Investigations on ancient knowledge about venoms and their medical use[1]

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Abstract: Very little is known today about the linguistics and facts relating to venoms in the ancient world. The following article concerns itself initially with the terminology: How were venoms conceptualized and what position did they occupy among medicines and other poisons? Additionally, ancient knowledge of the constitution and location of the venoms will be examined. Furthermore, it shall be outlined how it was perceived that the poisons actually took effect. The results of our investigations indicate that it was unlikely that venoms were used for medicinal purposes in ancient times.

Key words: poison – venom – venomous animals – poisonous animals – bee venom – snake venom – toxicology – ancient medicine – ios – pharmakon – venenum – virus

1. Introduction (pp. 319–323)[2]

"[…], adeo nullo omnia experiendi fine ut cogerent etiam venena prodesse."[3]

The contemporary concept of 'poison' is mostly formed by the harmful effect a substance can inflict on humans, animals, or plants.[4] According to this understanding, poisons are substances that, after being introduced into the body by absorption, ingestion, inhalation, injection or

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[2] The pagination refers to the first publication of this article – see fn. 1.

[3] Plin. Nat. hist. 25, 17, 37 – W. H. S. Jones translated: "[…] so unwearied have been researches in making every possible experiment, even to compelling poisons to be helpful remedies." (Pliny, vol. 7, p. 163).

[4] For a medical definition see Dorland (2011), p. 1480; for different kinds of definition see Hill (2016), pp. 181–182.; for historical aspects see Hayes (2008), pp. 4–43.

other types of exposure,[5] can cause severe harm, illness or even the death of an organism. The extent of toxicity is heavily dependent on the conditions under which the substance is taken. In the first place it depends on the dosage of the substance consumed. Also the kind of intake (oral, intravenous, and so on) and the constitution of an affected organism influence the extent of damage the substance will cause. The harmful effects can appear immediately after absorption of the substance, but it may also take time before the poison takes effect and starts causing damage. Some substances can induce tremendous harm very quickly, even in small amounts. These substances are known as 'highly toxic'. On the other hand, there are substances that take effect very slowly and are only dangerous in very high doses. Even though, according to a quantitative definition such as the well-known Paracelsian "Sola dosis facit venenum",[6] all substances can be considered to be poisonous, usually (and reasonably) only those substances that have a high potential to damage an organism and can be dangerous even in small amounts are regarded as poisons. Another important issue concerning the question of whether we consider a substance to be a poison or not is its specific kind of administration – penicillin, for example, taken for the antibiotic treatment of infections caused by germs, is not regarded as poison even if it kills the bacteria or parasites. In contrast, gas used in chemical warfare to harm or kill the enemy is, with good reason, considered to be poison.[7]

However, modern medicine, especially pharmacotherapy, uses the effects of 'poisonous' substances in many cases. Whether as chemotherapeutic, anaesthetic, analgesic or antibiotic agents, medication for congestive heart failure or as anti-aging drugs, just to mention some prominent examples, poisons have contributed greatly to our modern arsenal of pharmacopoeia. Besides the discussion in medical sciences about the right doses and the side effects of poisons, in particular their responsible use has become an important topic in current medical ethics.[8]

In recent decades a specific group of poisons – animal poisons[9] – has come more and more to the fore,[10] and this not only because snakebites yearly cause approximately

5 With the exception of radioactive radiation, which is normally not considered to be in the category of poisons.

6 Paracelsus, Septem Defensiones, 3. Defensio (1538).

7 For this example see Timbrell (2002), p. 2.

8 See, for example, discussions in Germany about botulinum toxin and its use as an anti-aging remedy used in face-lifting – one of the questions here is whether this face-lifting is a kind of disease treatment or whether it counts as so-called wish-fulfilling medicine that is unnecessary from a medical point of view; see Schweda/Marckmann (2012). Another example is the use of 'poisons' in palliative or terminal sedation and the thin line between that and euthanasia; see ten Have (2014).

9 At this point in my article, I use the general term 'animal poisons' to refer to both: the poison of animals that have developed a specialized apparatus (with an attached gland where the venom is produced) to inject a poison actively in order to defend themselves or capture their food (such as snakes or bees), as well as to the poison of animals that are not able to apply their poison deliberately (such as blowfish)

125 000 deaths and about three times as many amputations.[11] Even in the 19th century, bee venom was used in the treatment of rheumatic and other diseases. After its introduction as a homeopathic remedy called *Apis mellifica* by the German-born physician Constantin Hering (1800–1880),[12] it was also employed by conventional medical practitioners.[13] Especially in the first half of the 20th century, a lot of research into bee venom was conducted, mostly by German physicians and scientists.[14] Some of these scientists already claimed that the medical use of bee venom could be traced back to ancient times.[15] One of the goals of this article is to verify this claim with a more general approach: Is it possible that animal poisons were used in ancient medicine, considering ancient knowledge about animal poisons and ancient ideas about the mode of action of drugs?

Also in the first half of the 20th century it was discovered that the poison of the snake *Bothrops jararaca*, a species of pit viper endemic in parts of South America, drastically and very quickly lowered the blood pressure of a victim. In 1970, *Teprotid*, the substance responsible for this sinking of blood pressure, was first isolated by the Brazilian physician and pharmacologist Sérgio Henrique Ferreira (1934–2016).[16] In the same year it was synthesized by the Argentine-born American chemist Miguel A. Ondetti (1930–2004) and his research team.[17] This chemical synthesis also formed the starting point for the development of *Captopril* by Ondetti and his colleague the American chemist David W. Cushman (1939–2000) in

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because they have not such a specialized apparatus. Below, I will clearly distinguish between 'venomous animals' and 'poisonous animals'.

10 The first groundbreaking anthology was published by Bücherl/Buckley (1968–1971). Part of this book is also a chapter about the medical use of venoms: Klobusitzky (1971). Lewis/Garcia (2003) give an overview of research results in venoms since the 1970s.

11 This number is given by the *Global Snakebite Initiative* (*GSI*) – see: http://www.snakebiteinitiative.org/. (last access on 29th August 2016). In the 1990s, Habermehl estimated that the number of deaths after bee or wasp stings was even three times higher than the number of deaths after snakebites – Habermehl (1994), p. 4.

12 Hering (1857), pp. 171–422 (written in German).

13 The first works about the medical use of bee venom are all written in German: Terc (1888); Keiter (1914); Langer (1915). The first (short) reference to the medical use of bee venom in a non-homeopathic work I found in a French journal, written by an unknown author: 'Action curative du venin' (1864). The first important publication about bee venom therapy in the English-speaking world is written by Beck (1935). Some years before there was the first entry for 'apiotherapy' in Dorland's medical dictionary (Dorland (1927), p. 98), where it was defined as medical treatment with bee venom.

14 See, for example, Flury (1920); Flury (1923); Fehlow (1932); Kirschhock (1934); Müller (1939); Dyckerhoff/Marx (1943); Ackermann/Mauer (1944). A detailed overview of the bee venom research in the 1920s, 1930s, and 1940s, sorted by different indication areas, is given by Müsebeck (1953).

15 Kretschy (1928), p. 112; Gleichmann (1934), p. 561; Beck (1935), p. 16; Dirr/Graeber (1936), p. 1483; Feuchtinger (1937), p. 1286; and others. It is claimed in these works that Hippocrates, Celsus, and Galen already reported about the healing effects of bee venom, but in none of them are more specific references given. Recently, the same unfounded statements can be found in works about so-called Apitherapy – see, for example, Cassileth (2011), p. 221; Kim (2013), p. 78. But also outside the scope of these works the belief that bee venom was used as a remedy in ancient times can be found – Habermehl, 1994, p. 207.

16 Ferreira et al. (1970).

17 Ondetti et al. (1971).

1975, which is the lead substance of the first angiotensin-converting enzyme (ACE) inhibitor (trade name *Capoten*) and still today used for the medical treatment of hypertension and congestive heart failure.[18]

At this time, there are around a dozen drugs circulating on the market that are produced on the basis of various animal poisons. They are applied, inter alia, in pain management and in the treatment of diabetes and circulatory and blood clotting disorders. Further promising areas of application are in cancer research and in the treatment of obesity. Furthermore, venoms are used in basic medical research to examine various physiological mechanisms of human beings.[19]

At the moment a total of around 3500 animal toxins have been isolated, which are assumed to be only a small proportion of all the existing animal poisons (approximately 100 000 kinds of poisonous animals live worldwide). For this reason, hopes are high that more medically efficacious venoms will be discovered in the future. Therefore the EU, within the context of the *Seventh Framework Program* (*FP7 Health*) is supporting the international project 'Venomics'[20] (in which animal poisons are investigated) with yearly funding of six million euros.

In this article, the significance of animal poison for ancient medicine will be elaborated. The focus will be less on the treatment of those who were bitten or stung by venomous animals or who otherwise came into contact with animal poison. Instead, attention will mainly be drawn to the use of venoms as a potential cure. Nowadays there is general agreement that poison was already used for medical purposes in the ancient world – as a tranquilizer, analgesic or as a cure for different illnesses. However, relevant research work has been done almost exclusively on the medical use of herbal or mineral poisons,[21] whereas there is almost no mention of animal poisons in these works. Hence we know very little about elementary linguistic and factual aspects of these poisons and poisonous animals in antiquity. Therefore, the second chapter of this article deals with the specification of some important conceptual and linguistic issues concerning our topic: How were animal poisons conceptualized by ancient scholars, and what position did these poisons hold in ancient general classification systems of poisons and drugs? In the third part of this article the ancient knowledge about venomous animals will be examined, as well as the knowledge about the materiality and locality of ven-

18 Cushman/Ondetti (1991).

19 Utkin (2015).

20 For more information about this project, see this website: http://www.venomics.eu/. Information about the funding by the EU can be found here: http://cordis.europa.eu/news/rcn/35819_en.html (last access on 29th August 2016).

21 See, for example, Wittern (1982); Riddle (1985), pp. 104–115; Touwaide (1998); Horstmanshoff (1999), p. 49; Ihm (2005); Parascandola (2012), pp. 145–146.

oms. The general value attached to the administration of drugs in the context of ancient medical practices will be analysed in the fourth chapter, as well as the ancient ideas concerning the mode of action of drugs (including poisons) and how these ideas were connected with common humoral pathologic concepts in ancient medicine. In the conclusion, the results of our investigation will be summarized from the perspective of a possible use of venoms and poisonous animals in ancient medicine.

2. The ancient concept of poison (pp. 324–333)

2.1 The Greek-speaking authors (pp. 324–330)

‘Pharmakon’ – poison or remedy? (pp. 324–326)

In this chapter I summarize the development of the concept of ‘φάρμακον’ (‘pharmakon’) in the old Greek literature from Homer, Hesiod and Hippocrates to Ps. Aristotle and Galen. It will be shown that at the end of this process the term pharmakon was still ambiguous in that it could be used as a generic term for both poison and remedy, but that this ambiguity was mainly a linguistic, not a conceptual one. According to this conception, a substance was, depending on its so-called ‘εἶδος’ (‘eidos’), either a poison or a remedy, but not both at the same time. Besides this mainly ‘quality-based’ understanding of poisons, we can also find a kind of ‘quantity-based’ understanding, but only in the limited sense that the misuse (by administering too much) of a substance actually belonging to the class of remedies could lead to poisoning. In order to differentiate between remedies and poisons also on a linguistic level, the use of various adjectives grew more and more common. Some of these adjectives were later also converted into autonomous nouns such as, for example, ‘δηλητήριον’ (‘dēlētērion’: something that causes deletion; related to the English ‘delete/deleterious’) or ‘θανάσιμον’ (‘thanasimon’: something that causes death). At the end of this linguistic development, the term ‘pharmakon’ was applied mostly with its positive meaning of ‘remedy’, while the converted adjectives were applied to poisons.

‘Ios’ – venom (pp. 326–329)

In the second part of this section, the ancient Greek concept of ‘ἰός’ (‘ios’; pl.: ‘ἰοί’) will be introduced, which was mostly used to refer to venoms. I also give some suggestions as to how we can interpret the term ‘iobolon (zōon)’, which was first used by Aristotle to designate poisonous animals. Finally, I shall try to clarify the relation between ‘ios’ and ‘pharmakon’: According to my investigations, ‘ios’ was mostly used synonymously with ‘deleterion’ or ‘thanasimon’ relating to animals.

2.2 The Latin-speaking authors (pp. 330–333)

‘Venenum’ (pp. 330–332)

Even if most of the ancient ‘iological works’[22] (= treatises on poison) are written in Greek, I will also give an overview of the developments in the old Latin writings. One important observation is that the Latin term ‘venenum’, which was originally as ambiguous as the Greek term ‘pharmakon’, was later used almost exclusively with its negative meaning of poison, also including venoms, whereas for remedies the terms ‘medicamentum’ and ‘remedium’ were favoured. While in Old Latin the disambiguation process of the term ‘venenum’ resulted in a mainly negative meaning of the term, in Old Greek the disambiguation of ‘pharmakon’ led to a mainly positive meaning of the term.

‘Virus’ (pp. 332–332)

This part of my article deals with the Latin concept of ‘virus’ which can be seen as the counterpart of the Old Greek ‘ios’, going back to the same Indo-European root. I will show some similarities and differences between the two concepts.

3. Poisonous animals – ta iobola [zōa/thērion] (pp. 333–343)

3.1 On the classification of poisonous animals (pp. 333–338)

In the first part of the third section of my essay I try to specify which animals exactly were regarded as poisonous animals. For this purpose I investigate different sources, in particular the writings of Nicander of Colophon, Ps. Aelius Promotus, and Philumenos of Alexandria. One of the findings is that, whereas today we distinguish between poisonous and venomous animals,[23] ancient scholars referred to both of them as ‘iobola [zōa/thēria]’. In addition, animals that are not venomous or poisonous at all were also regarded as ‘iobola’, for example mosquitoes and dogs. These animals, as we know today, can sometimes transmit diseases without being poisonous or venomous themselves.

3.2 Location and constitution of venoms (pp. 339–343)

In the second part of this section I investigate what ancient authors thought to be the parts of the animals where the venom was stored, or which parts of their body were thought to be poisonous. The result of my investigation is that it was not very clear to ancient authors what kind of materiality venoms had – some authors presumed a kind of ‘ἄσθμα’ (‘asthma’) that was transmitted if a person was bitten or stung by a venomous animal. Other authors as-

[22] In this article I count only the works of the following authors in this corpus (strictu sensu): Nikander of Colophon (2nd century BC), Ps.-Aelius Promotus (1st/2nd century AD), Philumenos of Alexandria (2nd/3rd century AD), and Galen (AD 129 – AD 216). Following the interpretation of Morel (1928), Touwaide (1991, 1994), and Ihm (1995), the works of authors such as Oribasius (c. AD 320 – AD 403), Aëtius of Amida (AD 502 – AD 575), Alexander of Tralles (c. AD 525 – AD 605), and Paul of Aegina (c. AD 625 – AD 690) are not considered to be part of that corpus – they already belong to the late ancient or early medieval writers, which are not in the scope of my article. Also the writings of Pedanius Dioscorides (‘Peri dēlētēriōn pharmakon’) and Ps. Dioscorides (‘Peri iobolōn’) are not regarded as part of that corpus of ancient iological works – back in 1908, the German classicist Max Wellmann (1863–1933) proved that these writings were added in the early Middle Ages to Dioscorides’ ‘Materia medica’, depending entirely on Oribasius.

[23] See also above fn. 9.

signed the venom to specific parts of the body, for example the bile, the tail, or the vertebrae. I assume that this was one of the conditions for later recognizing that the 'ioi' were (mostly) liquid substances. Because there was no reliable knowledge about the location and constitution of venoms, ancient authors also hesitated to subsume the 'ioi' into the generic term of 'pharmaka': a pharmakon was mainly a substance that could be administered to patients – something that was not feasible with venoms.

4. Pharmaka and their expected mode of action (pp. 344–348)

In the fourth section I will give an overview of ancient ideas of drug mechanism. In this context, the Galenic distinction between four different classes of pharmaka will be presented. According to Galen, poisons were ranked among the first two classes of pharmaka, the class of the (1) 'dēlētēria' and 'φθαρτικά' ('phthartika'), and (2) the class of the only 'dēlētēria'. Poisons of the first class were considered to be deadly poisonous even in small doses. At least snake venoms, I will demonstrate, were subsumed into this group of poisons. These poisons were not taken as potential remedies, in contrast to the second class of poisons.

5. Summary (pp. 348–351)

At the end of my article I will summarize the results – ultimately, I must conclude that it is not very likely that venoms were used as remedies in ancient medicine. The main reasons for this conclusion are of both conceptual and factual nature: Venoms, especially snake venoms, were classified as poisons of the first (strongest) class, which were thought to be totally contrary to human nature and for this reason mostly deadly. Besides this, ancient knowledge about the location and constitution/materiality of venoms was so sparse that the deliberate extraction and application of venoms is hard to imagine. For this reason, the (as yet unproven) assertion of some modern authors that venoms were used as remedies even in ancient times must be rejected.

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