Famous Poisonings In History

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Editor's Foreword

The history of pharmacology is deeply intertwined with the history of poisons. Few topics so strikingly bridge mythology, medicine, and political intrigue as the use of toxins throughout the centuries. In his compelling article ***"Famous Poisonings in History"***, Professor Dr. Arturo J. Brugger Aubán from Valencia, Spain guides us through this fascinating intersection of science and human ambition, shedding light on how poisons have shaped civilizations, altered the course of power, and driven the evolution of toxicology as a scientific discipline.

Professor Brugger's authority in the field is unquestionable. A Doctor of Medicine and Professor of Pharmacology at the University of Valladolid (1977) and the University of Murcia (1980–2003), he holds the official title of Specialist in Clinical Pharmacology and has long focused on the molecular mechanisms of pharmacological agents. His distinguished career includes membership in the *Royal Academies of Medicine and Related Sciences of both Murcia and Valencia*, as well as active involvement in the *New York Academy of Sciences*. As a contributor to the *International Encyclopedia of Pharmacology* and supervisor of 47 doctoral theses—each awarded the highest distinction, with two receiving extraordinary honors—his impact on generations of scientists is profound.

Professor Brugger, who was my pharmacology teacher during my medical studies at the University of Murcia in Spain, has published over 170 scientific articles in high-impact journals and contributed chapters to eight leading pharmacology textbooks. His academic contributions extend beyond the laboratory and lecture hall: he has been an invited speaker at international congresses on topics such as uterine motility and fetal well-being, reflecting the breadth of his expertise.

In this article, he unites historical narrative with pharmacological insight to explore how poisons—from the mythological aconite of Medea to the refined toxic compounds used by European aristocracies—have not only caused suffering but also spurred scientific advancement. His discussion of classical toxicology, natural toxins, and the evolution of forensic methods reminds us that poisons, while feared, have also driven the progress of pharmacological science.

I invite readers to delve into this work not only as a chronicle of human history's darker chapters, but as a testament to the enduring importance of pharmacological knowledge. Professor Brugger's scholarship bridges past and present, science and society, in a way that enriches our understanding of both medicine and mankind.

As a former student of Professor Brugger and the current Editor-in-Chief of the Swiss Journal of Radiology and Nuclear Medicine, I am honoured to introduce this work.

Bern, Switzerland, June 2025

Frank Mosler

Abstract

The use of poisons spans human history, serving as tools for war, execution, assassination, revenge, and political control. Ancient texts like the "Rig Veda" mention poisoned weapons, and many civilizations used natural toxins—such as frog skin, snake venom, and plant extracts—for lethal purposes. Mythology reflects deep knowledge of poisons. Medea attempted to poison Theseus with aconite to protect her son's claim to the throne. Hercules used Hydra's venom to create deadly arrows. In historical contexts, figures like Socrates were executed with poison—hemlock in his case—which was reserved for elite criminals due to its cost. Classical toxicology began in Ancient Greece and continued through the Roman Empire. During Rome's imperial era, poisons were commonly used in power struggles. Tiberius' reign saw

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suspected poisonings of his potential successors, including Germanicus and Drusus. Caligula ultimately rose to power through such intrigue, killing his rivals. Notable toxicologists include Mateo Orfila, who advanced forensic detection techniques in the 19th century, and Juan Bautista Peset Aleixandre, who developed early devices to detect toxic gases in the blood. Natural poisons were also studied in modern science. Cobra venom contains dozens of toxic proteins, many of which disrupt nerve and muscle function. Aconitine, found in "Aconitum napellus", binds to sodium channels in nerves, keeping them open and causing fatal disruptions in cell signaling. Another plant-based toxin, protoanemonin from buttercups, causes painful spasms and ulcers, giving rise to the term "sardonic smile". In Renaissance and Baroque Europe, poisoners like Locusta in Nero's Rome and La Voisin in Louis XIV's court gained notoriety for their lethal skills. They supplied aristocrats with toxic mixtures to remove rivals or secure inheritances. One infamous potion, "Aqua Tofana", was linked to hundreds of deaths, possibly including that of Mozart. Venice's secretive Council of Ten used poison for state security, relying on anonymous citizen reports and aconite-based poisons. In France, women like the Marquise de Brinvilliers and La Voisin were executed for mass poisonings. These individuals often disguised their poisons as medicine or spiritual remedies, exploiting trust and social status. Through myth, science, and scandal, poisons have left an indelible mark on human history, both as instruments of death and as subjects of fascination and fear.

Keywords: *poisoning, history, celebrity*

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Inaugural address

Arturo J. Brugger Aubán
Professor of Pharmacology
Valencia, 2014 — Inaugural address upon admission as Honorary Academician at the Royal Academy of Medicine of the Valencian Community

Distinguished President of the Royal Academy of Medicine of the Valencian Community,
Honourable Deputy Mayor of the City of Valencia,
Honourable Vice-President of the Valencian Parliament,
Illustrious President of the Valencian Medical Institute,
Illustrious Academics, fellow alumni from Colegio del Pilar,
Classmates from our medical studies,
Ladies and gentlemen, dear friends who join me in this solemn act of my appointment as Honorary Academician of this prestigious institution, I am deeply honoured.
Dear José Luis, thank you very much for your kind introduction, undoubtedly inspired by a strong friendship.

When we reach what is often called the "third age"—which I personally think of as a mature youth—it is customary to look back and remember the teachers who, in one way or another, shaped my professional life. To all of them, my sincere thanks.

It would also be unfair not to mention the crucial role played by my beloved wife. With her understanding and support, she shared in my endeavours, devoting the best years of her life to a man absorbed in the daily work of research and study.

I would like to thank everyone present today for attending, once again affirming our mutual friendship and affection. Thank you all very much.

Valencia, 2014

Introduction

Poisons have been widely used throughout the ages of humanity: as weapons to defeat enemies, in hunting, as tools of execution, for mass extermination, suicide, elimination of rivals, acts of revenge, and even to hasten inheritance. Even today, poisonous substances are used in executions or to dispose of dissidents and inconvenient individuals in certain political regimes.

The Rig Veda, a sacred book of India written 3,600 years ago, describes the use of arrows and javelins dipped in aconite extract. Other civilisations and cultures poisoned their arrows or darts with substances that had empirically proven their lethal power: frog skin, viper venom, red ants, etc.

Poisons occupy a prominent place in mythological legends, which reflects the creators' deep knowledge of their effects. Medea, daughter of King Aeëtes of Colchis and the nymph Asterodia, after separating from Jason, joined Aegeus, King of Athens. She attempted to kill Theseus, the king's eldest son, by offering him a cup containing aconite extract, in defence of her own son Medus' right to the throne. The king recognised his son, who had returned in disguise and was carrying his sword, thus preventing the poisoning. (**Fig. 1**) Medea offers a cup of poison to Theseus.



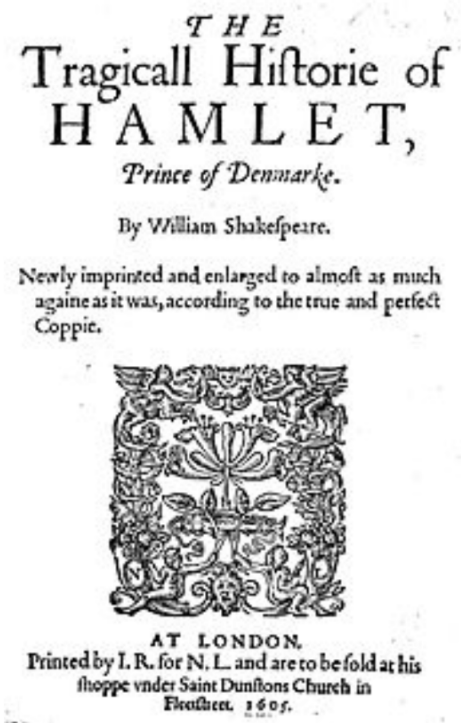
Figure 1: *Medea offers a cup of poison to Theseus*

Another myth tells of Hercules' victory over the Lernaean Hydra **(Fig. 2)**, with whose blood he poisoned the arrows he later used in battle against the Titans. One of these arrows accidentally wounded the centaur Chiron, causing him an extremely painful wound that would not heal. Chiron had to renounce his immortality in order to put an end to his suffering.

Poison has also occupied a prominent place in literature. William Shakespeare (1564–1616), in *"The Tragic History of Hamlet, Prince of Denmark"*, has the ghost of the Prince's father reveal to his son that he was poisoned: *"Thy uncle crept upon me in the hour of my rest, and with a vial of cursed poison in his hand, poured the leprous distillment into mine ear"* – Scene XII. It was probably an extract of henbane **(Figs. 3 & 4)**.



Figure 2: *Hercules fighting the Lernaean Hydra*



THE
Tragicall Hiſtorie of
HAMLET,
Prince of Denmarke.

By William Shakeſpeare.

Newly imprinted and enlarged to almoſt as much againe as it was, according to the true and perfect Coppie.

AT LONDON.
Printed by I. R. for N. L. and are to be ſold at his ſhoppe vnder Saint Dunſtons Church in Fleetſtreet. 1605.

Figure 3: *Cover of "Hamlet", 1605 edition*

In The Tragic Tale of Romeo and Juliet, Romeo says:

"Thou desperate pilot, now at once run on
The dashing rocks thy sea-sick weary bark!
Here's to my love! \[Drinks]
O true apothecary!
Thy drugs are quick. Thus with a kiss I die."
Act V, Scene III.

The poison is unidentified, possibly an extract of aconite, due to its rapid effect.

Oscar Wilde (1854–1900), in *The Canterville Crime of Lord Arthur Savile*, creates a complex plot and describes the toxic properties of aconite, although Lord Arthur never actually uses it.

In the 20th century, numerous writers of what were then known as detective novels—now referred to as crime or noir fiction — described poisonings involving a wide range of toxic substances, from arsenic to thallium, including carbon monoxide, cyanide, strychnine, curare, and others.



Figure 4: *Henbane flowers (Hyoscyamus niger) hyoscyamine*

Their works demonstrate extensive knowledge of these substances' toxic power and the methods of administering them to achieve lethal effect. Sir Arthur Conan Doyle was an ophthalmologist, Richard Austin Freeman a physician, Edgar Wallace served in the Army Medical Corps, and Agatha Christie was both a nurse and a pharmacist — circumstances which gave them broad knowledge of toxic sub-stances **(Fig. 4a)**.

Setting aside these literary observations and focusing on the core of this lecture, we shall define a series of terms related to the subject.
Poison can be defined as a highly potent toxin, used as a harmful agent, a weapon for carrying out judicial sentences, a deceitful tool for revenge, or an accelerator of death for political, financial, or suicidal purposes.

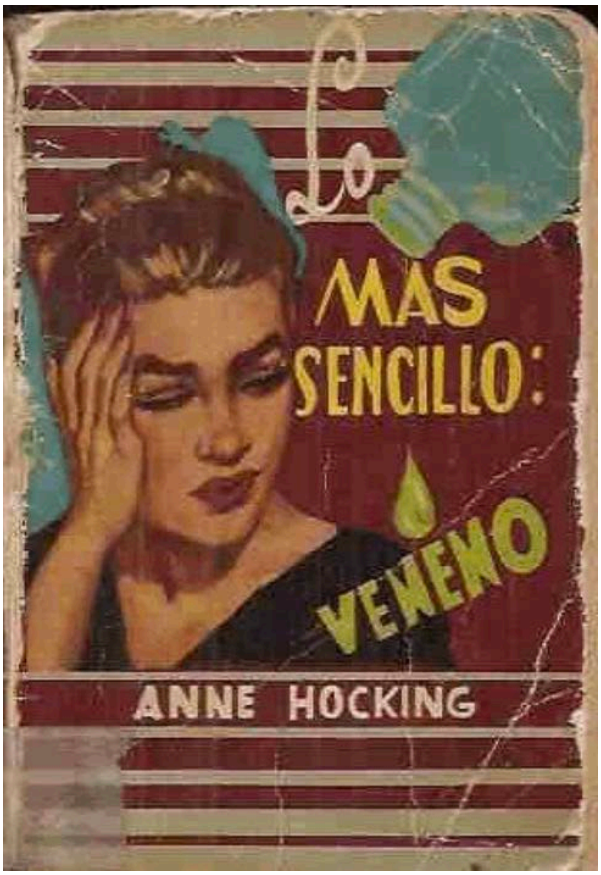


Figure 4a: *Cover of a novel*

Toxicology is the science that studies poisons, as defined by the Menorcan José Mateo Buenaventura Orfila (1787–1853), professor at the *"Faculté de Médecine de Paris"*, in his book *"Traité des Poisons"*. Years later, Pedro Mata (1811–1877), in his book "*Legal Medicine"*, defined it as: *"Toxicology is the science that deals with poisoning and the substances that cause it."* A more modern and precise definition was provided by the Valencian professor Juan Antonio Gisbert Calabuig (1922 – 2000): *"The science that*

studies toxins and poisonings; it investigates the toxic agent, its origin, its properties, its mechanism of action, the consequences of its harmful effects, methods of analysis and identification, and its prevention in the workplace. (1)"

A toxic substance is any substance capable of causing serious alterations in the physiology of a living being. Toxins may be natural or synthetic. According to Theophrastus Philippus Aureolus Bombastus von Hohenheim, better known as Paracelsus: *"Nothing is poisonous, everything is poisonous: the difference lies in the dose."* To this we may add: it also depends on the route of entry into the body, as well as the circumstances of the individual receiving it. A few examples help illustrate this assertion. Curare, used by the indigenous peoples of the Amazon rainforest **(Fig. 5)**, is a highly polar compound containing two quaternary ammonium groups **(Fig. 6)**, which means it cannot be absorbed orally. However, just a small amount (in milligrams) applied to a dart or arrow is enough to paralyse an animal, which can then be eaten safely by humans.



Figure 5: *Indigenous people of the Amazon hunting*

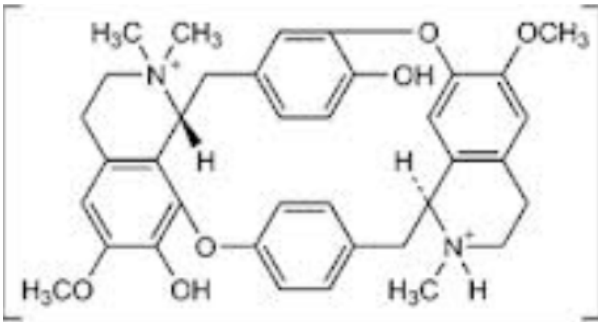


Figure 6: *Tubocurarine molecule*

In the year 1800, Alexander von Humboldt had the opportunity to witness the preparation of this poison. He tasted it, found it bitter, but experienced no ill effects — since, as previously mentioned, tubocurarine is not absorbed through the digestive tract. Today, chemical substances with a similar structure are widely used in surgery as muscle relaxants.

Medications that are initially only mildly toxic can become fatal in newborns, whose enzymatic systems responsible for inactivating and eliminating such substances are not yet fully developed. Similarly, this can occur in individuals with hepatic or renal insufficiency, or other pathologies. Even seemingly harmless substances can be dangerous: for instance, sodium bicarbonate can cause severe alkalosis when ingested in excessive amounts. Another example is liquorice, whose extract was used to treat stomach ulcers in the mid-20th century. It has since been found to have other promising properties, such as anti-cancer effects, liver protection, and improvement of cerebral ischaemia after trauma (2, 3, 4 and 5). However, excessive consumption can lead to severe intoxication, as its main component, glycyrrhizic acid, has a chemical structure similar to mineralocorticoids **(Fig. 7)**.

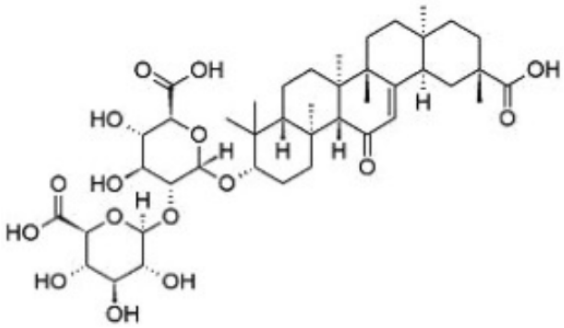


Figure 7: *Glycyrrhizic acid*

As a result, it can induce pseudoaldosteronism, with symptoms including hypertension, electrolyte imbalances, and severe hypokalaemia. This is due to the coexistence of three mechanisms of action:

1. Inhibition of 11β-hydroxysteroid dehydrogenase type 2, which converts cortisol to the less active cortisone;
2. Inhibition of 5β-reductase, which metabolises aldosterone; and
3. Binding to renal mineralocorticoid receptors, thereby activating them (6) **(Fig. 8)**.

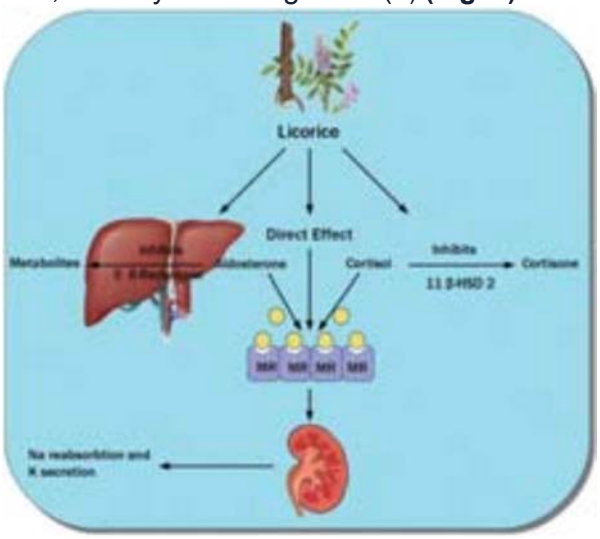


Figure 8: *Mechanism of action of glycyrrhizic acid*

Hypertension may in turn lead to intracranial haemorrhage and cerebral oedema (7, 8, 9 and 10).
The resulting electrolyte imbalances cause sodium retention, oedema, excessive potassium loss, muscle weakness, and even rhabdomyolysis (11 and 12).

Hammurabi, king of the Sumerians (1792–1750 BC), included in his famous code — engraved on a large basalt monolith — not only laws and rules for daily life, but also medicinal treatments and descriptions of toxic substances or poisons, generally of plant origin, used to carry out death sentences. The Ebers Papyrus (1500 BC) is a true treatise on medicine and surgery, compiled by Egyptian physicians on a hemp paper scroll measuring 20 metres in length and 30 centimetres in height. It describes more than 700 substances, mostly of plant origin, with healing or toxic properties. It is both surprising and remarkable that it also serves as a treatise on public health in Ancient Egypt, where the state funded healthcare, doctors were salaried, and they enjoyed great prestige and respect from the public.

Among our own historical figures, there have been renowned toxicologists, such as the Menorcan Mateo José Buenaventura Orfila (1787 – 1853), Professor at the Sorbonne, who played a decisive role in the trial of the poisoner Madame Lafarge, having detected arsenic in her husband's bones using the Marsh test. Another was the Valencian Juan Bautista Peset Aleixandre (1886 – 1941), Doctor of Medicine, Science, and Law, chemical and mechanical expert, Professor of Legal Medicine and Toxicology, and Rector of the University of Valencia. Drawing on his deep expertise, he designed the first device for detecting and measuring toxic gases in the blood, which was built under his supervision by the Jena glassworks **(Fig. 9)**.



Figure 9a: *table listing a series of historical milestones in toxicology*

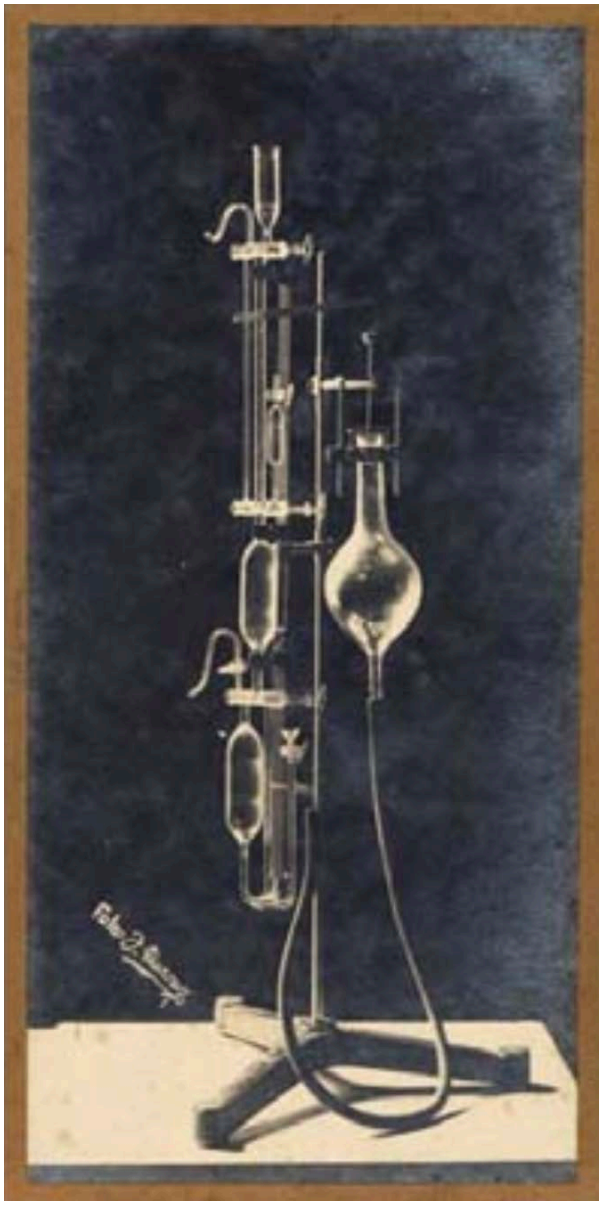


Figure 9: *Device for detecting toxic gases in the blood, designed by Dr Peset*

Fig. 9a shows a table listing a series of historical milestones in toxicology, which the authors considered relevant. These were compiled in 2005 by Steven G. Gilbert and Antoinette Hayes from the Institute of Neurotoxicology and Neurological Disorders and Northeastern University, respectively. However, due to the large volume of accumulated information, it is not easy to read or fully comprehend.

Historically, the use of poisons can be divided into three fairly well-defined periods: The first corresponds to the Classical World, from 4th century BC Greece until the decline of the Roman Empire in the 2nd century AD. The second spans from the turbulent late Middle Ages to the end of the 17th century. The third, which may be considered the modern era, begins in the late 19th century and likely continues to this day **(Fig. 8a)**.

We will now describe, without aiming to be exhaustive, some poisonings that have left a mark on history, either due to the individuals involved or the methods used.

In 4th century BC Greece, justice employed hemlock to carry out death sentences in a clean and relatively bloodless manner. However, due to the high cost and difficulty of preparing this poison, it was used sparingly and only in cases involving prominent citizens — such as the philosopher Socrates. His teachings, preserved by his disciples, remain relevant today. After the fall of the Thirty Tyrants, whose regime he had opposed, a fragile and unstable democracy was restored. Socrates' behaviour and philosophy earned him enemies among the aristocracy, the government, and even his own disciples, some of whom considered their association with him dangerous.

Accused of impiety — of not respecting the gods — and of corrupting the youth, he was sentenced to death. Though he could have escaped the penalty, his excessive pride led him to accept it. Plato, unable to bear witnessing the execution, faithfully recounts the events in *"Phaedo"*, based on the testimonies of other disciples who were present.

After drinking the hemlock given to him by the executioner **(Fig. 10)**, Socrates asked: *"Well, my friend, what must I do?"*

The executioner replied:
"Walk around until your legs begin to feel heavy. Then lie down, and the poison will do the rest."

Indeed, the paralysis ascended until the intercostal muscles and diaphragm ceased to function, making breathing impossible, and thus death ensued. It is believed that the hemlock was administered in an alcoholic drink, mixed with opium, to soften the convulsions and suffering caused by asphyxiation. This took place in the year 399 BC (13, 14, 15).



Figure 10: *The poisoning of Socrates in the presence of his disciples*

Hercules advises Dionysus to drink hemlock in order to enter Hades, as recounted by Aristophanes in his comedy *"The Frogs"*, written in 404 BC.
Hemlock (Conium maculatum) contains as its main active compound an alkaloid called coniine, which has a chemical structure similar to that of nicotine. Like nicotine, it activates nicotinic cholinergic receptors by depolarising the cells of effector organs that possess these ligand-gated ion channels (Na^+ channels) **(Fig. 11)**.
When acetylcholine or any other nicotinic agonist (e.g., coniine, nicotine, succinylcholine) binds to these receptors, the Na^+ channel opens, depolarising and stimulating the effector cell. If depolarisation persists, the cell becomes inactivated, leading to paralysis in the case of muscle tissue. The difference between the action of acetylcholine and that of the other compounds mentioned is that acetylcholine is rapidly degraded, allowing repolarisation and thus enabling an on-off cycle required for voluntary muscle contraction — something that becomes impossible after exposure to these depolarising agents (16).

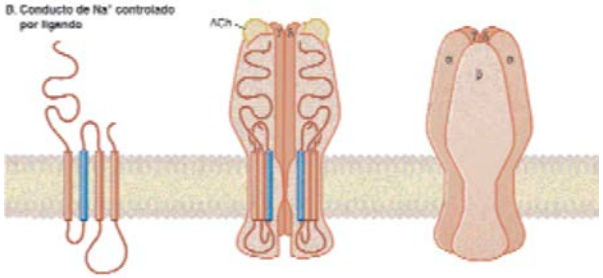


Figure 11: *Nicotinic cholinergic receptor, ligand-gated ion channel*

Hemlock also contains other toxic, non-alkaloid substances that contribute to its lethal effects, such as cicutoxin — a polyunsaturated hepadecadienol that acts as a potent non-competitive GABA antagonist. It crosses the blood – brain barrier and causes tremors, convulsions, and death (17, 18).

Hemlock also gained attention in the 18th century when paediatrician George Armstrong tested its use in treating whooping cough. A number of deaths occurred—curiously, the trials were carried out at the *Dispensary for the Infant Poor*, and never in his private practice (19).

Hemlock can also cause problems in livestock farming when free-ranging animals consume it along with other wild plants. Teratogenic effects have been reported, including skeletal malformations, cleft palate, etc., which vary depending on the stage of gestation during which the pregnant animals consumed the plant (20, 21). It causes paralysis and death in cattle, pigs, sheep, goats, rabbits, and can even be lethal to certain insects (16, 22).

It has been 2413 years since the death of Socrates, and in some U.S. states, one of the components — though not the only one — of the lethal injection (pancuronium) produces the same effects as hemlock, albeit through a slightly different mechanism of action. Pancuronium is a rigid molecule with two quaternary ammonium groups **(Fig. 12)**,

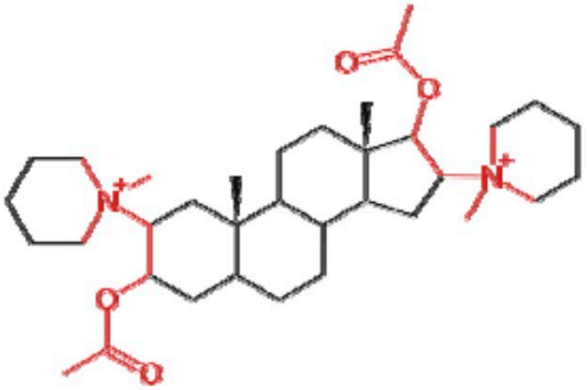


Figure 12: *Chemical structure of pancuronium showing the quaternary ammonium groups. The parts of the molecule that replicate the structure of acetylcholine are highlighted in red.*

which bind to the acetylcholine binding sites on the nicotinic receptor at the neuromuscular junction **(Fig. 13)**, preventing its activation and subsequent depolarisation. The result is the same: flaccid paralysis of the skeletal muscles. However, in this case, the muscle paralysis is easily reversible with the use of a cholinesterase inhibitor (23), as ob-

served in numerous clinical trials and doctoral theses we have conducted in collaboration with the Department of Anaesthesiology at the Virgen del Rosell Hospital, investigating the relationship between the pharmacodynamics and pharmacokinetics of various neuromuscular blocking agents **(Fig. 14)**.

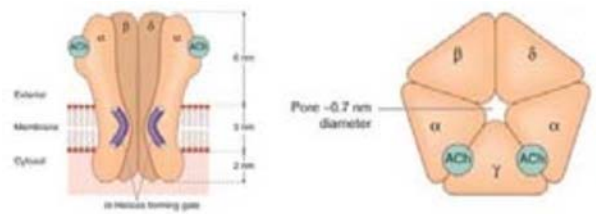


Figure 13: *Schematic representation of a nicotinic receptor, highlighting the acetylcholine binding sites, which are the anchoring sites for pancuronium.*



Figure 14: *Inhibitory effect of rocuronium on muscle contraction, similar to pancuronium, and its rapid reversal by a cholinesterase inhibitor.*

Another important aspect is that, as a compound with two quaternary ammonium groups, pancuronium is highly polar and does not cross the blood – brain barrier, and thus has no effect on the central nervous system. It is also not absorbed through the digestive tract. This compound has also attracted media attention, often inaccurately, as many journalists, lacking the necessary scientific background or information, make glaring factual errors. For instance, Kile Munzenrieder reported in the *Miami New Times* that a hospital was sued over the accidental injection of a drug used in executions.

The incident occurred as follows: On 30 July 2010, Richard Smith, a 79-year-old man, was admitted to the North Shore Medical Center with severe stomach pain. A nurse mistakenly injected him with pancuronium instead of famotidine, a gastric acid secretion inhibitor. The paralysing effects of the pancuronium were quickly reversed using a cholinesterase inhibitor **(Fig. 14)**, and the patient was discharged (25). However, he died a month later — possibly due to an unrelated pathology. This circumstance was used by journalists to blame the hospital and the nurse, and by the family to file a claim for compensation. Clearly, pancuronium could not have been the cause of death, as the newspaper headline falsely suggested (24).

During the 4th, 3rd, and 2nd centuries BC and beyond, the use of poisons was widespread. One such case was the death of Cleopatra, who was in her chamber accompanied by her handmaidens Iras and Charmian. There are various versions regarding where the snake bit her. The romanticised version — on the left breast, closer to the heart **(Fig. 16)** — is not supported; the prevailing theory is that the cobra delivered its venom into the veins of her arm. These events cannot be confirmed, as the tomb of Cleopatra and Mark Antony has never been found. Cleopatra died within minutes, embracing the lifeless body of Mark Antony — a romantic end to an extraordinary life.

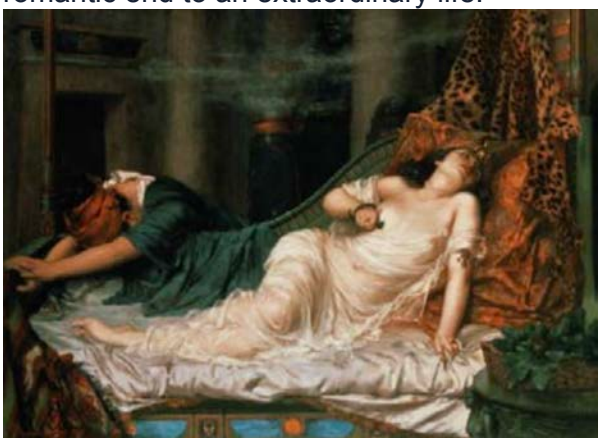


Figure 16: *Poetic depiction of Cleopatra's death*

The venom of cobras—and of elapids in general (a family of highly venomous snakes)—is highly complex. Proteomic analyses reveal that it contains 76 proteins grouped into 9 families. These include several paralysing neurotoxins, proteases, L-amino acid oxidases, muscarine-like toxins, phospholipases, metalloproteinases, cardiotoxins, cytotoxins, and others (27). Most of these are what are known as three-finger toxins (3FTx), which exert a range of effects on physiological pro-

cesses. Some resemble plasminogen activators found in prostate and testicular extracts and exhibit strong fibrinolytic activity (28). Others are neurotoxins that block pre- and postsynaptic nicotinic receptors (29), leading to flaccid paralysis (30, 31).

Interestingly, some proteins in the venom, although not toxic themselves, dramatically enhance the effects of the neurotoxins by forming highly active complexes with them (30). There are also toxins that block adrenergic and muscarinic receptors, calcium channels, and acetylcholinesterase (32). Cytotoxins and cardiotoxins lyse numerous cell types and depolarise cardiomyocytes (33), disrupting the lipid bilayer of cell membranes by binding to phosphatidylserine **(Fig. 17)**, ultimately causing cell death (33). All these actions combined can lead to death within minutes. While antivenoms do exist, they must be administered rapidly in order to neutralise the toxins effectively, as explained in an article by the Australian researcher Kornhauser and colleagues in *Basic & Clinical Pharmacology & Toxicology* (34).

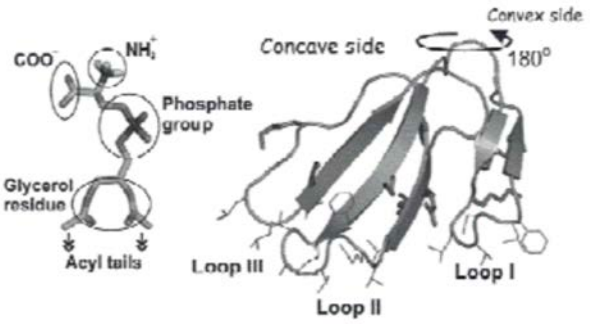


Figure 17: *Representation of the interaction between cardiotoxin (three-finger toxin) and phosphatidylserine*

After the defeat of the combined forces of Mark Antony and Cleopatra VII and their subsequent deaths, Octavian returned to Rome and declared himself emperor under the name Caesar Augustus. This marked the beginning of the Roman Empire — a period filled with intrigue, conspiracies, incest, assassinations, and poisonings.

Octavian was succeeded by Tiberius, during whose reign several of his natural heirs were poisoned. Germanicus, his nephew, was poisoned by Gnaeus Calpurnius Piso, although the specific poison used is not known. Agrippina the Elder, wife of Germanicus, suspected that Tiberius had orchestrated the poisoning to favour his own son, Drusus the Younger, in the line of succession. Drusus was married to Livilla, Germanicus's sister and alleged lover of Sejanus, who persuaded her to poison her husband.

After the deaths of Germanicus and Drusus the Younger, the imperial succession fell jointly to Tiberius's grandson and great-nephew — Tiberius Gemellus and Caligula. Caligula, however, conspired with Macro and smothered Emperor Tiberius with a pillow.

Once in power, Caligula ordered the murder of his cousin Tiberius Gemellus, becoming the sole ruler of the Roman Empire. His excessive spending, debauchery, and cruelty eventually led the Praetorian Guard to conspire against him and carry out his assassination.

With Caligula dead and most of his relatives executed, his uncle Claudius—who had hidden in the palace — was discovered behind a curtain by the Praetorian soldier Gratus and proclaimed emperor. He was later officially recognised by the Senate.

Caligula had a sister, Agrippina the Younger, who was first married to the Roman consul Enobarbus, who famously remarked, *"From my union with Agrippina, only a monster can be born."* And indeed, Nero was born. Agrippina would later play a major role in imperial affairs by marrying Claudius.

Claudius, from his third marriage to Messalina, had a son named Britannicus. After repudiating and executing Messalina for promiscuity, Claudius married his niece, Agrippina the Younger, and adopted her son, Nero.

An ambitious woman, Agrippina aimed to secure the imperial throne for her son Nero at the expense of Claudius's biological son, Britannicus. She flattered Claudius into naming Nero his heir. Around this time, a Gallic slave named Locusta — who had been condemned to death — was imprisoned. She had grown up in the countryside and possessed deep knowledge of the toxic properties of plants and minerals. Locusta had tested poisons on animals and even on slaves. Like Mithridates, she also ingested small doses of toxins to immunise herself against their effects.

Agrippina, aware of Locusta's abilities, offered to free her in exchange for helping her eliminate her aging husband, Claudius. Lo-

custa agreed, desperate to escape execution. It was October, and mushrooms —Claudius's favourite delicacy — were in season. Locusta prepared a dish of mushrooms, some of which included the highly toxic and deadly *Amanita phalloides*. After the official food-taster sampled only the harmless ones, Emperor Claudius **(Fig. 15)** devoured the rest of the dish with great appetite.

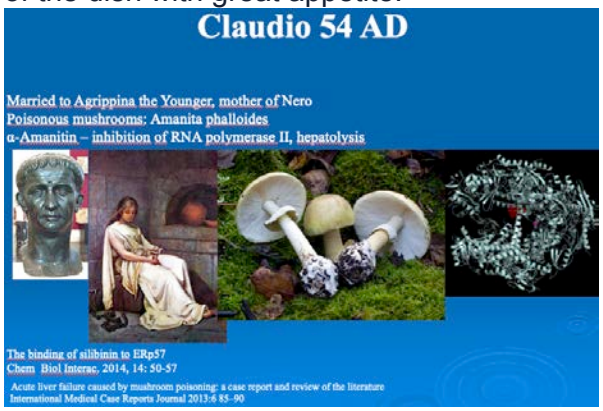


Figure 15: *Roman Emperor Claudius poisoned by mushrooms*

Soon after, he began to feel unwell, and his condition gradually worsened until he died three days later. It is likely that, in addition to the poisonous mushrooms, Locusta also added another toxin to the dish, as the symptoms did not exhibit the typical latency period associated with *Amanita phalloides* poisoning.

The *Amanita phalloides* mushroom synthesises a group of cyclopeptides **(Fig. 18)**, known as α-amanitin and β-amanitin, both of which are highly toxic, with α-amanitin being the more potent of the two. A dose as small as 0.1 mg/kg is sufficient to cause the death of an adult. α-Amanitin irreversibly occupies and blocks the active site of RNA polymerase type II **(Fig. 19)**, thereby halting protein synthesis (35).

The first cells affected are those of the gastrointestinal tract, resulting in vomiting and diarrhoea after a latency period of 6 to 8 hours. Hepatocytes are then affected, leading to hepatolysis. Hepatoenteric circulation prolongs the toxin's presence in the body, and kidney damage (hepatorenal syndrome) along with hepatic encephalopathy may follow. Blood tests reveal elevated levels of aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase — these enzyme levels help to assess the prognosis of the intoxication. Severe ionic imbalance and marked acidosis are also observed (36).

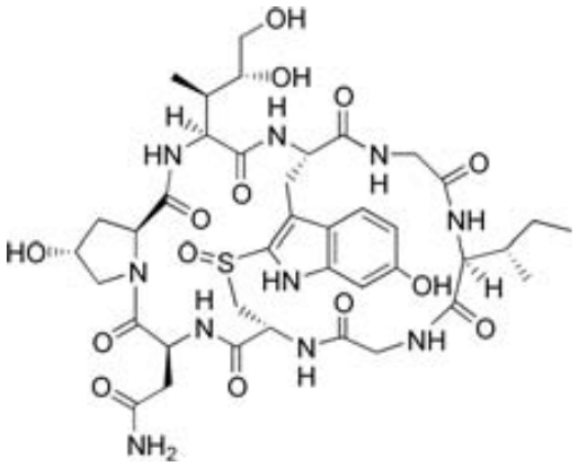


Figure 18: *α-Amanitin*

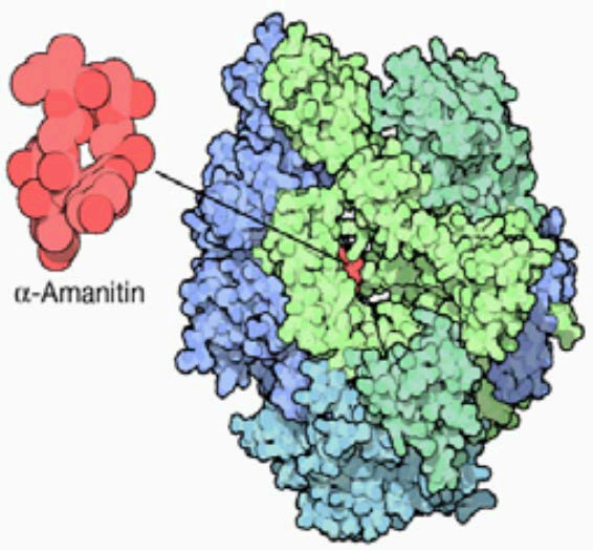


Figure 19: *Blockage of the active site of RNA polymerase type II by α-amanitin*

Treatment must begin very early; if more than 24–30 hours have passed, liver transplantation is virtually the only option—and even that is not always successful (37). Plasmapheresis has also shown poor outcomes. Several hepatoprotective drugs have been tested, including N-acetylcysteine, benzylpenicillin, thioctic acid (α-lipoic acid — a powerful antioxidant and free radical scavenger extracted from hops), cimetidine, and silibinin (38), although these do not always yield positive results (39).

Of particular interest is silibinin, a flavolignan extracted from the leaves, flowers, and seeds of milk thistle (Silybum marianum, **(Fig. 20)**. Structurally, it belongs to the flavanone class of compounds **(Fig. 21)**. Silibinin

binds to the protein disulphide isomerase ERp57, promoting the formation of the ERp57/REF1 complex, which protects against oxidative stress and supports the intracellular redistribution of ERp57 (40). When associated with the endoplasmic reticulum, ERp57 acts as a quality controller for newly synthesised glycoproteins, ensuring their proper folding and facilitating the formation of disulphide bonds in nascent glycoproteins (41). It also plays a role in the assembly of the major histocompatibility complex class I (MHC class I) and in DNA repair (42).



Figure 20: *Milk thistle*

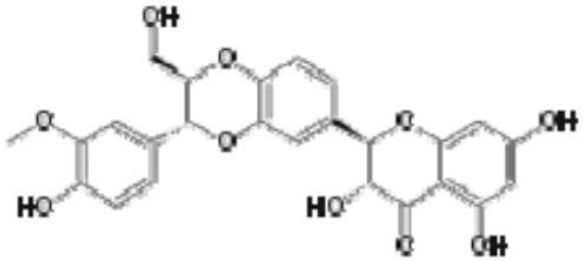


Figure 21: *Chemical structure of silybin*

Silibinin functions as a cellular protector in both the liver and kidneys (43). It has anti-inflammatory effects, shields epithelial tissues from irritants such as mustard agents (44) **(Fig. 22)**, and prevents UV-induced skin cancer (45). It is considered one of the treatment options of choice for all types of liver injury — including those caused by paracetamol — as well as for kidney damage resulting from chemotherapy with cisplatin or vincristine. Had these properties of milk thistle extract been known in the time of Claudius, he might have survived.

The interaction between silibinin and ERp57 —characterised by an almost nanomolar dissociation constant (40)—extends beyond cellular protection and protein quality control. Evidence suggests that it may also play a role in halting the development of melanoma (46) and breast cancer (47). Experimental studies have further shown that silibinin reduces the accumulation of β-amyloid plaques and the expression of the amyloid precursor protein (48).

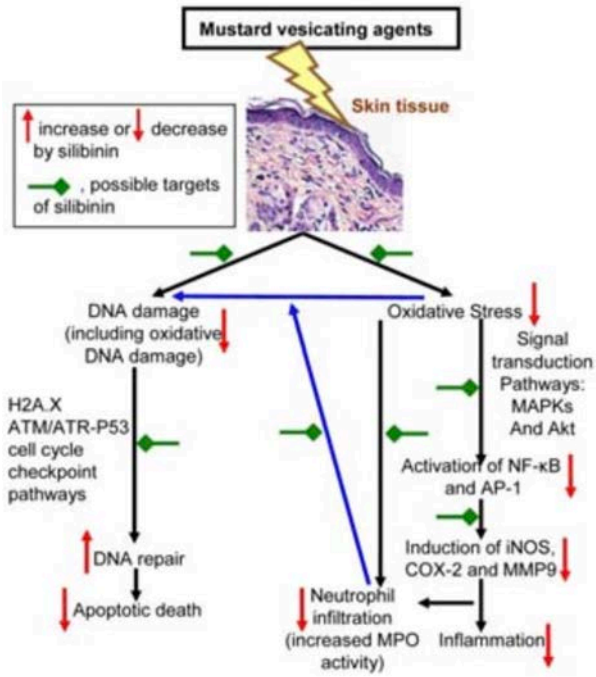


Figure 22: *Point of action of silibinin as a cellular protector*

Following the poisoning of Claudius, Locusta gained a prominent position in the imperial court, offering her expertise and services to wealthy patrician women who wished to rid themselves of rivals or unfaithful husbands. Nero, fearing that his cousin Britannicus might seize power, pressured Locusta to poison him. After an initial attempt that caused Britannicus nothing more than diarrhoea, Locusta — worried about possible reprisals from Nero — prepared a new potion with a high concentration of *sardonia*, the juice of a highly toxic buttercup species (*Ranunculus sceleratus*, **(Fig. 23)**.

Britannicus was served a dish that was deliberately too hot, so the official food taster ordered it to be cooled. Locusta used the opportunity to add the poison. Britannicus died within minutes, experiencing convulsions and a distorted facial expression resembling a forced grin (a *sardonic smile*), similar to that caused by tetanus toxin. This facial effect gave the poison its name. Nero claimed that Britannicus had died from an epileptic seizure, thereby becoming the sole emperor of Rome.



Figure 23: *Ranunculus scleratus, celery-leaved buttercup*

Sardonia, the juice of certain buttercup species, contains a glycoside called *ranunculin* — a simple molecule consisting of glucose and the lactone of γ-hydroxyvinylacrylic acid (49). It is highly irritating and toxic, even to insects, including some bee species that are not specialised in collecting pollen from buttercups (50). When hydrolysed and stripped of its glucose, the resulting lactone —*protoanemonin* **(Fig. 24)**—is even more active. It causes local blistering and slow-healing ulcers (52).

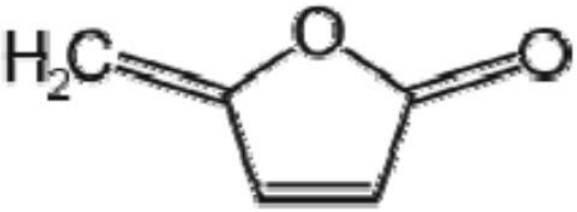


Figure 24: *Protoanemonin, a toxic compound found in buttercup species*

In India, professional beggars have been known to use it to keep wounds open in order to elicit greater sympathy (53), while some African tribes use buttercups in magical rituals to protect newborns from supposed diseases passed on by the mother's womb (54) — though the results are generally far from favourable. When ingested, it causes intense gastrointestinal pain, violent muscular contractions, and facial spasms that result in the characteristic *sardonic smile*.

There is no literature available on the toxic mechanisms of this substance — at least, I have personally been unable to find any. It appears that calcium redistribution might be involved, with a significant decrease in intracellular Ca^{2+} concentration, but studies have been conducted only on isolated vascular smooth muscle, making it risky to extrapolate the findings (55).

Buttercup species and other herbaceous plants that contain protoanemonin are responsible for what is known as "grass sickness" in horses in the United Kingdom (56), as well as for disorders in Irish cattle (57).

This potent poison has attracted the attention of homeopaths, who recommend it for weak, timid individuals longing for affection, those scrupulous in their habits, and for female ailments. However, like most homeopathic remedies, its effects should be no more than placebo. Still, caution is advised, as relatively serious studies warn that the daily limit should not exceed 180 µg, as exceeding this dosage could be dangerous (58).

Protoanemonin is a particularly intriguing compound: it spontaneously, or when exposed to heat, dimerises into anemonin **(Fig. 26)**, which is entirely harmless. In fact, it has been shown to possess anti-inflammatory properties and may even facilitate the recovery of brain neurons after a period of anoxia (59). These are experimental studies that may, in time, gain clinical relevance.

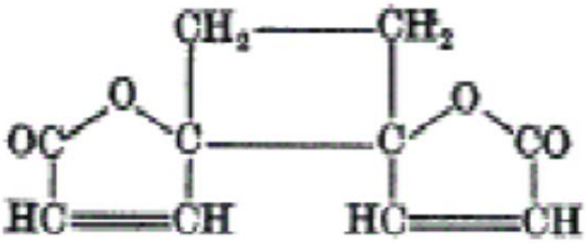


Figure 26: *Anemonin*

Locusta held a prominent position in Nero's court, assisting courtiers and patricians in eliminating inconvenient individuals. It is estimated that over 400 Romans died as a result of the potions prepared using the knowledge and dark arts of this botanical expert. When Nero committed suicide, the praetor Galba had Locusta arrested and ordered her to be torn apart by wild beasts. Nonetheless, her name became forever associated with devastation — Carl Linnaeus named the crop-destroying migratory locust *Locusta migratoria*. The Spanish word for locust, *langosta*, derives from the Latin *locusta*.

After the death of Nero, the Roman Empire entered a period of internal stability, although battles with border tribes continued. In 161

AD, Marcus Aurelius was proclaimed Emperor — the third Hispanic Emperor and the last of the so-called *"Five Good Emperors."* He died in Vindobona, present-day Vienna, from smallpox — not as portrayed in the two film versions of his death: "*The Fall of the Roman Empire"*, directed by Anthony Mann in 1964, or *"Gladiator"*, directed by Ridley Scott in 2000, both of which depict him as being poisoned.

He was succeeded by Commodus, a narcissistic and egocentric emperor obsessed with his physique and inclined toward extravagance and debauchery, depleting the imperial treasury through gladiatorial spectacles. His excesses provoked the anger of the military elite. At this point, the prefect Quintus Aemilius Laetus and the chamberlain Eclectus persuaded Commodus's lover, Marcia, to poison him. Commodus ingested the poisoned food but vomited it up and went to bathe. Fearing discovery of the plot and imperial retribution, the freedman Narcissus strangled him in the bath.

Middle Age

Leaving the classical period behind and entering the Middle Ages — a time equally rich in poisonings and prone to fantastical, unfounded stories—we encounter many accounts involving prominent families, often the targets of envious rivals hungry for power. These adversaries were willing to spread slander and legends that endured even centuries after their enemy's death.

In Rome, the Borgia family — originally Borja, from Valencia, which at the time held significant cultural and economic influence—had settled in the city after Pope Eugene IV appointed Alfonso de Borja y Cavanilles as a cardinal of the Curia. The Borjas, or Borgias in Italian, were not spared from the slanders and defamation spread by powerful Italian families who resented Spaniards occupying prominent positions in Rome and the Vatican.

Years later, Alfonso de Borja ascended to the Papacy under the name Callixtus III. He was an exemplary administrator who recognised the threat posed to Europe, but failed in his efforts to create a united Christian Europe to confront the Turks. Rivalries among the reigning monarchies prevented this vision from being realised. He rehabilitated the name of the Maid of Orléans (Joan of Arc), canonised Osmund, the Archbishop of Salisbury, and Saint Vincent Ferrer. Saint Vincent was 25 years older than Alfonso de Borja, and when the latter was still a child, he met the saint, who looked into his eyes and prophesied: *"You will be Pope, and you will raise me to the altars"* —as indeed happened (60).

Years later, Rodrigo de Borja was elected Pope under the name Alexander VI. He was a patron of the arts and sciences, a scholar of law and Canon Law, and a skilled diplomat. His election was met with enthusiasm by the Roman people, though not by the powerful families of the time (such as the Medici, Orsini, and Della Rovere). He supported the restoration and embellishment of churches, notably that of Santa Maria Maggiore, whose decoration is believed to have been funded with the first gold brought back by Christopher Columbus from the Americas. He skilfully resolved the dispute between Spain and Portugal over the division of the New World, issuing four papal bulls that led to the Treaty of Tordesillas.

Privately, however, this otherwise great pontiff led a life that was far from exemplary. He had several mistresses and numerous illegitimate children — though this was quite common among cardinals of the era. As the historian Dr. Ludwig Pastor remarked: *"A flawed setting does not diminish the intrinsic value of a gem."* Claims that his election was the result of vote-buying are unfounded. He did receive support from Cardinal Ascanio Sforza, whose cousin Giovanni had married the Pope's daughter, Lucrezia. The annulment of this marriage—allegedly unconsummated due to the husband's supposed impotence — was seen as an insult and provoked the wrath of the Sforza family, who then spread rumours of incestuous relations between Lucrezia and her father and brother, Cesare. These claims have no basis.

Likewise, the accusation that Alexander VI attempted to poison Cardinal Adriano da Corneto is not substantiated. Although several versions exist concerning his death — which occurred after a dinner at the cardinal's house — the most widely accepted explanation is that it was due to an infectious illness (possibly malaria), rather than poisoning. It is true that nearly all those present

at the dinner fell ill, but only Pope Borgia died (60).

His successor, Pius III, held the Papacy for only 26 days, and it is suspected that he may have been poisoned by Pandolfo Petrucci, an ally of the powerful Cardinal Giuliano della Rovere — an implacable enemy of Rodrigo Borgia. After Pius III's death, della Rovere was elected Pope in the shortest conclave in history (lasting just a few hours), taking the name Julius II.

Lucrezia Borgia, a highly cultured and beautiful woman, was merely a tool used by her father to forge alliances with the powerful families of the time. Her first marriage to Giovanni Sforza did not bring Pope Alexander VI the political advantages he had hoped for, and he declared the marriage null on the grounds of the husband's impotence. This enraged the powerful Sforza family, who launched a campaign of slander, accusing Lucrezia of incestuous relationships with both her father and her brother Cesare. They also portrayed her as a master intriguer with a deadly skill in administering poison—specifically a substance known as *cantarella*, which she was said to carry in a hidden compartment of an ornate ring.

These calumnies were popularised by Victor Hugo in his 1833 play "*Lucrezia Borgia*", by Gaetano Donizetti's opera of the same name based on Hugo's work, and more recently in Mario Puzo's purportedly historical novel "*The Family*" (2001). The truth, however, is far removed from these fictions. Lucrezia was a learned woman with expertise in botany, science, the arts, and literature. After her second husband was tragically stabbed to death by five masked men, she eventually married Alfonso d'Este, heir to the Duchy of Ferrara. As Duchess, she became a model of virtue, charity, and devotion to the sick, widely praised for her kindness and nobility (60).

In the Most Serene Republic of Venice, the Council of Ten governed with a firm hand during a period spanning from 1310 to 1797. It was both a legislative and executive body composed of ten members elected by the Grand Council of Venice (*Maggior Consiglio*) and presided over by the Doge. The council was renewed annually to avoid undue influence and corruption. It operated in secrecy and was not accountable to the courts of the Venetian Republic. Its rulings were final, swift, and, in some cases, included immediate executions. Some executions were public; others were carried out in secret by anonymous executioners, often through night-time drownings in the Venetian Lagoon. On occasion, poison was used — most often aconite extract.

In various locations, there existed a type of mailbox known as the *Bocca di Leone* (*"Lion's Mouth,"* **Fig. 27**), which resembled the mail slots still found in many postal offices. One such example still survives today in the Doge's Palace. Citizens could anonymously deposit accusations of crimes and conspiracies against the Most Serene Republic in these boxes. The Council of Ten would carefully analyse and investigate these reports, and, where warranted, issue the appropriate sentence. In cases where a death sentence was imposed, aconite extract was often the method of execution.



Figure 27: *Anonymous complaints box in the Doge's Palace (Bocca di Leone).*

Aconite (Aconitum napellus) is a perennial herbaceous plant that can grow up to one meter tall. It has striking, deep blue flowers **(Fig. 28)** and root tubers that resemble turnips — hence the name. All parts of the plant are extremely poisonous, containing a series of alkaloids, the most potent and toxic of which is aconitine. As little as 1 mg can be fatal to an 80 kg adult.



Figure 28: *Aconitum napellus (Photograph courtesy of Prof. Morales Olivas.*

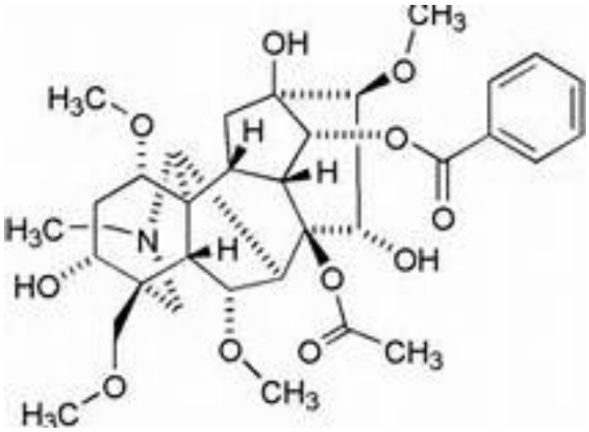


Figure 29: *Chemical structure of aconitine.*

Aconitine is a pseudoalkaloid diesterditerpene with a complex structure **(Fig. 29)** that belongs to the group of neurotoxins. It has a specific receptor located on the voltage-gated sodium channel, to which other neurotoxins such as batrachotoxin and veratridine can also bind — some of which are even more potent than aconitine itself. Once bound, these substances inactivate the sodium channel (61, 62), causing it to remain open and allowin ntinuous influx of Na^+ ions into excitable cells. This blocks repolarisation, severely disrupting cellular electrophysiology (63).

The voltage-gated sodium channel has a tubular structure, like all cellular ion channels. However, unlike the nicotinic receptor **(Fig. 13)** or the GABA receptor, which also function as ion channels, the sodium channel is composed of six subunits or domains rather than five. Its α-subunit contains six receptor sites that interact with specific ligands to alter the channel's conformation and function. Aconitine has a strong affinity for receptor site 2 **(Fig. 30)**, producing an allosteric change in the channel that permits the influx of Na^+ into the cell. Although its efficacy is not as high as that of batrachotoxin — meaning it acts as a partial agonist (63, 64) — this does not make it any less deadly.

The persistent activation of voltage-gated Na^+ channels leads to secondary activation of voltage-gated Ca^{2+} channels, resulting in increased intracellular calcium levels, which in turn enhances the presynaptic release of neurotransmitters (65).

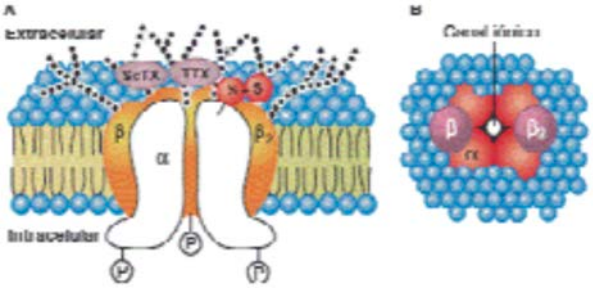


Figure 30: *Structure of the voltage-gated sodium channel.*

As previously mentioned, aconitine and other related diterpenes found in Aconitum species are highly active cardiotoxins and neurotoxins. Poisoning can occur through accidental ingestion of the wild plant or from consuming herbal decoctions containing aconite roots, which are commonly used in traditional Chinese cooking and medicine (66, 67). Only the roots of the plant may be used — and only after appropriate processing to reduce or hydrolyse the toxic components. However, excessive amounts or improper preparation can still result in intoxication.

Aconitine binds with high affinity to site 2 of voltage-gated sodium channels in excitable cells of the myocardium, nerves, and muscles, causing the channels to remain open. This leaves the cells in a refractory state, unresponsive to new stimuli. The result is arrhythmias caused by interference with post-depolarisation processes, muscle weakness and paralysis due to reduced acetylcholine release at the neuromuscular

junction, and tonic contractions of the ileum caused by excessive acetylcholine release from postganglionic cholinergic nerve endings (68).

Symptoms of poisoning include gastrointestinal issues — nausea, vomiting, diarrhoea, and severe abdominal pain — alongside neurological symptoms such as perioral and limb paraesthesias and muscular weakness. Cardiovascular symptoms include hypotension, chest pain, palpitations, extrasystoles, arrhythmias, ventricular fibrillation, and asystole — often refractory to cardioversion or antiarrhythmic drugs — and are typically the cause of death (68). There is no specific antidote for aconitine poisoning. Interestingly, amiodarone and/or flecainide —agents that prolong the myocardial refractory period — are recommended for treatment in less severe cases (68).

Experimental studies in rats have shown that tetrodotoxin, which binds to site 1 of the voltage-gated sodium channel and blocks it, offers partial protection against ventricular fibrillation, thereby reducing mortality (69). Similarly, arctigenin has been shown to delay the onset of aconitine-induced arrhythmias in rats, although its precise effects on sodium and calcium channels are not yet fully understood. It does, however, reduce Na^+ and Ca^{2+} influx into cardiomyocytes, thereby shortening the repolarisation time both in control subjects and in those treated with aconitine (70).

Forensic studies in suicide cases show that aconitine distributes widely throughout the body. It has even been detected in the vitreous humour, although in low concentrations; the highest concentrations are found in the liver, kidneys, and urine (71), significantly exceeding those detected in blood or brain tissue (72).

Aconitine degrades almost completely in samples stored at 20°C for 30 days, whereas no appreciable degradation occurs at 4°C or lower temperatures (71).

In the spring of 1944, the Allies intercepted a secret German message requesting the capture of two Soviet agents armed with Mauser pistols, calibre 7.65 mm — an unusual weapon for Russian forces. They had shot the SS chief in Minsk, and although the wounds caused by the bullets were not considered life-threatening, Kurt von Gottberg died six hours later, showing clear signs of poisoning. During the autopsy, several strange small-calibre (7.65 mm), 4-gram bullets were recovered. Examination in Gestapo laboratories in Berlin revealed that they were designed to release a toxic payload (28 mg of aconitine) upon impact **(Fig. 31)**.

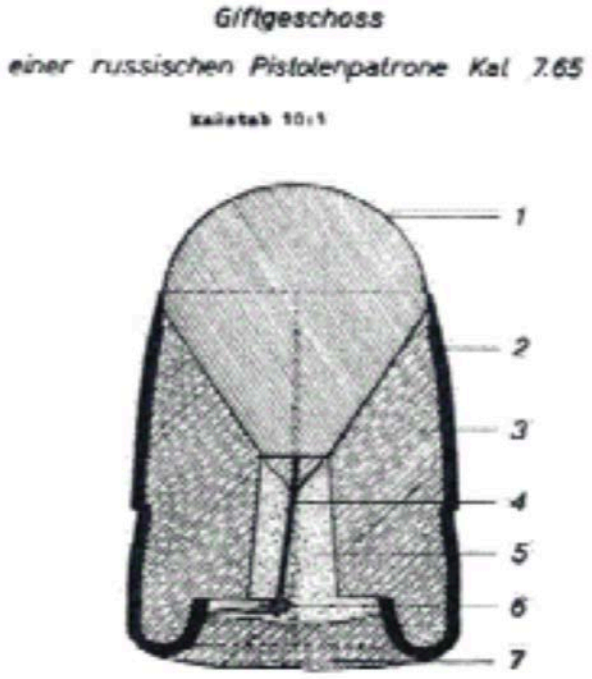


Figure 31: *Design of the 7.65 bullet that contained aconitine in the area marked with No. 5.*

SS Reichsführer Heinrich Himmler ordered the production of similar projectiles with an improved design and had them tested at the Sachsenhausen concentration camp on five prisoners sentenced to death. The test subjects were shot in the thigh: three of them died within two hours, showing clear signs of poisoning; the other two survived because the projectiles passed cleanly through their thighs without releasing the poison. These tests were conducted on 11 September under the supervision of Oberführer Joachim Mrugowsky (73).

Aside from the extensive use of poisons by the Most Serene Republic of Venice, the 17th century was prolific in its use of poisons and other concoctions — some used as love potions, others to eliminate troublesome, hated, or unfaithful individuals. Interestingly, the majority of those skilled in the preparation, supply, and administration of poisons were women. One of the most notorious among them was Teofanía d'Adamo, founder

of a dynasty of poisoners: her daughter Giulia d'Adamo and granddaughter Girolina d'Adamo inherited the secrets of a deadly poison known as *"Aqua Toffana"*. This substance was reputed to act with varying speed depending on the dose administered, influencing both the onset of symptoms and the rapidity of death.

The composition of *"Aqua Toffana"* remains unknown, but it is believed to have contained arsenic and an extract of Cymbalaria. It was reportedly a colourless, transparent, and tasteless liquid. According to Teofanía's own confessions before her execution, it was made from a blend of plant essences that left no suspicious trace in the victim and had no known antidote. Teofanía d'Adamo lived in Sicily, and she and her descendants became known as the *"Toffanas".* Their poisoning activities remained undetected until a neighbour attempted to poison her husband by dressing his salad with *"Aqua Toffana"*. When she briefly left the kitchen, the husband switched their plates, resulting in her own death. Before dying, she confessed her plan and revealed the source of the poison.

This led to the corresponding investigation, arrest, and torture of Teofanía d'Adamo, who was executed on 12 July 1633. She was held responsible for more than 600 poisonings.

Giulia, the daughter of Teofanía d'Adamo, moved to Naples, where she improved her mother's formula and renamed it "*Aqua di Napoli"*. She continued the lucrative business of supplying poisons, mainly to scorned women and impatient heirs. When rumours about her activities began to circulate, she relocated to Rome, where she continued her profitable trade until a rare case involving a survivor of poisoning led to her exposure. She was tried and executed in 1659.

Her daughter, Girolana, carried on the business and was also eventually executed, with some 580 poisonings attributed to her. The secret of *"Aqua Toffana"* did not die with them, however — their collaborators and assistants spread knowledge of the poison throughout Central Europe.

It is suspected that Mozart, who died in 1791, may have been a victim of this poison. He reportedly told his wife Constanze, six months before his death, that he feared he had been poisoned by unknown individuals using *"Aqua Toffana"*. This account was recorded by Mary and Vincent Novello in their book "*A Mozart Pilgrimage"*, based on interviews they conducted with the composer's widow in 1829.

At the French court of Louis XIV, Catherine Deshayes Monvoisin—better known as **La Voisin** — was a prominent figure due to her influence and her role as a supplier of love potions and powerful poisons to courtiers eager to enhance their sexual prowess or increase their fortunes. The poison concocted by this sorceress-like woman was a mixture of arsenic and lead acetate, known as *"succession powders"* or *"Saturn's sugar"* — names referring either to their use in hastening inheritances or to their lead content. To these chemical elements, La Voisin added ingredients such as toad bones, mole teeth, blowflies, human blood, iron filings, and powdered human remains—all finely ground.

She was arrested in 1679 and sentenced to be burned alive **(Fig. 32)**, alongside her apothecary, Esteban de Vray. The sentence was carried out on 22 July 1680. The nobles who had made use of her services were exiled.



Figure 32: *Execution of the La Voisin.*

The Marquise de Montespan, mistress of Louis XIV, was one of La Voisin's most frequent clients, seeking love potions to maintain the affections of the king. When the Affair of the Poisons erupted and her name emerged in the scandal, Louis XIV distanced her from the court, although he did grant noble titles to the seven children he had with her. The Marquise died at the age of 67, having led a quiet and devout life in stark

contrast to the passions and intrigues of her youth.

Marie-Madeleine d'Aubray, Marquise de Brinvilliers, was another of the notorious poisoners at the court of Louis XIV. Her lover, the Marquis de Sainte-Croix, had learned the art of poison-making from the Italian chemist Egidi. Together, the lovers became acquainted with a well-known apothecary named Glasier, who supplied them with raw materials — primarily arsenic — for the preparation of poisons. The Marquise tested these poisons during her charitable visits to hospitals, which invariably resulted in the deaths of several patients. She later experimented on her servants and had become so skilled in the administration of poisons that she could induce illness or recovery at will. She used her expertise to eliminate her father and brothers in order to seize the considerable family fortune. An investigation following the accidental death of Sainte-Croix led to the discovery of a chest containing the Marquise's correspondence, in which she detailed her criminal activities. The chest also contained several vials of poison. These findings led to her arrest at the behest of King Louis XIV.


L'EXECVTION
REMARQVABLE,
DE MADAME DE BRINVILLIERS;
qui a esté condamnée à faire Amande honorable devant Nostre-Dame, & de là conduite à la Grève, pour y estre décollée & ensuite jettée au feu, pour avoir empoisonné son Pere, ses Freres, & quantité d'autres gens de Condition.

Figure 33: *Execution of the Marquise de Brinvilliers.*

After a swift trial, the Marquise de Brinvilliers was subjected to torture and subsequently beheaded **(Fig. 33)**, as she was of noble status. The apothecary was hanged. Their bodies were incinerated, and their ashes swept away and scattered to the wind.

Arsenic has long been—and likely still is—one of the most widely used poisons, due to its broad availability and extensive use in various industrial sectors such as LED and semiconductor manufacturing, ceramics, pyrotechnics, insecticides, and more. Its toxic appeal is also due to its organoleptic properties: its salts are tasteless and odourless. Arsenic is a metalloid that can act in either a trivalent form (As_2O_3) or a pentavalent form (As_2O_5), with the trivalent salts being significantly more toxic (74). However, organic arsenic compounds are practically non-toxic.

Arsenic inactivates around 200 enzymes, especially those involved in cellular energy production (by disrupting oxidative metabolism) and those responsible for DNA replication and repair. It binds to the sulphur atoms of cysteine residues, altering the spatial structure of proteins **(Fig. 34)**, and can substitute for phosphorus in ATP molecules, causing intracellular ATP depletion (75). In fact, arsenic interferes with numerous metabolic processes **(Fig. 35)**.

Acute arsenic poisoning causes nausea, vomiting, and profuse watery diarrhoea due to serum leakage, along with severe abdominal pain. These symptoms also occur when arsenic is administered intravenously, as in documented suicide cases (76). Death typically results from multi-organ failure, with notable damage to the liver, kidneys, gastrointestinal mucosa, lungs, heart, and blood vessels. If death is delayed, secondary symptoms may include skin rash, convulsions, psychosis, peripheral neuropathy, and hematological disorders.

In subacute or chronic intoxication, arsenic accumulates in the liver, kidneys, lungs, gastrointestinal tract, and bones. It damages the myelin sheaths, causing a syndrome similar to Guillain–Barré (77). It also accumulates in keratin-rich tissues, such as the skin — causing hyperpigmentation and keratosis on the hands and feet—as well as in the nails (where Mee's lines may appear) and in the hair (74). Arsenic can even be detected many years after death, as shown in the most recent investigations into the death of Napoleon (78).

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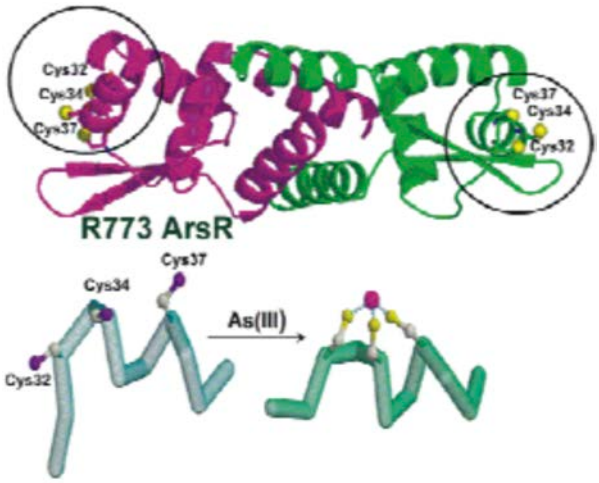


Figure 34: *Arsenic-induced disruption of protein tertiary structure.*

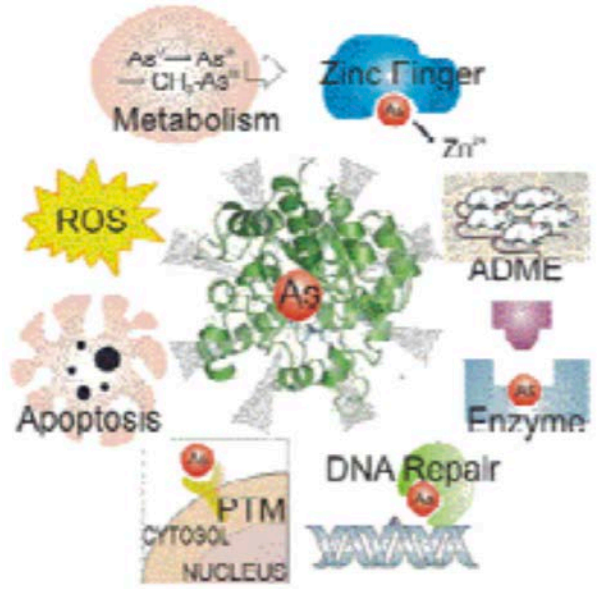


Figure 35: *Multiple points of metabolic interference by arsenic*

Acute arsenic poisoning can be treated — if detected early — with chelating agents. These can be administered orally to prevent the absorption of arsenic in the digestive tract, or intravenously to inactivate circulating arsenic (74, 76). Chronic poisoning, however, is more difficult to manage, as it often results in irreversible damage to several vital organs, including the liver and kidneys. Experimentally, antioxidant agents and nucleic acid protectors such as curcumin (79) or silibinin — previously mentioned (38, 40, 41, 42, 80) — have been tested with some promise.

19th Century

The 19th century was rich in discoveries, revolutions, and scientific advances. Many alkaloids were discovered, and there was a healthy rivalry among French, German, and British scientists. In Edinburgh, Sir Robert Christison — a renowned physician and expert in toxicology who had studied in Paris under Professor Orfila — learned from Rev. Mr. Waddell, a missionary in Nigeria, of a strange ritual practiced by the native Efik tribe in the Calabar River region. This ritual, akin to a trial by ordeal, involved forcing suspected individuals to ingest the seeds of a leguminous plant (Physostigma venenosum) known as *"Calabar beans"*. Those deemed guilty would die in convulsions, their hearts stopping; the innocent, on the other hand, would survive after severe vomiting.

How could this be explained? The answer is simple: the Calabar bean contains, among other substances, an alkaloid called physostigmine (or eserine), which inhibits cholinesterase, thereby preventing the breakdown of acetylcholine throughout the body. Because it crosses the blood–brain barrier, its effects are systemic. An innocent person, confident in their innocence, would ingest the Calabar seeds quickly and without fear. This would release enough physostigmine locally to induce vomiting, thereby expelling the toxin. Conversely, a guilty person, fearful and hesitant, would consume the seeds slowly, releasing physostigmine gradually in amounts insufficient to trigger vomiting. The toxin would then be absorbed and cause a systemic cholinergic syndrome, similar to that caused by organophosphate insecticides or nerve agents.

The treatment for such poisoning consists of the early administration of atropine, either intravenously or intracardially (15, 26, 81) — as depicted in the film *"The Rock"*, starring Sean Connery and Nicolas Cage.

On December 17, 1830, Simón Bolívar — also known as *"El Libertador"* — died in Santa Marta, Gran Colombia. His death remains shrouded in mystery, with no certainty about the results of the autopsy conducted by Dr. Reverend, who attended to him in his final days (82). After a series of intense military campaigns that severely weakened his health, Bolívar is thought to have contracted pulmonary tuberculosis, which is listed as the cause of death in many historical records. However, the reality may be quite different.

Indeed, Bolívar likely suffered from tuberculosis or another severe pulmonary illness. Gravely ill, he arrived in Santa Marta, where he came under the care of Dr. Reverend — whose legitimacy as a physician is now questioned. He treated Bolívar with poultices made from powdered cantharides **(Fig. 36)**, a highly vesicant substance that produces blisters which merge into bullae filled with yellowish fluid. These were thought to help expel harmful humours. In truth, cantharidin, a relatively simple molecule, is a potent and highly irritating toxin.

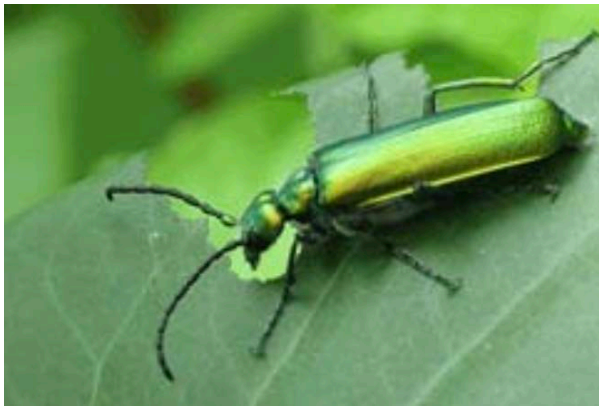


Figure 36: *Spanish fly (Lytta vesicatoria), a blister beetle containing cantharidin.*

It was widely used as an aphrodisiac due to its ability to induce priapism. However, ingestion of even slightly excessive amounts causes nausea, vomiting, severe bloody diarrhoea, painful priapism, vesical tenesmus, urinary retention, hypotension, bradycardia, delirium, coma, and death. Not all studies of Bolívar's remains support this theory; some suggest he died from paracoccidioidomycosis complicated by chronic arsenic poisoning (83).

On his deathbed, Bolívar reportedly said to his aide Palacios: *"Carajo! How will I ever get out of this labyrinth?"* — a phrase that later inspired writer Gabriel García Márquez to pen his novel *"The General in His Labyrinth"*.

20th Century

At the end of the 19th century and the beginning of the 20th, a figure emerged in Tsarist Russia under Nicholas II — a man who was part mystic, part sorcerer: Grigori Yefimovich Rasputin, known as *"the mad monk"*. His charisma, stemming from a combination of factors — his fixed and penetrating gaze, very light blue eyes, fluent and deliberately ambiguous speech — earned him a reputation as a prophet and a supposed healer. This gained him the protection of the Tsar's family and the favour of the Russian aristocracy.

Nicholas II reportedly made no decision without first consulting him. Rasputin eventually became the personal healer of the Tsarevich Alexei, who suffered from haemophilia, and his apparent healing abilities earned him the special protection of the Tsarina.

The Russian government and royal court considered Rasputin's influence over the Tsars to be harmful and detrimental to the state. Consequently, a plot was devised to eliminate him. On December 16, 1916, Prince Yusupov, the leader of the Duma, and Grand Duke Dmitri invited Rasputin to a reception at the Yusupov Palace. The desserts were laced with lethal doses of cyanide **(Fig. 37)**. However, no matter how much he ate or drank of the sweet wine, the poison appeared to have no effect.



Figure 37: *Prince Yusupov's dinner with Rasputin.*

Frustrated by the failure of the poison, Prince Yusupov shot Rasputin several times. Believing him dead, they were shocked when he suddenly fled through a side door. They chased after him and shot him again multiple times, even delivering a final shot to the head. They then wrapped his body in a carpet and threw it through a hole in the ice into the Neva River. When the body was recovered, the autopsy revealed that Rasputin had died by drowning.

Glucose breaks down cyanide in acidic conditions, forming a heptose and thereby detoxifying it. This is likely what happened at Prince Yusupov's dinner. It is also presumed

that the nervous tension and darkness contributed to the ineffectiveness of the final shot.
Zyklon B, infamously used during the Holocaust, consisted of hydrogen cyanide adsorbed onto diatomaceous earth, which released its deadly gas in the presence of humidity.

Cyanide interferes with oxidative processes in the enzymatic cellular respiratory chain, preventing oxygen from reaching the cells and causing death. As with carbon monoxide poisoning, the corpse typically presents with a pinkish hue, as the red blood cells remain saturated with oxygen.

Cyanide is reputed to be a highly potent poison, due in part to stories by Agatha Christie and other authors. However, the data does not fully support this reputation. According to the Merck Index, the lethal dose of cyanide in mice is between 10 and 15 mg/kg, depending on whether it is in sodium or potassium salt form. Extrapolated to an adult weighing around 75–80 kg, nearly one gram of cyanide would be required to cause death. In experiments we conducted in 1966, we determined a median lethal dose in dogs of 6 mg/kg when administered intravenously (84).

Hydrogen cyanide gas was used in the United States as a method of execution for death row inmates. When inhaled, it is more effective than when ingested orally.

In Stalin's Soviet Union, Grigori Moissevitch Mairanovski, a brilliant biochemist and expert in toxicology, was appointed director of the first toxicological laboratory, founded and supervised under the strictest confidentiality and secrecy by Lenin. Later, Lavrentiy Beria established Laboratory No. 1 of the NKVD, which Dr Mairanovski headed, for the development and testing of lethal poisonous substances, which were tried on prisoners of war or dissidents of the Soviet regime. This earned him the nickname *"Dr Death"*, *"Professor Poison"*, and later *"the Russian Mengele"*.

After the Second World War, he travelled to Germany to study the toxins developed by the Nazis, only to confirm that those produced in his own laboratory far surpassed the German ones. Mairanovski's goal was to design a poison that was undetectable both in terms of its organoleptic characteristics and in post-mortem analysis. He experimented with aconitine, digitalis, thallium, ricin, and many other poisons, which were used during the Cold War. It is likely that the aconitine bullet mentioned earlier originated from this laboratory. Even today, it appears that some of the knowledge developed by Mairanovski is still in use, as will be shown later. He was responsible for the deaths of more than 250 people, among them the Archbishop of the Ukrainian Greek Catholic Church, Theodore George Romzha. The murder of the prelate was organised in collaboration with Nikita Khrushchev.

In most of the autopsies carried out on his victims, no toxic agent could be found, and the cause of death was diagnosed as acute heart failure. Did Mairanovski discover the perfect poison? If so, he took the secret to his grave, as in 1964 he died mysteriously and unexpectedly, a victim of acute heart failure — likely poisoned on Khrushchev's orders to conceal his activities.

In the early hours of 5 August 1962, Eunice Murray discovered the lifeless body of the famous film actress Marilyn Monroe. She was lying naked on the bed. The initial results of the autopsy revealed a high concentration of the barbiturate Nembutal in her blood, suggesting that the actress had taken her own life, as she had recently been abusing medication and alcohol. However, more detailed autopsy reports showed that no trace of the barbiturate was found in the stomach or small intestine. Instead, large amounts of Nembutal were discovered in the rectum. The conclusion was clear: the barbiturate had been administered via enema, after Marilyn had been rendered semi-conscious by alcohol or another sedative. This ruled out the theory of suicide and strongly supported the hypothesis of murder — committed by as yet unknown individuals.

Barbiturates bind to an accessory site on the GABA receptor, enhancing the binding of GABA to its specific receptor. This increases the influx of Cl^- ions into neurons and decreases the Ca^{2+} current, resulting in hyperpolarisation and inactivation of the neurons. Depending on the dose, barbiturates can cause sedation, hypnosis, anaesthesia, and death due to paralysis of the brainstem's respiratory and vasomotor centres **(Fig. 38)**.

On 7 September 1978, Georgi Markov, a Bulgarian dissident writer in exile in London and outspoken critic of the communist regime led by dictator Todor Zhivkov—who, coincidentally, turned 68 that day — was walking to his job as a reporter at the BBC. Upon reaching the bus stop at Waterloo Bridge, he felt a sharp prick in the back of his thigh, apparently caused accidentally by a man carrying an umbrella, who politely apologised. Shortly after arriving at work, Markov experienced pain and inflammation at the site of the puncture and mentioned the incident to his BBC colleagues. That evening, he developed a high fever and was admitted to hospital, where he died on the 11th.

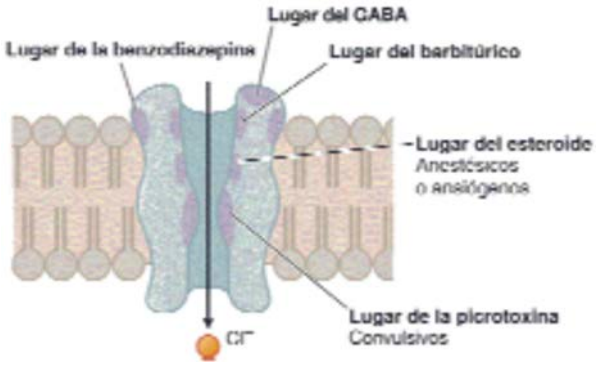


Figure 38: *GABA receptor with specified binding sites for the various ligands.*

Puzzled by the rapid progression of this mysterious illness, doctors suspected poisoning. A meticulous autopsy revealed a 1.5 mm platinum-iridium pellet, pierced with two 0.35 mm holes, in which traces of ricin were found. The volume of ricin that the pellet could contain — 0.266 mm³ — gives an idea of the potency of the toxin. It is believed that the murder was carried out by Bulgarian agents with support from the KGB, and that both the weapon and its ammunition originated from the SMERSH secret laboratory (85).

Just days earlier, another Bulgarian dissident journalist, Vladimir Kostov, had survived a similar murder attempt in a Paris metro station. He felt a jab in the back—this time from a weapon hidden in a handbag. Feeling unwell, he was admitted to hospital, where doctors removed a pellet similar to the one found in Markov. However, this projectile had failed to release its full toxic load, and Vladimir recovered after 12 days.

Ricin is a toxalbumin composed of two subunits, A and B, and is found in the seeds of the castor bean plant (Ricinus communis). It has extremely high toxicity when introduced into the body via parenteral routes (86, 87). Doses as small as one-tenth of a milligram can kill an adult within five days. The symptomatology is nonspecific and confusing, involving fever, muscle weakness, myalgia, nausea, diarrhea, liver and kidney failure, multi-organ failure, and ultimately death. There is currently no known antidote to this poisoning, although some vaccines that might neutralise the toxin are being tested (88).

Ingesting castor seeds is generally less dangerous and usually not fatal (89), though it can cause severe diarrhea and intense abdominal pain. The protein nature of the toxin likely allows for partial degradation by digestive proteolytic enzymes. Once inside the cell, ricin is transported from the Golgi apparatus to the endoplasmic reticulum, where it splits, and the A subunit returns to the cytosol. There, it binds to the 60S subunit of ribosomes and inactivates them by removing an adenine at position 4324, thereby inhibiting protein synthesis and causing cell death (90).

These cytotoxic properties have been exploited by attaching ricin to fragments of monoclonal antibodies (minibodies or diabodies), which serve as guides directing the toxin to cancer cells (91), where it accumulates in high concentrations and exerts its toxic effect, showing the relationship between plasma and intracellular concentrations — where the latter is approximately 60 times higher than the blood concentration.

A similar case, though with differences in cause and outcome, involved the British national Jo Wolacott, who in 2010 purchased a beautiful bracelet for €1 on eBay. From the moment she put on the bracelet, she began to experience symptoms: hallucinations, nausea, vomiting, diarrhea, and shock, followed by potentially fatal kidney failure. After spending a year in hospital with doctors unable to diagnose her illness, she eventually decided to remove the bracelet — upon which her condition began to improve, eventually leading to full recovery.

The bracelet was made from the seeds of "*Abrus precatorius*", a striking red seed with

a small black apical spot resembling a ladybird without its dots **(Fig. 39)**. These seeds contain a toxalbumin called abrin, which is similar to ricin but significantly more toxic (92). Deaths have been reported among workers who manufactured these bracelets and necklaces, simply from pricking themselves with the needle used to thread the seeds. It is estimated that a single British company marketed around 2,800 pieces made with these poisonous seeds before the British Public Health Agency managed to recall nearly all of them from the market.



Figure 39: *Seeds of the rosary pea (Abrus precatorius).*

On October 23, 2002, a Chechen terrorist group armed with machine guns stormed the Dubrovka Theatre, taking 850 spectators hostage. Three days later, special forces commandos pumped an unknown paralysing gas through the ventilation system, resulting in the deaths of 29 terrorists and 128 hostages. Many of the surviving intoxicated individuals recovered following intravenous administration of naloxone, an opioid antagonist, suggesting that the gas used may have been a gaseous opioid.

One particularly high-profile case was that of Viktor Andriyovych Yushchenko, the pro-Western Ukrainian leader who, during the 2004 presidential election campaign, was poisoned with the most potent form of dioxin (tetrachlorodibenzo-p-dioxin) on September 5, during a dinner with a group of Ukrainian businessmen and senior Russian officials. Initially misdiagnosed with pancreatitis, the subsequent appearance of chloracne, which permanently disfigured his face, confirmed dioxin poisoning. Despite the high concentrations of the toxin found in his blood, Yushchenko survived and won the election on December 26.

That same year, on September 1st, a group of 39 Chechen terrorists stormed the school in Beslan (North Ossetia), taking 1,181 hostages, including schoolchildren and teachers. Two days later, Russian special forces stormed the school, resulting in 370 deaths, including 171 children. The tragedy was covered by Anna Politkovskaya, a Russian-American journalist highly critical of the Russian political regime and the war in Chechnya. Anna was poisoned with tea during her flight to Beslan, but survived. She attempted to mediate in the school crisis, though unsuccessfully, and later published a highly critical report on the incident. On October 7th, she was shot dead in the elevator of her apartment building in Moscow. The newspaper Las Provincias, on June 10, 2014, reported that the Chechen assassins of Anna had been sentenced to life imprisonment, while three other individuals involved received sentences of 10 to 20 years in prison.

Alexander Litvinenko, a former colonel in the Russian secret service, had denounced irregularities within the Federal Security Service (FSB) and became a vocal opponent of Vladimir Putin. In 2001, he sought political asylum in the United Kingdom, published several books strongly critical of the Russian regime, collaborated with MI6, began an investigation into the death of journalist Anna Politkovskaya, and worked with the Spanish anti-corruption prosecutor's office, contributing to the arrest of several Russian mafia leaders operating in Spain. These activities triggered alarm in various sectors of the Russian government. On November 1st, after a lunch at a London hotel with two former KGB officers, Andrey Lugovoy and Dmitry Kovtun, Litvinenko suddenly fell ill. His condition worsened, and he was hospitalized, dying on November 23rd. Only after his death was it determined that he had been poisoned with polonium-210, a radioisotope that emits only alpha particles, which cannot be detected with standard radiation detectors and require specialized equipment. His widow, Marina Litvinenko, is currently seeking to uncover the full circumstances of her husband's death in British courts.

In Spain, in the year 2011, there were two cases of poisoning in restaurants. In Gijón, the kitchen assistant, known as Andrés *"el Candasu"*, of the El Lavaderu cider house, tapas bar, and restaurant, driven by a desire

for revenge against his coworkers, systematically added calcium cyanamide to their food. This compound inhibits aldehyde dehydrogenase, an enzyme essential in alcohol metabolism for converting acetaldehyde into acetic acid, which can be easily incorporated into the tricarboxylic acid cycle or cholesterol synthesis. Calcium cyanamide, like disulfiram, is used in alcohol withdrawal treatments, as its inhibition of aldehyde dehydrogenase causes acetaldehyde accumulation in the body, leading to vasodilation, flushing, and general discomfort; if the accumulation is significant, it can result in death.

In the "*Chef Rubio"* restaurant in Empuriabrava, the cook E.H. Zoubida was caught adding a green powder to the food — rat poison? — presumably as an act of revenge against the owner, Radia-el-Amrani. Fortunately, she was caught in time.

In Chinese restaurants, where large amounts of monosodium glutamate (MSG) are often added as a flavor enhancer, a condition known as *"Chinese Restaurant Syndrome"* may occur after eating. It involves a throbbing, intense headache, attributed to cerebral vasodilation caused by MSG.

In Japan, a highly prized delicacy is *"fugu"* fillet, made from the pufferfish, which contains tetrodotoxin — a very potent toxin found in its skin and internal organs. This toxin acts on site 1 of the voltage-gated sodium channels **(Fig. 30)**, blocking them (63, 68, 69). This property gives carefully prepared fugu fillets, which contain trace amounts of the toxin, a very peculiar and appreciated flavor, along with a sensation of slight tingling on the tongue. More than one Japanese chef and some diners have died due to inexperience or carelessness in preparing this delicacy.

In the summer of 2011, during an especially hot season, on August 28, with an ambient temperature of over 40°C, a rave party was held at the ruins of the Monastery of Aldehuela, in Perales de Tajuña (Getafe). During this event, a tea or infusion made from jimsonweed (Datura stramonium) was distributed. This plant contains high levels of hyoscyamine, a powerful anticholinergic that crosses the blood-brain barrier, causing hallucinations, and inhibits sweating, thus preventing heat dissipation from the body. This can lead to death by heatstroke, as happened to two attendees of that so-called *"party"*.

I finish with a sunset in the Albufera, Valencia and a sunset on the island of Mykonos. The sunsets in Mykonos are reputed to be among the most beautiful in the world.

I have spoken.
Valencia, 2014

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