

CORRESPONDENCE

Mithridates VI Eupator of Pontus and mithridatism

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We greatly appreciated the paper by Ring and Gutermuth, '100 years of hyposensitization: history of allergen-specific immunotherapy (ASIT)' (1). Some points referring to Mithridates VI of Pontus deserve, in our opinion, to be further addressed (e.g. '... King Mithridates... used increased doses of snake venom to make himself immune against the toxin...').

Mithridates VI (132-63 BC), who ruled the northern part of Anatolia and waged a hard-fought war against the Romans, was interested, like other hellenistic sovereigns, in science, particularly poisons and antidotes (Fig. 1). His celebrated 'universal antidote' later came to be known as 'Mithridatium' (2).

Aulus Gellius (*Attic Nights* 17.16) states that Mithridates used to mix the blood of Pontic ducks, whose flesh was toxic from their ingestion of plants poisonous to humans, with other substances reputed to 'expel' poisons. He also apparently obtained immunity to otherwise fatal doses of arsenic by ingesting tiny amounts over many years. His 'theriac' recipe was said to contain more than 50 ingredients, consisting of poison counteracting 'drugs' (3). He was known to display his 'immunity' to poison plots at banquets, inviting his guests to sprinkle his food and drink with deadly substances. Dio Cassius (*Roman History* 37.13) reports that Mithridates protected himself by taking his secret 'antidote' formula every day. Pliny the Elder (*Natural History* 25.3) states that Mithridates, through experiments, came up with a daily regimen of taking poison along with 'remedies'. Appian (*Mithridatic Wars* 12.16) says that Mithridates accustomed himself to poisons by taking small doses every day. The original formula of the famous mithridatium has not survived, but it is unlikely that a snake venom was employed, as stated by Ring and Gutermuth. In fact, because of the enzymatic/proteic nature of their lethal active principia, reptile venoms taken orally are inactivated by proteolysis in the gut, being able to exert their effects only in the presence of lesions of the inner surface of the first digestive tract. The fact that snake venom could be safely ingested was known in antiquity. For example, the Roman writer Lucan (*Bellum Civile/Pharsalia* 9.614) stated that 'snake venoms are dangerous only when mixed to the blood'.

The word 'mithridatism' is currently used to mean tolerance or unresponsiveness to a toxin, which is acquired by taking gradually larger doses of it. The reported continuous *per os* assumption of 'hemetics, antidotes, poisons, remedies and/or (unspecified) drugs' probably determined Mithridates' resistance to toxins more by functional and/or metabolic changes than by immune mechanisms. In this regard, gut irri-



Figure 1 Portrait of Mithridates VI Eupator by Cristiano M. Ferretti. Mithridates is represented as Hercules wearing a lionskin. The sketch was inspired by the sculpture at Louvre museum (courtesy of the artist).

tation (impairing the absorption of the poison itself as in the case of chronically taken low doses of arsenic) and/or induction/activation of drug-biotransforming enzymes are likely to have been involved. Such resistance was said to have resulted in an unwonted effect when, in 63 BC, Mithridates tried unsuccessfully to empoison himself to avoid to be captured alive by his enemies. Appian states that Mithridates 'mixed' the poison and shared the dose with his two young daughters, then swallowed the rest. The two girls died immediately, but Mithridates only became weak (Fig. 2). The composition of this suicide poison is unknown. The effectiveness of poison in rapidly killing Mithridates' daughters following oral ingestion suggests a nonproteic nature of the poison itself and, therefore, it is unlikely that Mithridates' tolerance was based on an immunological mechanism. He had shared the single dose with his two daughters and the remaining amount was sublethal, also due to his tolerance.



Figure 2 The death of Mithridates. After having empoisoned his daughters Mithridates asks his bodyguard Bituitus to kill him by sword (courtesy of Ms. Adrienne Mayor, 3).

To look at Mithridates VI Eupator as forerunner of ASIT (1, 4–6), therefore, appears to represent a very broad view of the concept of mithridatism. Indeed, this belief presumes that repeated *per os* consumption of (small) amounts of antigen, regarded as a poison or toxin, induces tolerance or resistance to the antigen itself by predominant immune mechanisms. In addition, such a belief would also make Mithridates VI King of Pontus into a forerunner of vaccinations. However, there is no reported historical evidence for such an assumption.

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Conflict of interest

None.

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