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LESSONS FROM HISTORY

The Honey, The Poison, The Weapon

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The honey produced on the mountains that run parallel to the shore of Turkey's Black Sea coast is known to have toxic qualities.[1] A toxin known as grayanotoxin is responsible for this poisoning. The toxin is thought to come from the nectar of the plant species *Rhododendron luteum* and *Rhododendron ponticum*, important components of the natural vegetation cover of the Black Sea region forests. Cases have also been reported from the United States, Korea, Germany, and Austria.[1] Incidence is uncertain. A significant number of the cases reported originate from Turkey.[1,2]

Mad honey is generally reddish-brown in color, with its own sharp scent. It is thought that its toxicity will disappear if it is boiled and stored for a long time. This honey is popularly boiled with milk and believed to become nontoxic when the froth is consumed during the boiling process. This honey is commonly known as "mad honey" or "sharp honey" in Turkey. In addition to the medical literature, noteworthy references to it can also be found in historical literature.

Mad honey poisoning was first described in 401 BC by the Athenian historian and army commander Xenophon (430–355 BC).[3] Xenophon fought the Makrons in what is now the Turkish province of Trabzon, and in his "Anabasis, The March of the Ten Thousand," he describes in detail the effects of mad honey poisoning on soldiers.[4,5] For the most part, there was nothing in Trabzon that they found unusual except the numerous swarms of bees and an abundance of honey. However, soldiers who ate a lot of the honey all went "off their heads," suffered from vomiting and diarrhea, and none of them could stand up. Those who had eaten very little were like people exceedingly drunk, while those who had eaten a great deal appeared crazy or, in some cases, looked like dying men. They lay there in great numbers as though the army had suffered a defeat, and great despondency prevailed. The next day, however, no one had died and they began to come to their senses at approximately the same hour as they had eaten the honey. On the third and fourth days they got up, as if from being drugged. From there they marched 2 stages, 7 parasangs, and reached the sea at Trapezus, an inhabited Greek city on the Euxine Sea, a colony of the Sinopeans in the territory of Colchis.[3]

Mad honey was also used in Northern Anatolia against the armies of Pompey by King Mithridates Eupator of Pontus in 97 BC. On the advice of his chief counselor, the Greek Kateuas, Mithridates placed combs full of mad honey in the path of the advancing Romans and staged a strategic withdrawal. The Romans who ate the honey from these combs collapsed with fatigue and were easily overcome. Strabo (64 BC – 21 AD) mentions the subject as follows in his work:

> The Heptacomedes destroyed three Roman detachments belonging to Pompey as they passed over the mountainous country. They placed mad home obtained from the boughs of trees into bowls and left these on the road. When Roman troops ate the honey and lost consciousness, they attached easily and disposed of them all.[6]

A similar incident involving this honey also appears in Russian history. When the Russian Queen Olga defeated the rebel forces by a ruse and captured the city of Kiev, they accepted several tons of honey liquor from Olga's allies. We do not know whether this liquor was reinforced with mad honey, but sources report that 5000 Russians were killed by sword as they lay drunk on the ground.[7]

In the chapter on plants in his famous *Naturalis Historia*, the renowned ancient naturalist Pliny the Elder, who lived between 79 and 23 BC, provides the following information about mad honey:

> Indeed the food of bees is so important that it may be poisonous for us. In Pontus, in Herakleia, different honeys from same bees may be fatal after a few years. However, the authorities had not stated the type of flowers from which these honeys were made. There is a specific plant that meets these conditions and has proved a fatal danger, especially for goats and pack animals, and is called 'ae-

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> golcthron.' It makes interaction with poisonous toxins sprouting in the steppes during spring rains. A poisonous honey has a dense appearance and an abnormally red color and its smell causes sneezing. However it is much more effective than a similar good quality honey.[8,9,10]

In the next part of his work, Pliny refers to the effects of this honey as a means of treatment. Elsewhere in his work he states:

> In the country of Sanni, located on the shore of Turkey's Black Sea coast, there is another type of honey causing madness. It is called 'maenomenon.' This poison is generally related with the *Rhododendron* flower which exists in thick forests. Although people here pay tax to the Romans for it, they cannot gain any income from this honey because of its very harmful effects.[8]

Pereira, who performed a voyage of exploration in the Northeast Anatolia region in 1970, mentioned economic activities in his discussion of Trabzon. He stated that beekeeping was widespread in the region and that the honey on sale there was known as "Thousand and One Flower Plateau Honey."[11]

Cases of mad honey poisoning were reported in Europe and North America in the 18th century.[17] Speaking at the annual meeting of the American Pharmacists Union in 1896, Kebler added cases of mad honey poisoning in the United States to the literature.[12] That publication described 8 cases of poisoning in Princeton, New Jersey and Kebler discussed previous research as well as his own cases. According to Kebler, Barton was the first American to report the effects of mad honey poisoning. Barton first read his findings at a meeting of American philosophers in 1794, subsequently publishing these in 1802. The case involved a 54-year-old woman who ingested mad honey. She presented to hospital with a burning forehead, facial pallor, breathlessness, and an irregular pulse. The patient suffered visual hallucinations, subsequently lost mental awareness, and had a generalized tonic-clonic seizure for a short period of time. The patient regained mental awareness after vomiting, but lingual numbness and mydriasis remained.[12] Kebler also refers to the Coleman's 1853 study that documented 1 fatality from mad honey poisoning (out of 14 affected) in New Jersey and 3 (out of 20 affected) in Branchville, South Carolina. Additionally, Plugge conducted a study of several plants from the Ericaceae family in 1891 and discovered that the active substance in these was andromedotoxin (grayanotoxin).[12] His 1899 paper, republished in the *British Medical Journal* in 1999, was about typical mad honey poisoning.[13] Dioscorides, Diodorus of Sicily, and Aristotle also refer to the intoxicating effects of honey collected from a species of Rhododendron in Haraclea Pontica at certain times of the year. Joseph Pitton de Tournefort described poisonous honey as originating from *Azalea pontica* and said "whoever eats of this honey becomes intoxicated."[12]

The first study of mad honey in Turkey was by Bucak, who examined the honey microscopically and isolated Rhododendron pollens in it.[14] Biberoğlu et al investigated 16 patients poisoned by mad honey between 1984 and 1996, identifying grayanotoxin in that honey.[15] In 1991, Onat et al injected mad honey into the peritoneum of rats and observed decreased heart rate and shallow respiration.[16] Özhan et al retrospectively investigated 19 suspected cases of honey poisoning applying to the emergency department and determined sinus bradycardia in 15 cases and full atrioventricular (AV) block in 4. Patients were determined to have ingested 30 to 180 mg of honey. All responded to 0.5 to 2 mg of atropine within 2 to 9 hours, and blood pressure stabilized within 24 hours.[17]

Mad honey poisoning may cause a wide variety of dysrhythmias, such as nonspecific bradycardia, sinus bradycardia, nodal rhythm, second degree AV block, complete AV block, and asystole. The most common form of dysrhythmia found in case series was sinus bradycardia.[1,18] Cardiac arrest developed in a patient subjected to mad honey poisoning reported by Gündüz et al in 2007. The patient was admitted to intensive care, and a pacemaker was inserted following atropine and fluid resuscitation.[19]

Grayanotoxins have a toxic cellular effect on the sodium channel. The work of a number of researchers was summarized by Maejima et al,[20] who stated that grayanotoxins act in 3 ways on the voltage-dependent sodium channel: 1) the grayanotoxin binds to the voltage-dependent sodium channel in its open state; 2) the modified sodium channel is unable to inactivate; and 3) the activation potential of the modified sodium channel is shifted in the direction of hyperpolarization.[1] The amount of honey needed to produce toxicity is quite small. The average amount of ingested honey in one report was 13.45 $\pm$ 5.39 grams (5–30 grams). Symptoms began 1.5 to 3 hours after ingesting the honey.[4] Poisoning was generally observed to have occurred following the ingestion of 1 spoonful (15 grams).

In untreated cases of severe intoxication, the worst signs and symptoms last about 24 hours. By the end of that time, the patient is alert and vital signs are normal. Complete recovery may take several more days.[1] There are no detailed studies of the duration of individual signs and symptoms in severe mad honey poisoning in the modern medical literature. Duration of signs and symp-

toms in recent studies are similar to those previously reported.[20] Patients were discharged within 5 hours of admission and in the third hospital, patients were generally monitored in the emergency department for 18 to 24 hours under the protocols of the hospital, regardless of the patients' clinical conditions. In the same hospital, 1 patient diagnosed with complete AV block was admitted to intensive care and monitored for 1 day.[1]

Although the symptoms and signs of honey poisoning can be alarming, and sometimes life-threatening, supportive care with electrocardiographic monitoring, normal saline infusion, and intravenous atropine is usually sufficient to ensure recovery.[1,21] A temporary pacemaker may be needed on very rare occasions. Some previous reports detail cases returning to a normal rhythm with sufficient fluid support and the administration 0.5 to 2 mg of atropine.[17,21] In those rare cases when atropine and intravenous saline are not adequate, Advanced Cardiac Life Support bradyarrhythmia protocols should be considered.[1]

Mad honey poisoning continues to represent a significant public health problem in inhabited areas along the Black Sea coast of Turkey, where it is endemic. Plants of the species *Rhododendron*, the source of mad honey, are distributed across a wide part of the Earth's surface. Despite these plants covering such a wide area, the fact that nearly all the case reports of mad honey poisoning originate from Turkey continues to be puzzling. Recent case series and scientific studies have generated important clinical and experimental data about this poisoning. Interesting literary and historical case report, however, have not been fully available to modern readers of medical literature and are helpful in fully elucidating the signs and symptoms of mad honey poisoning.

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