Developments in the treatment of promyelocytic leukaemia may provide the answer. Treatment with arsenic trioxide is occasionally complicated by a polymorphic ventricular tachycardia (*torsades de pointes*) and sudden death. In other contexts, predisposing factors for the arrhythmia include hypokalaemia, genetic defects involving myocyte ion channels ('long QT syndromes') and treatment with non-arsenical drugs including astemizole, cisapride, terfenadine and quinidine. Although more than twenty distinct ion channels have been identified in the heart, nearly all the drugs known to cause *torsades de pointes* are blockers of I_{K_r} , the repolarizing rapid delayed rectifier potassium current.⁵

Tissue culture studies have shown that arsenic blocks both I_{K_r} and I_{K_s} channels and, at the same time, activates I_{K-ATP} channels. The effects of arsenic on the various channels appear to cancel each other out, and in most patients cardiac repolarization is undisturbed. The QT interval prolongation and ventricular arrhythmias arise when the blocking and activating effects get out of balance.⁶ Clearly there are numerous extrinsic and intrinsic forces that might have this effect. Hypokalaemia, for example, favours QT interval prolongation, and chronic exposure to arsenic favours hypokalaemia.⁷

INTERACTIONS AND PHARMACODYNAMICS

There are other reasons for assuming that the Emperor was hypokalaemic. Napoleon suffered from intermittent nausea and vomiting for most of the eight months before his death, and he was frequently given tartar emetic (antimony potassium tartrate) to relieve his symptoms.⁷ The day before his death the group of English physicians who ultimately controlled the Emperor's care insisted, against Antommarchi's violent, almost physical objections, that

Napoleon be given a 10-grain (600 mg) dose of calomel (mercury chloride)—roughly five times the customary dose. Elemental mercury is not well absorbed via the gastrointestinal tract, which is the reason it causes diarrhoea. Diarrhoea would, in turn, lead to potassium loss, predisposing to *torsades de pointes*.

Still another destabilizing factor would have been the tartar emetic. Over and above any effect drug-induced vomiting might have on potassium balance, antimony ions bind to the inner regions of potassium channels,⁸ causing conformational changes in the channels.⁹ These actions might well have disrupted the delicate balance of arsenic's own effects on potassium channels. Finally, even though none of the earlier hair testers have sought the evidence, Antommarchi clearly states he was treating the Emperor with 'bark'. 'Jesuit's bark' was in wide use in the early 1880s, and the quinine it contains likewise binds within the potassium channel;¹⁰ indeed, quinine-related *torsades* is well recognized.¹¹

The argument for an arrhythmic death depends on extrapolation of results from the therapeutic use of arsenic, which would yield higher blood levels than chronic exposure. According to Wu *et al.*,⁹ arsenic trioxide concentrations as low as $1 \mu\text{mol/L}$ (200 ng/mL arsenic) produce measurable dysfunction in rabbit heart. In a therapeutic study, mean peak arsenic concentration after intravenous injection was 1370 ng/mL ($6.85 \mu\text{mol/L}$), with a decline to 200 ng/mL within ten hours.¹² Chronic exposure to arsenic, whether accidental or deliberate, is unlikely to yield peak concentrations of this order, but blood levels well above the 'clinically significant' 200 ng/mL have been recorded from environmental exposures in the absence of symptoms—for example, $>250 \text{ ng/mL}$ in certain forest workers exposed to the arsenic-containing herbicide cacodylic acid.¹² In healthy US residents, plasma arsenic concentrations range from 2 to 62 ng/mL.¹³

CONCLUSION

We propose that the immediate cause of the Emperor's death was neither gastric carcinoma nor 'classic' arsenic poisoning, intentional or otherwise, but *torsades de pointes*. The cause of death might then be classified as medical misadventure (of course, if the arsenic poisoning was intentional, it would still be homicide). Had Napoleon not been given calomel and tartar emetic, arsenical effects on cardiac conduction would have remained balanced; he would then have lived to die a natural death, probably from gastric carcinoma.

Physicians of Napoleon's time were blissfully unaware, or at least unconcerned, that medications designed to combat disease often have side-effects. It is now clear that some drugs interact with cardiac ion currents to produce

unwanted effects. In addition to disturbance of ion channel subunits, a whole range of mutations and single nucleotide polymorphisms can predispose to drug-induced cardiac arrhythmia.¹⁴ A drug interaction is not nearly so impressive a cause of death as arsenic poisoning, but reality is often less exciting than conspiracy theory.

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