Perspective

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Murders by drugs – past and present

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Murder by poisoning has always been considered as an especially inhuman kind of killing because this malicious crime could be committed without being suspected or – for a long time – detected. The use of poisons to the disadvantage of humans reflects the dilemma that substances can be essential, harmless or toxic depending on circumstances – in particular on the dose.

Life, from its very origins, has encountered harmful substances, and living entities produced harmful chemicals themselves. Living organisms never had the opportunity to develop mechanisms to exclude harmful substances or to compensate for their harmful action.

Mankind developed the ability to avoid poisoning – in the beginning by 'trial and error' in the course of evolution; later by information conveyed through generations by genetic mechanisms or by instinct, and finally based on knowledge. This was when we learned that substances had the potential to be used for good or bad purposes.

The ancient oriental king Mithridates Eupator (120–63 BC) ordered the preparation of a legendary antidote, *theriak* (later also called *mithridaticum*) as a precaution against being murdered by poison.[1] In those times this was a common fear among prominent people, in particular rulers, who have been always been surrounded by enemies, competitors or envious 'friends'. In about 200 BC, the Greek author Nikandros described, in two books, remedies against bites from poisonous animals and remedies against the uptake of poisoned food (*alexiphamaka*).[2] Dioscorides, a Greek physician in service at the time of Emperor Nero, also complained of the difficulty in recognizing poisonings: 'Prevention against poison is difficult, because those who administer poisons in secrecy do it in such a manner, that even the most experienced are deceived.'[3] Likewise, the Roman author Marcus Fabius Quintilianus remarked: 'Credite mihi judices, difficilius est venenum invenire quam inimicum') 'Believe me, judges: it is even more difficult to detect poison than an enemy.'[4]

Nevertheless, the choice of potentially deadly poisons suitable for murders seems to have been rather restricted in ancient times, from our perspective, and legendary reports about poisonings often resemble fairytales. On the other hand, there was ancient knowledge of quite a number of poisons, which enabled us to avoid them as well as to use them for doing harm. These included poisons from animals, preferably snakes (the legendary suicide of the Egyptian Empress Cleopatra), plants containing strong-acting alkaloids (the paralysing alkaloid coniine was used in the sacrifice of Socrates by Conium Maculatum) and mineral poisons like arsenic or mercury compounds.[5]

This was the situation for many centuries. 'Trial and error' and observations of toxic actions – on victims, on animals, as consequences of overdosed therapeutic administration – led to empirical knowledge. But in its essence, the understanding of the nature of poisons remained mystical – they were similar to magic, to witchcraft. For example, the belief that amulets would act as antidotes, that they would enable us to avoid or to compensate for the action of poison, even if carried above garments or as jewels in finger rings, shows that incorporation, absorption, real interaction with 'living matter' was not considered as a fundamental precondition for toxic action.

A good example is the attempted murder of Snow White by her envious stepmother in the well-known fairytale. The stepmother tried to poison Snow White using a poisoned comb, which she gave to her while in the guise of a merchant. Even if we assume that the poison – which could never act through hair – might have acted after percutaneous absorption or even through small lesions, the symptoms would not have disappeared suddenly when the dwarves removed the comb. Then the stepmother poisoned one half of an apple, offered it to the girl and ate the other half to make the stepdaughter sure of her good intentions. Snow White fell down, the dwarfs found her apparently dead and put her into a coffin of glass. When one of the carriers stumbled as the coffin was brought to the burial, the apparently dead Snow White spit out the swallowed part of the poisonous apple and awoke suddenly to life.

It was a difficult task, in those times, to poison half of an apple sufficiently. Obviously, absorption of the poison was not considered necessary and if poisoning had occurred the removal of the apple piece would not have reversed the action.

Too much analysis for a fairytale? Yes, but even fairytales always carry 'a grain of truth' and reflect a general contemporary understanding. And this understanding of the nature of poisons and poisonings centuries ago was obviously more mystic than characterized by objective observation.

Numerous other examples of this mystic understanding can be found in the literature. What kind of poison was suitable for administration in the form of a few droplets introduced into the ear, as in Shakespeare's *Hamlet*? Could poisoned gloves or boots or a poisoned coat cause a fatal poisoning even when not worn on the naked skin (as in reports concerning John of Castile and Henry IV)? An agent killing somebody by its presence in the smoke of a candle or torch, even in a small room (for example, as reported from Popes Clemens II and III) would have to be extremely toxic and stable in the presence of heat. These examples have been cited in history textbooks,[6,7] but they seem to bear the influence of fantasy.

On the other hand, we find a very strange interruption in the somewhat mystical darkness of the two millenia between the oriental antique and the birth (or inauguration or occurrence)

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of toxicology (as a scientific discipline) of toxicology as a new science around 1800: in the fifteenth century there was an historic milestone in the form of a famous comment by Theophrastus Bombastus Aureolus von Hohenheim (called Paracelsus) on the distinction between poisons and beneficial drugs/agents. A physician experienced in the diseases of miners in Switzerland, Austria and Germany, he was accused of deliberately poisoning his patients by the use of new – mainly mineral-based – drugs and felt urged to defend his concept. So he wrote in the third of his *Septem Defensiones* (seven defences) the legendary sentence: 'Everything is poison, nothing is without poison, only the dose makes no poison', postulating that with the adequately low dose an agent can cure, while with a higher one it will become toxic.[8,9]

Two points are particularly interesting about this thesis. First, it later became known and mostly cited in the anonymous Latin translation, whereas Paracelsus wrote it – contrary to the contemporary scientific and especially medical custom – in German. Even more astonishing: the translation 'Dosis sola facit venenum' transforms the original meaning of this sentence to its opposite. Paracelsus intended to explain that a substance known for its toxic qualities could act as a remedy, despite being commonly called poison. The second phenomenon – truly to be regretted – is the fact that, to the best of our knowledge, the statement of Paracelsus remained unadopted, forgotten or neglected for some centuries.

It was not cited or considered until the nineteenth century, when many new (but ultimately unsuccessful) attempts were made to create 'absolute' definitions of poisons instead of this earlier, relative understanding. They clearly intended to define poisons as a peculiar category of substances to be distinguished completely from other, harmless or curative ones.[10–12] Only later did a relativist approach to the definition of poisons prevail.

Nevertheless: on closer inspection, the common understanding of poisons as substances whose action depends on conditions – mainly on dose or concentration – has really been adopted only since the second half of the twentieth century and still seems to be missing sometimes even nowadays in public discussion and in the media. J. C. Kapeghian commented on this in 1989: 'Unlike the other hard sciences, the early history of toxicology with its many cases of contrived poisonings for murder or suicide reads more like an Agatha Christie novel than an introduction to a scientific discipline. In this case, toxicology, as an organized science based on solid research principles, is still wet behind the ears.'[13]

At the end of the eighteenth century, a new era arose with the appearance of several textbooks,[14–18] numerous descriptions and objective observations of poisonings, experiments on animals, views about the definition and the various categories of poisons, as well as on their classification, and the invention of principles for the detection of poisons. This was the origin of the scientific discipline of toxicology.

In parallel, the isolation and structural elucidation of the active ingredients of natural poisons – mainly of alkaloids – and afterwards the beginning of the organic synthesis of numerous (known, natural, and new) pharmaceuticals initiated the development of toxicology to a widespread, nowadays multidisciplinary science. When at the end of the nineteenth-century 'encyclopaedists' such as Louis Lewin (1850–1929)[5,7,19] and Rudolf Kobert (1854–1918)[20] could still represent all toxicological knowledge of this time. The accumulated knowledge of toxicology has since long become overwhelming.

Cooperation with various related sciences such as chemistry, biology and medicine and social and behavioural sciences, law and politics, is essential for toxicology. The lack of chemical knowledge to assist the detection of poisonings was probably one reason for the 'popularity' of poison murders for centuries, if not for millennia. Poisons have been an 'arrow from the dark', and instead of reasonable diagnoses, suspicions had to be proven by erroneous assumptions or by ordeals. According to common understanding, either quick or uncommonly slow putrefaction of corpses justified the assumption of poisoning as the cause of death. Scientific diagnoses only became possible from the nineteenth century. Autopsies had been carried out earlier (the first one, conducted by Bartolomeo Varignana 1302 in Bologna for the elucidation of a suspected poisoning, is reported by Mondini de Luzzi, cited by M. Geldmacher-von Mallinckrodt)[21] but they had not become common. In 1800, the Physicians G. A. Welper in Berlin and Johann Daniel Metzger in Koenigsberg still assumed that the corpses of victims of arsenic poisoning would either not putrefy or would develop bluish stains (the normal livores).

A rare exception to this situation in forensic medicine was the proposal by the physician Schreyer from Zeitz, Germany, of an objective test (the 'lung swimming test') to decide whether a newborn found dead had been born alive or stillborn.[22] This had already been suggested in 1692 by Samuel Stryk. It had not been accepted when Schreyer first used it, but it was finally adopted as an essential step when assessing relevant causes of death.

In contrast to the slow development of both the definition of poisons and the 'emancipation' of toxicology as an institutionalized scientific discipline, toxicological analysis experienced a steady and rather quick growth from about 1800.

J. J. Plenk had written in 1785: 'Unicum signum certi dati veneni est analysis chemical inventi veneni mineralis, et notitia botanica inventi veneni vegetabilis (seu notitia zoological inventi veneni animalis.' ('The only certain sign of poisoning is chemical analysis for the recognition of mineral poisons, and botanical cognition for vegetable poisons, or zoological characteristics for animal poisons.')[14]

The first chemical detection methods were used around 1800 to detect lead in wine with H_2S by Samuel Hahnemann (1755–1843),[23] A. F. de Fourcroy (1755–1809)[24] and Heinrich Rose (1795–1864)[25] after earlier suggestions of Robert Boyle (1685)[26] and Immanuel Weissmann (1707)[27] of arsenic in foodstuffs (and in other biological material) by James Marsh (1794–1846),[28] followed by the isolation of alkaloids by Jean Servais Stas (1813–1891).[29] The first attempts at systematic toxicological analysis were made by Carl Remigius Fresenius (1818–1897)[30] and Julius Robert Otto (1809–1870). New analytical principles and methods were quickly applied in toxicology. This has lead to our impressive arsenal of detection and quantitation methods.

The first chemical detection methods, from Hahnemann to Marsh, had solved the forensic toxicological need of objective criteria, and constituted the beginnings of classical microchemical analytical methods in general. Analytical toxicology later became more-or-less an applied science, using developments of the classical disciplines analytical and physical chemistry, immunology and engineering.

Notwithstanding the enormous progress in our analytical ability the interpretation of analytical findings remains a persistent problem due to the biological variability. This is especially true regarding conclusions on the cause of poisonings in fatal cases where there is a possibility of murder. While generalizations can be made about toxic risks for populations using statistical methods, reaching a conclusion about an individual case based on a range of statistical data remains a matter of probability instead of certainty: the same concentration of a poison in blood may have been found already in lethal cases as well as in surviving persons.

This represents a certain discrepancy between the nowadays common accuracy and precision of- so to say- unequivocal analytical results and the relative character of poisons as a category (whose action depends always on several conditions).

But analytical toxicology is undoubtedly one of the pillars of multidisciplinary toxicology and their applications in medicine, ecology and in the protection of the environment, in doping analysis, in control of agricultural and food control. Research still aims to fill gaps in our knowledge. *Natura non salta* ('nature does not jump') and perhaps the future will bring the explanation for some natural variation, - e.g. in the activity (qualitively and quantitatively) of drugs and poisons which cannot yet be completely understood.

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