

Mithridatium (Universal Antidote), Mithridatism and Mad Honey Chemical Warfare

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Solve the mystery:

- What could be the potential medicine or chemical that Mithridates used to immunize himself?
- What mechanisms can you suggest?

Take a guess (or confirm the given diagnosis), and email in your response to be entered into the BCTOX drawing for a \$20 gift card (Deadline: June 15, 2018).

- If you send just a diagnosis, you will be entered once.
- If you send the justification of your diagnosis, you will be entered twice.

--- There is no right or wrong answer for this competition. You may select a given diagnosis or provide a new one.

Mithridates VI (Mehrdad IV)

Mithridates VI or Mehr-dad VI "Persian; gift of Mithra" was the king of Pontus (in eastern modern Turkey), Persia and Greece from 113[?]-63 BCE. He claimed descent from Persian Cyrus and Darius the Great, and Regent Antipater, a Greek-Macedonian general.

Mithradates VI saw himself as bridging the East and West together and as the defender of the East against Roman domination.[1] --- At the same time, another King, Mithridates II reigned (121 – 91 BCE) Persia and Babylon (modern Iran and Iraq), and claimed descent from Cyrus the Great.

Mithradates VI and Mithradates II were Zoroastrian kings, but were highly influenced by Greek culture, which is clear from their coins written in Greek. The latter is more well-known, as he concurred Babylon, but is not the topic of interest within this article.



Mithridates VI – Sketch is based on his silver coin. YA®

Mithridates VI's life was like a fairy tale. His father, Mithridates V, was allegedly poisoned by his mother, queen Laodice VI, in 120 BC. His mother favored his brother, and during his teenage years Mithridates VI was forced to escape and go into hiding from a plot planned by the queen. He eventually claimed the kingdom as his own, imprisoned his competitor brother, and his mother to death.

He was a visionary rebel with charisma and determination. However, he'd been thought to be ruthless, strange and suspicious by everyone throughout his entire life. He even married his younger sister in an attempt to "preserve the purity of his bloodline" and legitimize his children for succession. And in autumn of 88 BCE, he massacred more than 80,000 civilians, of which majority were Roman.[2]

He was also an erudite patron of science, particularly concerned with poisons and antidotes.[3] He often displayed his life-long arrogance by bragging about his immunity to poisons through invitations to guests to eat his food and drinks concocted with deadly substances. Mithridates VI inspired Mozart's first opera, and Machiavelli has praised his military genius.

For over 50 years, he fought the Romans several times as their most resilient enemy in the, so called "Mithridatic Wars". Eventually he was defeated, and escaped to Crimea. In attempt to avoid being captured by the Romans, he attempted to commit suicide by poison; unsurprisingly, he failed. Two of his daughters even ingested the poison and died soon after.¹ Poisons seemed ineffective at killing Mithridates VI, and eventually, at his request, his loyal friend, Bituitus, ended his life by sword.

Toxicological breakthroughs by Mithridates VI

Although underappreciated; Mithridates IV is the pioneer of clinical toxicology,[4] [5] and is suggested to be the father of "empirical toxicology".[6]

➤ He is recognized for:

- ✓ Testing poisons on condemned criminals.[1]
- ✓ Developing a 'universal antidote' or "Mithridatium"[5], which was later named "theriaca".
- ✓ Establishing Mithridatism, which is a long standing school of thinking in clinical toxicology, defined as "tolerance to a poison acquired by taking gradually increased doses of it".[7]
- ✓ Using grayanotoxin-containing honey, or mad honey, in 67 BCE against the troops of Pompey the Great, which is the first recorded use of a biotoxin in warfare.[6] He developed a tactical retreat leaving mad honey, containing honey combs, in the path. The Roman troops who consumed the honey were later treated easily.[8] Mithridates IV's soldier also used poisoned arrows dipped in snake venom to cut down masses of legionaries, and stinging hornets and slaving bears to attack the Romans.[2]

Mad Honey (Grayanotoxin) Poisoning

Certain plants of the Ericaceae family, including the Rhododendron, Pieris, Agarista and Kalmia, contain diterpene grayanotoxins. Consuming these plants causes dizziness, hypotension and atrioventricular block. [9]

Grayanotoxins can also be consumed by honey bees and, subsequently, concentrated in honey. Mad honey is purchased by lay individuals even today for its alleged effects on sexual performance.[10] [11]

Grayanotoxin causes cholinergic toxidrome resulting in an altered mental state and incapacitating bradycardia, hypotension, myocardial infarction,[12] nausea, vomiting,[11] hypothermia[13] and death or so called mad honey poisoning. [8] Symptoms are experimentally imitated in human. [14]

Mithridatism

As previously mentioned, Mithridatism is defined as "tolerance to a poison acquired by taking gradually increased doses of it".[7] It is postulated that poisons can be *beneficial*, as well as *lethal*.

Mithridates IV frequently experienced, and was always suspicious of, treachery. To protect himself, he continuously consumed small doses of poison in increasingly greater amounts in order to build up tolerance. And eventually, Mithridates IV attempted suicide by poison and failed. Thus, it is unclear whether his practice was successful, but at least it may have deterred others from attempting to poison him.

¹ Mithridates' life, reign and death have been portrayed differently by the Romans, Greek and Persians.

Mithridatism - Potential poisons that Mithridates used to immune himself

Although historically and scientifically highly controversial, Mithridates VI's immunity to poisons is documented to be related to:

- Increasing doses of *snake venom*[15] or flesh of vipers.[5]
- Frequent doses of *arsenic* by ingesting tiny amounts over many years.
- A mixture of the *blood of Pontic ducks, whose flesh was toxic from their ingestion of plants poisonous* to humans, with other substances reputed to 'expel' poisons.[3]
- A mixture of over 50 ingredients, consisting of poison counteracting 'drugs[?]'.[1]
- **Snake venom**

Science has proven that peptide venoms, such as snake venom, are disabled in the gastrointestinal system and are ineffective on intact stomachs and intestines. Therefore, snake venom would be ineffective. This fact can be experimentally proven easily, particularly since he was performing experiments on condemned criminals. Thus, although ineffective, he may have knowingly ingested snake venom in his lavish ceremonies as a dramatic display of his power.

A single dose of an "orally" ingested poison that "rapidly" killed his druthers indicates that poison was not a peptide, like snake venom.[3]

➤ Arsenic

Arsenic was a commonly used poison during Mithridates era, so it is plausible that he used it in an increasing matter. Rat studies have shown that pre exposure to arsenic may magnify certain mechanisms of actions in detoxifying poisons; a finding which is controversial, dangerous and counterproductive.

Upregulation of glycolysis and oxidative phosphorylation,[16] erythrocyte antioxidant defense systems and lipid peroxidation,[17] indirect and direct inhibition of glutathione reductase leading to apoptosis, [18] oxidative stress in the liver [19], etc. are reported as a result of sub-chronic or chronic exposure to low doses of arsenic. Additionally, low dose arsenic exposure is carcinogenic, however, Mithridates lived long for his era.

➤ Blood of Pontic ducks, whose flesh was toxic from their ingestion of poisonous plants

Set aside the complexity of this innovative experiment, it is scientifically plausible that ingested poisons, or their metabolites, would end up in the bloodstream. Moreover, as the duck survived the experiment, the dose would not have been high.

Mithridatism and immunology[20] - Vaccination

Mithridates VI's practices, including alleged increases of small doses of snake venom, also make him a forerunner of Immunology[20] [21] and vaccinations.

Immunotherapy (also called desensitization or hyposensitization) is the treatment of diseases by inducing, enhancing, or suppressing an immune response. For example, immunotherapy can reduce sensitivity to allergens and lessen their severity through the "administration of slowly increasing doses of a specifically relevant allergen in the treatment of IgE-mediated allergic diseases, until a maintenance dosage is achieved or the patient is free of symptoms".[21]

The human immune system can learn to produce antibodies against antigens that are commonly used in vaccines. Additionally, early exposures may explain the reason that peanut and non-food allergies are relatively less common in Canadians of Asian descent [22]

Mithridatism is effective with complex biological poisons, such as wasp stings. However, having said that, immunotherapy could not explain

Mithridates' immunity towards other poisons, like chemicals. A more plausible explanation for his experience would be a toxicological mechanism.



Furthest extent of Mithridates VI Empire. Scheme based on a map from. [2]

Mithridatism and toxicology

The mode of action for Mithridatism could be explained by activation of the immune system or by mechanistic pathways of functional biotransformation (detoxification). Hepatic enzyme induction, including auto-induction, is well recognised in the use of long-term medications.

Certain medications including alcohol enhance the number of enzymes, including microsomal and mitochondrial CYPs. CYPs can be found in almost any tissue, such as the liver, kidney, lungs and brain, and play an important role in the intra-cellular metabolism of drugs and xenobiotics.

If that happens, larger doses of the same medication/chemical or shorter intervals of use are needed to have a similar effect. Increased doses of alcohol in heavy drinkers is a well known example of this phenomenon.

Enzyme induction could provide a more suitable explanation than immunologic mechanisms for Mithridatism. (see under arsenic for more information)

Mithridatism and Homeopathy

Mithridatism may have also influenced the development of "Homeopathy". Homeopathy, or like cures, was introduced by Samuel Hahnemann in 1767, and is highly controversial. In this school of thinking, chemicals that may cause a particular symptom are considered to be a cure for the same symptom that is caused in a particular disease. To use the chemical, it should be diluted to extremely low concentrations, or perhaps to zero concentration. To date no well-established research has supported homeopathy.

Question

What do you think? What could be the potential medicine or chemical that Mithridates used to immunize himself? What mechanisms would you suggest?

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(Deadline June 15, 2018)

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