**REVIEW ARTICLE** 



# Rabies: known and unknown historical aspects

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#### **ABSTRACT**

Aim: To provide a comprehensive historical overview of rabies, with a focus on its early recognition, cultural significance, and advancements in treatment from antiquity to the modern era.

Materials and Methods: A literature review was conducted using electronic databases such as Scopus and PubMed to gather data on rabies incidence, transmission patterns, and public health interventions across various Latin American countries. The search covered publications from 1950 to 2025. The following keywords and their combinations were used: rabies, hydrophobia, Lyssa, Lyssavirus, history of rabies, rabies vaccine, Louis Pasteur, ancient medicine rabies, rabies Greece, canine rabies, public health interventions.

Conclusions: Although significant progress has been made in reducing rabies cases in Latin America through widespread vaccination campaigns and animal control strategies, the disease continues to pose a public health concern in certain areas. This persistence is particularly attributed to challenges in rural and remote regions, bat-mediated transmission, and deficiencies in disease surveillance. Continued investment in preventive measures, public education, and targeted interventions—especially among vulnerable populations—is crucial for achieving the complete elimination of rabies in the region.

**KEY WORDS:** bite, deity, madness, Lyssa, hydrophobia, Lyssavirus

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## INTRODUCTION

Rabies, a viral disease affecting the nervous system, has been known since antiquity, with references dating back thousands of years. The disease progresses through several stages, each marked by specific pathological changes. In its advanced stages, symptoms such as hydrophobia (fear of water) and aerophobia (fear of drafts) frequently appear. These symptoms are often accompanied by severe spasms of the muscles involved in swallowing and breathing. [1]

In antiquity, rabies was primarily associated with infected dogs and the transmission of the disease through their bites. Although other animals were capable of transmitting rabies, this concept was not widely accepted by physicians of the time. Some, such as Caelius Aurelianus (c. 5th century AD), acknowledged that humans could also contract rabies from wolves, bears, leopards, horses, and donkeys. Nonetheless, due to the high incidence of rabies in dogs and their close interactions with humans, canines were viewed as the primary source of transmission. This close contact made rabies a particularly troubling condition for many ancient medical practitioners.[1]

Rabies was often categorized as a form of animal poisoning, akin to envenomation caused by reptiles and insects, with a strong focus on the mode of transmission. Despite this classification, rabies occupied a distinct place in ancient medical literature due to its unique effects on the human mind and body. The disease's mental and neurological symptoms—such as agitation, paranoia, and especially hydrophobia—led to the metaphorical use of the term "lyssa" in ancient Greek to denote delirium and madness. [1]

#### AIM

To provide a comprehensive historical overview of rabies, with a focus on its early recognition, cultural significance, and advancements in treatment from antiquity to the modern era.

## **MATERIALS AND METHODS**

A comprehensive literature review was conducted using major electronic databases, including PubMed, Scopus, and Google Scholar, supplemented by targeted searches in JSTOR, ProQuest, and specialized repositories in the libraries of the National and Kapodistrian University of Athens.

The search covered publications from 1950 to 2025 for public health studies, while no chronological restriction was applied for historical and classical sources (ancient, Byzantine, and medieval texts).

The following keywords and their combinations were used: rabies, hydrophobia, Lyssa, Lyssavirus, history of rabies, rabies vaccine, Louis Pasteur, ancient medicine rabies, rabies Greece, canine rabies, public health interventions.

In total, around 60 references were initially identified. After screening titles and abstracts, approximately 30 were excluded due to irrelevance, duplication, or lack of accessible full text. The final review was based on 30 sources, including both primary historical texts and secondary peer-reviewed articles.

Inclusion criteria were:

- a. Historical sources referring to rabies in antiquity, Byzantium, and later European traditions.
- b. Peer-reviewed public health studies in English, Greek, Latin, or French.
- c. Publications providing data on rabies incidence, transmission, vaccination, or medical perceptions across different periods.

Exclusion criteria and limitations:

- a. Non-scientific or anecdotal reports without verifiable historical or medical content.
  - b. Articles without accessible full text.

## **REVIEW AND DISCUSSION**

## **ANCIENT GREEK TIMES**

The term rabies originates from the Latin verb rabere, meaning "to rage", which may itself derive from the Sanskrit word rabhas, meaning "to do violence". Acute, progressive, and fatal encephalomyelitis is caused by neurotropic viruses of the genus Lyssavirus, a name derived after the Greek word lyssa, meaning "frenzy" or "madness". [1]

Lyssa (also spelled Lytta) was the Greek goddess of rage and frenzied fury. She was closely associated with the Maniai, the daemons of madness and insanity, and had dominion over rabies in animals. Rather than being one of the Olympic gods, Lyssa was a primordial spirit (daimon), believed to have existed before the rise of the Olympian pantheon. At the command of the gods, she could provoke blind rage in both mortals and deities, although she was often reluctant to do so. Known also as Madness, she was considered a dark deity and was commonly referred to as a daughter of Nyx (Night) and

Ouranos (Sky). This parentage was attribute to her by Euripides (480-406 BC), although the Roman author Hyginus (64 BC-17 AD) later described her as a daughter of Gaia (Earth) and Aether (Air). [2-4]

As a goddess, Lyssa wielded power over humanity but remained subservient to more powerful deities, particularly those on Mount Olympus. This hierarchy is evident in the myth of Heracles, as dramatized in Euripides' "The Madness of Heracles". When Heracles (Hercules) was married to Megara, daughter of Creon, Hera sought vengeance upon him, the illegitimate son of her husband, Zeus. She sent the messenger goddess Iris to command Lyssa to drive Heracles mad. Though Iris brought Lyssa to the city of Heracles, Lyssa hesitated, declaring that such a deed was wicked. Nevertheless, Iris overruled her, and Lyssa ultimately afflictedHeracles with uncontrollable rage, leading him to murder his wife and children. His rampage was halted only through the intervention of the goddess Athena. [2]

Lyssa also appears in other Greek myths, often indirectly through the consequences of her influence. For instance, some ancient sources attribute to her the madness that caused Actaeon's hunting dogs to devour their master after he saw the goddess Artemis naked. Dionysus is also said to have invoked Lyssa's power to drive the daughters of Minyas mad, resulting in the dismemberment of King Pentheus. Similarly, Lyssa was blamed for the madness that led the daughters of the Athenian king Cecrops to leap to their deaths from the Acropolis. [4]

In ancient Greece, early descriptions of rabies date as far back as the 9th and 10th centuries BC, often appearing in literary texts through metaphor. For example, in Homer's Iliad, the expression "raging dog" is used for Hector, and hydrophobia is metaphorically represented in the eternal torment of Tantalus in Hades. The philosopher Aristotle (4th century BC) observed that dogs were susceptible to rabies, a condition that could be transmitted to other animals through biting. Both Democritus (460–370 BC) and Hippocrates (460–370 BC) described symptoms consistent with rabies. Although Hippocrates did not name the disease, he described patients as "persons in a frenzy drink very little, are disturbed and frightened, tremble at the least noise, or are seized with convulsions". [5]

#### **ROMAN PERIOD**

The Romans were keen observers of disease, and their understanding of rabies, though limited by modern standards, was remarkably advanced for their time. Much of their knowledge stemmed from careful observation of infected animals—primarily dogs—and

the subsequent transmission of the disease to humans. Rabies was a recognized affliction in Roman times, and both Roman literature and medical texts offer valuable insights into how the disease was perceived and managed.

One of the most notable Roman sources on rabies is Pliny the Elder (23/24–79 AD), a Roman author and naturalist. In his encyclopedic work Naturalis Historia, Pliny describes the symptoms of rabies and highlights the link between the bites of rabid dogs and the onset of hydrophobia—a hallmark symptom in human rabies cases, marked by an extreme fear of water. [6]

Another significant Roman figure, Aulus Cornelius Celsus (25–50 AD), a medical writer of the early 1st century AD, provided one of the earliest systematic medical accounts of rabies in his seminal work De Medicina. Celsus detailed the manifestations of the disease in both animals and humans, and proposed treatment strategies based on the prevailing medical knowledge of the time. He described the progression of rabies with remarkable accuracy, noting initial symptoms such as fever, anxiety, and hallucinations, followed by hydrophobia and, ultimately, death. His observations underscored the futility of treatment once clinical symptoms appeared, as rabies was almost universally fatal. [7]

Galen, (129-216 AD), the prominent Greek physician, also described the signs of hydrophobia in detail:

"Hydrophobic individuals fear any liquid so intensely that even the mere mention of it causes them to lose control, crying out, trembling, sweating with fear, and chattering their teeth. As the condition worsens, they exhibit all these symptoms even in the absence of water. They become alienated and mutter to themselves, fearing the sound of water, growing heavy and emitting sudden cries. Their trembling is not constant but occurs during hallucinations. Their extremities turn cold, their pulse quickens, and they become weak. If someone offers them a drink, they recoil, scream, and breathe in sobs like children about to be thrown into deep water, unable to swim. As the condition progresses, sobs intensify, the voice weakens, and their speech takes on a barking quality. Some, due to the severity of their agitation, die in convulsions while resisting the illness". [8]

Furthermore, Galen emphasized the seriousness and complexity of rabies, clearly distinguishing it from common wounds. He observed that while ordinary wounds could be treated with simple remedies—such as vinegar-soaked sponges—bites from rabid dogs required aggressive intervention. This included cauterization, potent pharmaceuticals, and long-term care. Galen warned of the grave consequences of untreated rabies, including spasms, delirium, hydrophobia, and ultimately death:

"The Methodists claim it is useless to know the causes of diseases. Yet they study the usefulness of Theriac, a medicine that often cures hydrophobia—among the worst of diseases—and remarkably counters the onset of such evils. Victims experience not only convulsions and extreme internal fever due to dryness but also mental insanity. They fear water; though they crave fluids, they refuse to drink due to madness. I marvel at the Methodists, who say that knowledge of causes is irrelevant to treatment. How can they cure such cases, when the bite seems no different from that of a non-rabid dog?". [9]

Galen's insights reflect the depth of medical understanding in antiquity regarding rabies and its outcomes: "For common diseases, especially febrile ones, we must ask essential questions. If the wound is from a dog, we must determine whether the dog was rabid—this makes a great difference. For a simple wound, a blood-based remedy or a sponge soaked in vinegar may suffice. But for a rabid dog's bite, even a very small wound must be cauterized. Strong medicines and prolonged care are required. Effective treatments include wormwood, Aristolochia, lycium, boiled water from river crabs, garlic, parsley, and the root known as gentian. Cleansing with hellebore is also beneficial. Without such treatment, spasms, madness, hydrophobia, and death may result". [8]

The Romans also recognized the importance of preventive measures. They understood that rabies was transmitted through the bite of infected animals and took practical steps to reduce its spread. In rural areas, where encounters with wild or stray animals were more frequent, efforts were made to control stray dog populations and to avoid contact with potentially rabid animals. Columella (4–70 AD), a Roman agricultural writer, advised in De Re Rustica that farmers should exercise caution and kill rabid dogs to prevent disease transmission. [10]

Despite their efforts and observations, the Romans had limited means to control or treat rabies effectively. The absence of knowledge about the viral nature of the disease and the lack of vaccines or post-exposure prophylaxis meant that rabies remained a feared and frequently fatal condition. However, Roman medicine did make use of various folk remedies and medicinal plants believed to possess protective or healing properties. For instance, Pliny the Elder (23/24–79 AD) mentioned the plant Dictamnus (Dittany of Crete), which was thought to have curative effects for wounds and bites. [6]

Additional detailed descriptions of rabies symptoms in animals, particularly dogs, are found in the works of the Stoic philosopher Epictetus (1st century AD) and the physician Galen (2nd century AD). Both noted that rabies frequently affected dogs and that hydrophobia was a defining symptom. Other ancient physicians, in-

cluding Philumenus and Dioscorides (both 2nd century AD), provided in-depth accounts of the disease's manifestations in canines, noting their aggressive behavior and fear of water. They also described early therapeutic attempts, such as a mixture of crab ash and gentian dissolved in aged wine. In the 5th century AD, Caelius Aurelianus reported similar diseases occurring in Crete, with consistent symptoms including hydrophobia. [5]

These records suggest that rabies was present in Ancient and pre-Byzantine Greece as early as 2,000 to 3,000 years ago, particularly among dogs, which acted as reservoirs for the virus. However, it is also possible—though unlikely—that some ancient references to rabies were describing other illnesses with similar neurological or behavioral symptoms. Moreover, fatalities resulting from dog bites may, in some cases, have been attributed to general sepsis rather than specifically to rabies. [5]

#### BYZANTINE PERIOD

The existence and recognition of rabies during the Byzantine period are well-documented through various scholarly and medical works. The term lyssodi (meaning "rabid") was frequently used by theological authors such as Gregorius Nysenus (4th century AD) and Michael Psellus (11th century AD) to describe aggressive behavior or erotic passion, reflecting an understanding of the disease's symptoms beyond a purely medical context. [5]

Prominent Byzantine physicians like Aetius Amidenus (5th–6th century AD) described a condition in dogs known as lyssa (rabies). Aetius observed that the severity of the disease worsened under extreme weather conditions. He noted a range of clinical symptoms in affected animals: loss of voice and recognition, hydrophobia despite thirst, protruding tongue, foaming saliva, drooping ears and tail, sluggish gait, somnolence, and fear of reflections, which often triggered aggressive responses. Aetius also described similar symptoms in humans bitten by rabid dogs, especially hydrophobia. [5, 11]

Other significant contributors to rabies literature in this period include Apsyrte (a veterinary surgeon under Emperor Constantine), Eumelos Pelagonius, Vegetius (4th century AD), and Paul of Aegina (7th century AD). Apsyrte and Eumelos offered early observations on equine rabies, while others contributed to the general understanding and attempted treatment of the disease in both animals and humans. [11]

The most comprehensive discussion of rabies in antiquity comes from Caelius Aurelianus (c. 5th century AD), who drew heavily on Soranus of Ephesus (1st–2nd century AD). Aurelianus described rabies patients with

considerable detail, emphasizing the paradoxical intense thirst coupled with an irrational fear of water. He differentiated this fear from rational avoidance of water due to poisoning concerns. [12]

Aurelianus also categorized symptoms by disease progression: early stages included unjustified worry, irritability, insomnia, and mental and physical weakness. Later stages presented with acute hydrophobia, fear triggered by the sound or mention of water, and hypersensitivity to weather changes. Attempting a differential diagnosis, Aurelianus compared rabies with mental illnesses such as mania and phrenitis, rejecting Eudemus's view that rabies resembled melancholy, since the latter was chronic while rabies was acute. [12]

He also addressed claims that hydrophobia resembled aerophobia seen in phrenitis, arguing that hydrophobia was more specific and consistent, unlike the more generalized fears in mental illness. These distinctions reflect the broader struggle of ancient physicians to classify rabies as either a physical or mental illness. Some suggested that the irrational behaviors pointed to a mental disorder, while Aurelianus firmly attributed the disease to physical causes, particularly the bite of a rabid animal. [13]

#### META-BYZANTINE PERIOD

In the meta-Byzantine period (10th–14th centuries), physicians such as Theophanes Nonnos (c. 10th century), Nicholas Myrepsos (c. 13th century), Demetrios Pepagomenos (c. 1200–1300), and Joannes Actuarios (c. 1275–1328) discussed rabies and proposed treatments based on natural remedies. Pepagomenos notably suggested surgical removal of parts of a dog's tongue as a preventive measure—an idea that persisted until the 19th century. Much of their work echoed earlier classical Greek medical knowledge. [5]

In Western Europe, Arnaldo de Villanova (1235–1313)—a physician, alchemist, and astrologer—believed that rabies in animals was caused by ingestion of carcasses. Cauterization remained a widely used treatment, supplemented by plant-based poultices. [5, 14]

During the Middle Ages, despite the persistence of Hippocratic principles, diseases were frequently attributed to supernatural or religious causes. Pagan traditions blended with Christian teachings, often linking illness to sin. Treatment frequently involved prayers, penance, and saintly intervention. Saint Hubert (656–727) became known as a patron against rabies. Rituals invoking his protection included branding bitten dogs with the "keys of Saint Hubert", the use of iron rings as amulets, and placing threads from the saint's stole under the skin of bite victims. These practices sparked

debate between religious authorities and early scientific institutions like the Sorbonne. [14]

#### **RENAISSANCE TO 18TH CENTURY**

The Renaissance marked a transition toward modern science and public health. As medieval thought gave way to empirical investigation, rabies treatment evolved. Though knowledge remained limited, practices like cauterizing wounds, cleaning bite sites, and using substances such as mercury gained popularity. While not scientifically precise, these methods reflect a rudimentary understanding of the need to disinfect and inhibit viral spread. [14]

During the Ottoman Empire, historical data on rabies is sparse. By 1500, rabies cases in dogs were reported in Spain, and by the late 16th century, outbreaks had reached Austria, Hungary, Flanders, and Turkey. By 1604, rabies was endemic in Paris, and by the early 1700s, wildlife-transmitted rabies had spread across Central Europe. [5]

#### 19TH AND 20TH CENTURIES

The 19th century brought major breakthroughs in the understanding and treatment of rabies. At that time, rabies remained highly feared due to its near-universal fatality once symptoms appeared. Transmission via the bite of infected animals, particularly dogs, was well understood, and hydrophobia was recognized as a hallmark symptom. [15, 16]

A transformative moment occurred in 1885 with the work of Louis Pasteur (1822–1895), who developed the first effective rabies vaccine. His method involved attenuating the virus by passage through rabbits and preparing vaccines from dried spinal cords. The first successful human application was in July 1885, when Joseph Meister, a nine-year-old boy bitten by a rabid dog, was treated and saved. This success laid the foundation for modern vaccination and post-exposure prophylaxis. [14, 15, 17]

Although comprehensive epidemiological data on rabies in 19th-century Greece are lacking, the disease was known to be both widespread and deadly. During the period of British rule in the Ionian Islands (1815–1864), rigorous preventive regulations were established to control its spread. These included several strict measures: a) all dogs were to be kept tethered within residences, and hunting or herding dogs had to be constantly supervised by their owners; b) suburban dogs were required to remain tied from sunrise

until two hours after sunset; c) stray dogs—whether truly homeless or simply wandering—were to be killed immediately; and d) guard dogs had to be restrained from early morning until 8 p.m. Furthermore, in cases where a dog displayed symptoms of rabies, behaved abnormally, or was seen being bitten by another dog, its owner had the legal obligation to report the incident to the local police authorities without delay. [18]

In August 1894, Panagiotis Pampoukis (1858–1956), a pioneering Greek microbiologist trained at the Pasteur Institute, established the "Lyssiatrion" (Anti-Rabies Clinic) in Athens. The clinic addressed rabies outbreaks in both rural and urban areas. Pampoukis secured a 15-year state funding agreement to cover treatment costs for indigent patients. Rabies in Greece at the time was transmitted by dogs, cats, foxes, and wolves. [18]

The early 20th century saw the expansion of dog vaccination programs, drastically reducing rabies cases in many regions. In the United States, national efforts included pet and wildlife vaccination, resulting in a significant drop in human infections. [19, 20] Diagnostic progress included the introduction of the direct fluorescent antibody (DFA) test in the 1950s, which enabled rapid and reliable identification of rabies in brain tissue—a gold standard still in use. [21, 22]

Despite such advances, rabies persisted in developing countries, where vaccine access and medical care were limited. Global health bodies like the World Health Organization (WHO) launched widespread campaigns for dog vaccination, public awareness, and improved access to post-exposure prophylaxis. [23]

Later in the 20th century, safer and more effective cell-culture-based vaccines—such as the human diploid cell vaccine (HDCV) and the purified chick embryo cell vaccine (PCECV)—replaced older nerve-tissue formulations, significantly reducing side effects and improving immunity. [24-28]

## **CONCLUSIONS**

Rabies, a disease documented since ancient times, has remained a persistent threat to both human and animal health. Although enormous strides have been made in understanding, preventing, and treating rabies—particularly through vaccination, public education, and global collaboration—challenges remain, especially in rural and low-resource settings. The history of rabies is not only a medical narrative but also a testament to humanity's persistent pursuit of scientific advancement and collective action in confronting one of the oldest known and most feared diseases.

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#### **CONFLICT OF INTEREST**

The Authors declare no conflict of interest

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