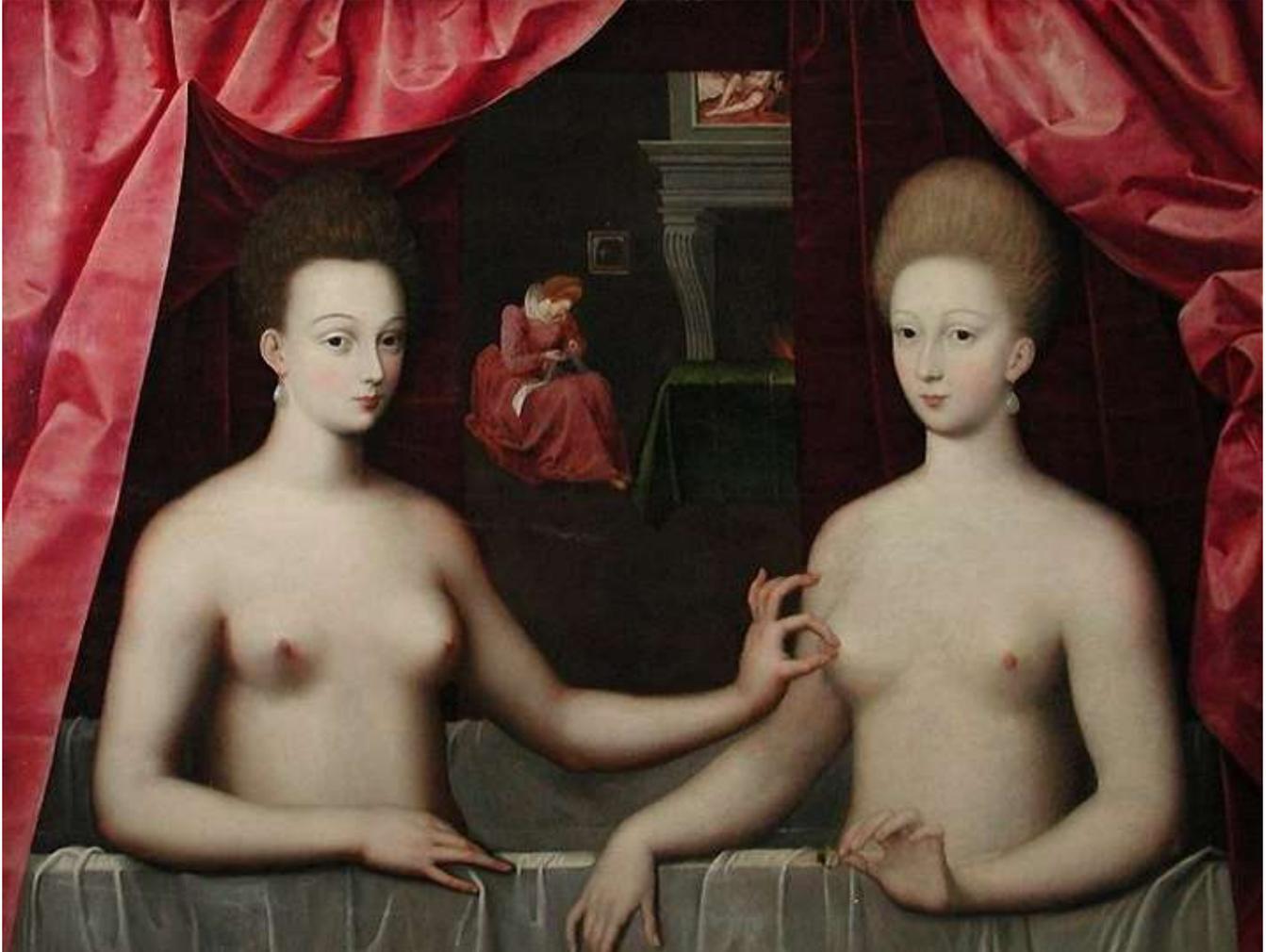


**STRYCHNINE POISONING**



*“Gabrielle d’Estrées and One of Her Sisters”, oil on canvas, School of Fontainebleau, artist unknown, c. 1599.*

*“The King is a decent man, but he keeps a dreadful whore who is ruining us all”*

*The artist of this enigmatic and startling late Sixteenth - early Seventeenth Century French painting is unknown. It is unsigned, possibly because the artist wished to remain anonymous. Its date cannot be established with accuracy; however the hair styles of the two women in the tub can be dated to between 1594 and 1598. An inscription on a later copy of the work states that the blonde woman on the right was Gabrielle d’Estrees, mistress of Henry of Navarre, and very nearly the Queen of France. Gabrielle was one of the most infamous courtiers in Europe in the late Sixteenth Century. She was considered the most beautiful woman in France, but she was also one of the most envied and hated. “The King is a decent man”, a poor Seine fisherman once told the King, not recognizing him in his hunting outfit, “but he keeps a dreadful whore who is ruining us all”. The King was greatly amused and laughed heartily. Gabrielle was fifteen when she arrived at the*

*court of Henry III, a decadent and scandalous monarch who liked to dress up in women's clothing. In this hotbed of scandal, Gabrielle was reported to have had numerous affairs, including one with the master of the royal stables M de Bellegarde. Following the death of Henry III, Henry of Navarre became King of France having converted from Protestantism to Catholicism to do so. This was a great scandal to all Protestants. France had been locked in bitter religious conflict for decades. To rule a united France and to end the horrific bloodshed undertaken in the name of the "true religion", which invariably meant one's own, it was necessary for Henry to convert. He was one of the few men of his time who remained free of religious zeal and superstition, in fact he happily converted on more than one occasion, as political circumstances necessitated. He was an agnostic in any case. The Catholics had the ascendancy by the time Henry came to the throne. On his accession, Bellegarde proudly introduced his beautiful lover to the new King - a mistake on his part as Henry was immediately and hopelessly captivated by her. To get Bellegarde out of the way Henry had Gabrielle married off to an impotent and loyal courtier, then promptly took her for his own mistress.*

*Henry had been estranged from his Queen, Margaret of Valois, from whom he had long been living in separation. As a consequence France had no heir to the throne, a situation that on Henry's death threatened to plunge the nation back into internecine religious war. Gabrielle at this point became pregnant by Henry, who now to the great scandal of the realm determined to make her the Queen of France and their illegitimate child, the heir to the throne. Henry sought to dissolve his marriage and to the horror of his ministers prepared to make plans for his marriage to Gabrielle, whose marriage had also been annulled on his orders. France would have an illegitimate Queen as well as an illegitimate heir to the throne. Gabrielle by this time had begun to arrogantly act the part of Queen in all but name. She accumulated titles from Henry and great wealth. Members of the court could not approach her without kissing the hem of her robe. As if all this were not bad enough, Gabrielle, although a great beauty, came from a most scandalous family on her mother's side, a family which the chronicler Tallemant des Reaux described as, "the richest in spirited ladies that France had ever seen," - and France had seen quite a few, "there are at least twenty-five or twenty six of them, nuns and married ladies alike, all of whom delight in sexual congress". Among the married ladies was Gabrielle's mother who abandoned the family for her lover, when the children were very young. One of the nuns was Gabrielle's sister, the abbess of Maubuisson. She was forced to leave the convent after bearing a number of children to different fathers.*

*The Fontainebleau painting shows Gabrielle in the bathtub with yet another of her sisters, Julienne d'Estrees, the Duchess of Villars. This sister fancied a certain Capuchin monk, so she would sit below the pulpit exposing her breasts whilst he was preaching. The God-fearing monk was forced to flee the confessional because of her advances, eventually even the city. Julienne, the abbess, Gabrielle, three further daughters, and one other son of M. d'Estrees became widely known as the "seven deadly sins". Gabrielle was said to be the deadliest of all the seven sins. The Fontainebleau painting depicts the evils of the d'Estrees sisters, but not in any way that is apparent to the sensibilities of those of the 21<sup>st</sup> Century. To truly understand the work it needs to be viewed through the eyes of the early Seventeenth Century. When this painting was done, very few took baths, indeed the sisters appear in full make up and jewellery, the last thing on their mind is to get wet! Baths were considered an unhealthy pass time, associated with the "loose*

*morals” of the public bathing houses of antiquity and the Middle East. Diabolical magical powers were attributed to bathing in certain liquids, such as wine or milk. Witches were said to take baths in order to copulate with the devil, who would then empower them to do magic. Gabrielle had bewitched the King. In a gesture guaranteed to draw the attention of the viewer, Julienne touches the nipple of her sister. To the 21<sup>st</sup> Century viewer this inevitably implies a lesbian relationship; however through Seventeenth Century eyes the gesture had quite a different meaning - that Gabrielle was pregnant. Today we look to the belly for the first signs of pregnancy, however in the Seventeenth century a protruding belly was considered very beautiful, to depict Gabrielle with this would not necessarily have got the message across! Normally pregnancy was symbolized by the hand placed on the belly; in Gabrielle’s case a more erotic version of hand placement in keeping with her reputation was taken. Her child is the King’s illegitimate heir. We know this as Gabrielle is seen displaying a ring in her left hand. This ring was placed on her finger by the King on 2<sup>nd</sup> March 1599. It was the investiture ring which the King received at his coronation and he gave it to Gabrielle as an engagement ring when she fell pregnant. In the background between the drawn curtains sits a woman possibly a wet nurse, however in superstitious eyes this is actually a witch or “Fate” casting a spell on Gabrielle that will end her life - she is unpicking the “thread of life”. Next to her is a coffin covered with velvet of green, the Queen’s favourite colour. The mirror over the head of the Fate, shows no reflection in it, a symbol of witchery and death. Above the dwindling flame of the fireplace hangs a painting showing a glimpse of naked flesh, an allusion to Gabrielle’s decadent life. The picture foretells the death of the one who has bewitched the King.*

*On the 5<sup>th</sup> of April, 1599, Gabrielle was sent back to Paris, to stay with a wealthy Italian banker, by the name of Zamet, in order to give birth. The delivery did not go well. She gave birth to a stillborn child, and very soon after became extremely unwell. On the 9<sup>th</sup> of April the King was grief stricken to hear that Gabrielle had died. It was reported that her death was a horrible affair, “a revolting and terrible death, her eyes rolling, her neck contorted and bent back upon itself”, a doctor reported, “it was the hand of God”. Many at the time however thought that the nature of her death was more like “the hand of the devil”. The official version given out by the French court was that Gabrielle had died of the complications of childbirth. Many however did not believe this. Tallemant des Reaux, for example assumed that someone had poisoned her, possibly Zamet, and so “had done Henry a great service”.*

*From a distance of over three hundred years it is impossible to say how Gabrielle d’Estrees died. Death in childbirth, the official court version, is entirely possible given the hazards of a Sixteenth Century delivery. Her manner of death however is intriguing. Doctors recorded that she died in an “unnatural” manner, with her “neck arched back on itself”. Many of the Seventeenth century would attribute this to the dark magic of witchcraft. From a 21<sup>st</sup> Century medical perspective however two striking possibilities are raised. The extreme opisthotonic posturing suggests tetanus, a not uncommon septic complication of Sixteenth Century childbirth. However for those who believed that Gabrielle was poisoned a second distinct possibility comes to mind. She was poisoned with a substance that very closely mimics tetanus - strychnine, a poison commonly used throughout history to kill - and it provides a “most revolting and terrible death”.*

## STRYCHNINE POISONING

### Introduction

**Strychnine** is occasionally used as a rodenticide.

It is an extremely toxic plant alkaloid.

Deliberate self ingestion leads to generalized skeletal muscle spasm within 30 minutes and death from respiratory muscle paralysis shortly thereafter.

Paralysis, intubation and ventilation are life saving if instituted early enough.

### Source:

Strychnine is a plant alkaloid that is extracted from the seeds of the tree, **Strychnos Nux Vomica**, found in South East Asia. India is the main commercial source.

### History



As in the case of many other naturally occurring poisons, strychnine in the past was used in carefully controlled doses for a host of supposed medicinal purposes!

In the case of strychnine none of these were in any way justified.

Because of its extreme toxicity packaging was a vital consideration when prescribed.

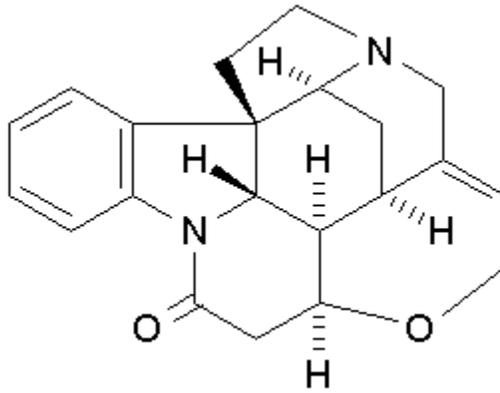
Distinctive shapes colors and textures helped the illiterate and the visually impaired to distinguish poison bottles from other containers.

*Strychnine sulphate, Eli Lilly & Company, c.1910, National Museum of American History, Behring Center, Smithsonian Institution.*

### Chemistry

Strychnine is a heterocyclic **ergot type alkaloid**.

Its molecular formula is  $C_{21}H_{22}N_2O_2$  and its chemical structure is represented as below.



### Preparation

Rodenticide preparations include:

- 0.3 % strychnine
- 0.5% strychnine

Available only to licensed exterminators:

5% strychnine

100% strychnine

### Toxicology

Strychnine **competitively inhibits** the central inhibitory neurotransmitter **glycine** by blocking **post-synaptic** glycine receptors within the brainstem and spinal cord.

In contrast, tetanospasmin the neurotoxin of tetanus which produces a clinically similar picture to strychnine poisoning, results in an inhibition of the release of glycine (and GABA) from *presynaptic* nerve endings.

GABA is *not* affected by strychnine.

Strychnine's glycine antagonism results in a **loss** of the normal descending inhibitory motor tone which leads to increased skeletal muscle tone and spasms.

### Pharmacokinetics

#### Absorption:

- Strychnine is rapidly and completely absorbed following ingestion or inhalation.
- It is not absorbed across intact skin.

### Distribution:

- It is a lipophilic drug with a large volume of distribution, at 13 L/kg.

### Metabolism and Excretion:

- Around 70% of an ingested dose is metabolized in the liver by microsomal (cytochrome p450) enzymes to inactive metabolites
- Around 30% is excreted unchanged in the urine.
- Its elimination half-life is 10-16 hours.

### Risk assessment

Ingestion by as little as **30-100 mg** by an adult is potentially lethal, (ie 1 gm of 0.03% powder). An accidental taste is potentially lethal to a small child.

**Any deliberate ingestion of this amount is rapidly lethal (within 30 minutes) without early intervention.**

**Muscle spasms herald the imminent onset of lethal muscle rigidity.**

Even an accidental taste can be lethal in a small child.

### Clinical features

**Mild intoxication** is characterized by muscle twitching *without* painful generalized skeletal muscle spasms or ventilatory impairment.

The full clinical picture of poisoning is as follows:

1. Initial symptoms appear within minutes of ingestion and include:
  - Nausea/ vomiting.
  - Muscular twitching
2. Skeletal muscle spasms precipitated by external stimuli then herald the imminent onset of lethal muscle rigidity.
3. This will be followed by generalized rigidity and muscular spasms that can be precipitated by any minor stimulus.

Characteristic features are similar to tetanus and include:

- Trismus

- Risus sardonicus
  - Opisthotonus (a generalized arched hyperextension of the back)
4. **Loss of consciousness does not occur**, until there is significant hypoxia from ventilatory failure.
  5. Repeated muscular spasm can have secondary complications similar to status epilepticus and may include:
    - Hyperthermia
    - Rhabdomyolysis
    - Lactic acidosis
  6. Death eventually occurs from respiratory muscle spasm and ventilatory failure.
  7. If the acute phase is survived, secondary complications may include:
    - Hypoxic brain injury
    - Renal failure.
  8. Resolution:
    - Providing ventilation and oxygenation are provided, rigidity and muscle spasms resolve within 24 hours.

### Differential Diagnosis

The diagnosis is given when there is a clear history of strychnine ingestion.

When this is not known differentials may include:

#### 1. **Tetanus**

- This will be the main differential diagnosis to strychnine poisoning.

Differentiating factors that may help include:

- Nausea and vomiting is uncommon in tetanus
- A history of up to date tetanus immunization make tetanus very unlikely.
- Strychnine has a quicker resolution of symptoms compared to tetanus.

- There is said to be more complete muscle relaxation between spasms in cases of strychnine poisoning.
2. Severe dystonic reactions.
  3. Seizure activity.
  4. Severe hypocalcemia with clinical muscular spasm.
  5. Hysterical conversion reactions.

### Investigations

There are no specific investigations, apart from strychnine levels but these are not immediately available and do not assist in management. Serum and urine levels may be done retrospectively in forensic cases.

Initial investigations will be directed toward looking for secondary complications **once the patient has been stabilized** by intubation, paralysis and ventilation.

Investigations may then include:

#### Blood tests:

1. FBE
2. U&Es/ glucose
3. VBGs/ lactate
4. CK and myoglobin levels
5. Consider coingestion, alcohol and paracetamol.

#### ECG:

As for any seriously unwell patient.

#### CT Scan:

CT brain may also be considered

### Management

**Strychnine poisoning is a time critical life-threatening emergency.**

1. ABC issues:

- **Muscle spasms herald the onset of imminent lethal generalized muscular rigidity.**
  - **Immediate neuromuscular paralysis, intubation and ventilation are then indicated and will be life saving.**
  - **Note that patients are not unconscious and if intubated, sedation is essential.**
2. Following intubation, treatment is supportive.
- Dialysis is not indicated, unless there is secondary renal failure.
3. Activated charcoal:
- Airway management takes priority over charcoal, which should *not* be given initially in view of the potential for seizures and muscle paralysis.
  - It may be given to patients who have been **intubated**.
4. In cases of *mild* intoxication:
- This will be manifested by minor muscular twitching without generalized muscular spasm or ventilatory compromise.
  - This can be managed by IV boluses of 5 mg of diazepam, every 5-10 minutes, titrated to clinical effect.

### Disposition

Exposed patients who are clinically well without twitching or muscular spasm at **4 hours post ingestion** can be medically cleared

Patients with twitching or spasm are managed in an intensive care unit.

References

1. Strychnine in: Murray L et al. Toxicology Handbook 3rd ed 2015.

Further reading:

Hagen R.M, Hagen R. "What Great Paintings Say", Taschen, 2007

Dr J. Hayes

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