SPECIAL ARTICLE

Caveat Cenans!*

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CASE PRESENTATION

In October, a 64-year-old man developed postprandial abdominal pain and vomiting. He had been feeling well until passing out during a banquet at which he had consumed a large quantity of wine and food. One dish that was composed of mushrooms was a longtime favorite. On regaining consciousness shortly thereafter, he complained of severe abdominal pain. He vomited and felt somewhat better.

Prior to this illness, the patient had enjoyed reasonably good health for over a decade. However, he had been sickly early in life. He was born prematurely (after 7 months of gestation), and as a child, had suffered from a succession of obstinate disorders, including milk allergy and frequent febrile illnesses. He is also believed to have had malaria, measles complicated by unilateral deafness, erysipelas, and colitis. Since early childhood, he had had weakness of both legs that was so pronounced that he limped noticeably and could not walk more than short distances without assistance. He had longstanding tics and jerks of his head and hands, as well as a stammer and drooling, which were most pronounced when he became excited. He was also prone to fits of inappropriate laughter. He ate and drank in excess regularly, rarely leaving his dining room until he was "stuffed and soaked." Thus, it was not unusual for him to fall asleep immediately after dining and to have to be carried unconscious to his bed. He gained considerable weight in later years and complained of heartburn that was so frequent and severe that he contemplated suicide as his only means of relief.

The patient's father died of trauma at the age of 28; his mother committed suicide at age 73. He had one brother who had died at age 34 of a mysterious illness manifested by progressive wasting with terminal acrocyanosis and a trunkal rash. His sister was executed for adultery at the age of 34. There was no family history of neurologic abnormalities similar to the patient's.

The patient was born in France, but had spent most of his life in Italy. He had been married 4 times and had numerous extramarital, heterosexual relationships, including several with prostitutes. He had 3 children, all of whom were alive and well at the time of his illness. He was a politician and a historian.

Physical examination showed an obese man in moderate distress. His temperature was normal, his eyes were injected, his hearing was impaired unilaterally, and his abdomen was mildly tender throughout. His voice was hoarse and indistinct, and he stammered uncontrollably in response to questioning, with considerable slobbering and rhinorrhea. His neck muscles were enlarged. The muscles of his upper extremities were well developed and strong, whereas those of the lower extremities, especially the calves, were weak and atrophied. When the patient walked, he dragged his right foot.

A physician induced additional vomiting by placing a feather in the back of the patient's throat. Shortly thereafter, the patient's condition deteriorated; he became confused and exhibited signs of unremitting abdominal pain and fecal incontinence. He died 12 hours after the onset of his illness.

DIFFERENTIAL DIAGNOSIS

Dr. William A. Valente

To summarize the case history, this man was born prematurely at 32 weeks of gestation, which was near the limit of survival prior to the advent of modern advances in neonatal intensive care. He had several childhood illnesses that are rarely seen today: measles, malaria, erysipelas, colitis, and obstipation. He had weak legs, unusual tics, and a stammer, and he drooled. His laughter was oddly timed. He died after a large meal that featured one of his favorite dishes, mushrooms. At the time of his death, he was an obese, elderly man, with impaired hearing, ocular injection, and a hoarse voice. His neck muscles were enlarged. His arms were strong, but his legs weak.

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*Banqueter beware!

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He dragged his right foot. He became confused terminally and had excessive salivation, unremitting abdominal pain, and fecal incontinence.

Who might this person have been? The facts are limited, and the possibilities seem endless. Nonetheless, we have several clues. Since this is a historical clinical pathologic case presentation, we can assume that he was a historically important person. He had enjoyed the company of many women, in spite of odd physical attributes, and he consumed fine food and wine excessively. Although born in France, if French, he would not likely have spent most of his life in Italy. Hence, he must have been Italian. The case history suggests further that he was an ancient Italian, Roman in fact, who would have to have been the emperor with the "shaking head"—Claudius I (1).

Let me begin with the differential diagnosis of our subject's chronic disabilities and then address his terminal illness. Our patient was born prematurely and experienced various "typical," Roman, childhood illnesses. He also had a stable, nonfamilial neurologic syndrome that was characterized by "tics," head jerks, odd motor movements, and stammering speech—all of which worsened with activity. He had strong neck and arm muscles but weak legs. Even so, he was an accomplished historian and politician, suggesting not just intact cognitive skills but a high degree of intelligence as well. He must not have been physically grotesque, as he did, after all, have several wives. His neurologic abnormalities are consistent with one of the "movement disorders," the dyskinesias, of which there are several classifications (2–4). These include the rhythmic alternating contractions of tremor, the continuous, slow, writhing motions of athetosis, and the random jerks of chorea.

Since I have not had the advantage of examining our patient to identify his particular dystonia, I looked to some of the ancient sources for additional information on his condition. Gaius Suetonius Tranquillus, who wrote in the early second century CE, described Claudius as follows (5):

> Claudius had a certain majesty and dignity of presence, which showed to best advantage when he happened to be standing or seated—and especially when he was in repose. This was because, though tall, well-built, with a handsome face, a fine head of white hair and a firm neck, he stumbled as he walked owing to the weakness of his knees; and because, both in his lighter moments and at serious business, he had several disagreeable traits. These included an uncontrolled laugh, a horrible habit, under the stress of anger, of slobbering at the mouth and running at the nose, a stammer, and a persistent nervous tic of the head, which was apparent at all times but especially when he exerted himself to the slightest extent.

More clinical information can be gleaned from the writings of Lucius Annaeus Seneca ("the younger Seneca")

Figure 1. A coin image of Claudius I depicting marked hypertrophy of the anterior neck musculature. From Virtual Catalog of Roman Coins. Available at: http://artemis.austinc.edu/acad/cml/rcape/vcrc/.

(6), who knew Claudius personally. Unfortunately, his description was satirical and hence of uncertain reliability:

> An announcement was made to Jupiter that there was a visitor of respectable size and with very white hair. He was making some sort of threat, as he kept shaking his head; he was also dragging his right foot. When he asked his nationality, he had made some answer with a confused noise and *in indistinct* tones [emphasis added]. It was impossible to understand his language: he was neither Greek nor Roman, nor of any known race . . . Hercules was badly shaken by the first sight of him . . . seeing the strange sort of appearance and the weird walk and hearing the hoarse and incomprehensible voice that belonged to no land creature but seemed more appropriate to a sea-monster, he thought his thirteenth hour had arrived.

Finally, there is the image of Claudius preserved on coins minted during his reign, which depicts massive enlargement of the sternocleidomastoid muscle (Figure 1) (7).

How might one explain these signs and symptoms? One explanation is that Claudius may have had Gilles de la Tourette's syndrome, which generally begins in childhood, with motor and vocal tics that typically involve the face and eyes. Interestingly, the tics can sometimes be suppressed voluntarily, only to be followed by rebound accentuation. Often, there are associated obsessive-compulsive or self-destructive activity, mood swings, and odd sexual behavior. The syndrome usually improves markedly after adolescence. Claudius' symptoms differ in too

many aspects to give Tourette's syndrome more than passing consideration as the cause of his neurologic complaints.

Chorea would be worth considering if we had evidence of a hereditary disorder and if Claudius had not retained his excellent cognitive skills. Thus, Huntington's disease cannot be considered. The history of erysipelas raises the possibility of Syndenham's chorea, although the two conditions are not associated. If Claudius had had erysipelas as a child, he would almost certainly have had streptococcal pharyngitis as well, which is associated with Syndenham's chorea. There have been reports of recurrent rheumatic chorea. However, they have not been described as of the duration and frequency of Claudius' condition.

Another disorder worth considering is PANDAS—a syndrome of *p*ediatric *a*utoimmune *n*eurologic *d*isease *a*ssociated with *s*treptococcal infection (8). This is a disorder of abrupt onset, characterized by obsessive-compulsive behavior following a recent streptococcal infection. Like rheumatic fever, PANDAS is thought to represent a "molecular mimicry" illness, in which antistreptococcal antibodies cross react with normal tissues, in this case with neuronal antigens in the basal ganglia. The net result is a syndrome involving distinctive movement and behavioral abnormalities. Occasionally, PANDAS is persistent, presumably because of repeated streptococcal infections leading to permanent destruction of areas within the basal ganglia. Although intriguing, PANDAS is not a particularly good fit.

Claudius' symptoms may be best explained by one of the dystonias. These movement disorders are characterized by sustained contractions of agonist and antagonist muscle groups that worsen during voluntary movement. During early stages of the disease, the dystonic movements, while typically variable, are most pronounced late in the day. Patients attempt to compensate for their dystonia by using counterposing voluntary movements called "gestes antagonistes," resulting in the characteristic dystonic tremor. Higher cortical function and intelligence are generally preserved.

The cervical dystonias are the most common dystonias in adult patients. They include torticollis (head turning), antecollis (neck flexion), and retrocollis (neck extension). They are characterized by spasmodic contractions, with rhythmic jerking and hypertrophy of the neck muscles. Laryngeal involvement is common and associated with dysphonia.

The limb dystonias are most common during childhood, and involve the foot, causing it to twist at rest and to assume an equinovarus deformity during running. As the disease progresses, these crural abnormalities may become fixed.

Primary dystonias are typically autosomal dominant disorders that begin in childhood, often affecting the feet first (4,9). In time, additional muscle groups are involved, leading to dystonic movements of the trunk, neck, shoulders, and arms (10). Cranial-cervical involvement is associated with dysarthria, dysphonia, difficulty controlling salivary secretions, and hypertrophy of the neck muscles.

In the primary dystonias, basal ganglia dysfunction is prominent, and yet structural abnormalities of the basal ganglia are all but undetectable. Recently, an abnormality of the *DYT* gene has been identified in some patients with primary dystonias. This particular gene resides on chromosome 9Q34.1 and codes for torsin A, an adenosine triphosphate–binding protein that is prevalent in the substantia nigra, cerebellum, hippocampus, and cholinergic tonic neurons of the striatum. Several other abnormal genes have been identified on chromosomes 14, X, 8, 1, and 19 in such patients (2). Some patients have responded favorably to treatment with dopamine agonists and anticholinergic drugs.

Although Claudius' illness had many of the features of a primary dystonia, there is no evidence that any of his relatives had similar disorders. Therefore, I must discard primary dystonia as an explanation for his chronic neurologic abnormalities, and turn instead to secondary dystonias, in particular, the heredodegenerative dystonias.

The heredodegenerative dystonias include Wilson's disease, iron storage disorders, and various lipidoses, glycogenoses, aminoacidopathies, and other degenerative processes. Lacking evidence of a familial disorder, or of multiorgan dysfunction or cognitive impairment, I can exclude these latter disorders. A dystonia caused by a congenital or acquired structural defect, however, is worth considering, given Claudius' extremely premature birth (11). A traumatic delivery at 32 weeks' gestation or delayed adverse effects of prematurity itself might have damaged the basal ganglia and produced neurologic disabilities that became apparent only later in childhood. One wonders if his "succession of obstinate childhood disorders" was simply a ruse promulgated by the family to hide Claudius' movement disorder from public view. He had had several serious infections during childhood, one possibly having been encephalitis, which could have resulted in a postencephalitic dystonia. However, encephalitis is unlikely, because if it had been severe enough to cause dystonia, it would probably have caused cognitive dysfunction as well. We can also eliminate medications and neoplastic diseases as the cause of his dystonia for obvious reasons; several toxic and metabolic disorders are associated with dystonia. However, there is nothing in the case history to suggest hypocalcemia, chronic heavy metal poisoning, or Wilson's disease.

Using just a touch of literary license, I am going to suggest one last cause for his dystonia: the "Claudian Complex"—a stable, lifelong, nonprogressive dystonia, with primary involvement of the cranial-cervical muscle groups, less prominent involvement of the arms and legs,

and a normal life span. The likely etiology is an acquired abnormality of the basal ganglia related to premature birth. It is also possible, although less likely, that his Claudian Complex was due to a postinfectious encephalopathy or a random somatic mutation in the *DYT* gene complex. One of these secondary acquired childhood dystonias might manifest as a dyskinetic cerebral palsy, athetoid cerebral palsy, or striatal necrosis with delayed onset (12–15).

What of Claudius' terminal illness? We are told that he had syncope after overindulging at a banquet. He regained consciousness only to become increasingly ill. Terminally, he had injected sclerae, hoarseness, rhinorrhea, and excessive salivation. There was also unremitting abdominal pain, abdominal distension, and fecal incontinence. He died within several hours of the onset of the illness. In view of his age and weight, he might have died of a catastrophic vascular event (16), such as an acute myocardial infarction of the inferior wall or a ruptured abdominal aortic aneurysm. He might also have aspirated or, as many have suggested, have been the victim of poisoning.

Poisoning is of special concern, given the social and political intrigues that plagued the emperors of Rome. Sudden gastrointestinal abnormalities develop in acute arsenic poisoning. However, bloody diarrhea is common, and we have no such evidence in the case history. Antimony causes similar but more acute gastrointestinal symptoms. Cyanide from amygdalin, which is present in the pits of stone fruits, and a popular ancient poison, aconite, would have acted faster. Ergot from tainted grain would have produced evidence of vasoconstriction. Only poisonous mushrooms could have caused the kind of terminal illness described.

Harvesting wild mushrooms for consumption, especially during the summer and fall, has been a preoccupation of epicureans throughout the world for centuries (17,18). Given the difficulty in differentiating edible from poisonous mushrooms, it is surprising that more people do not fall victim to mushroom poisoning. Ingestion of as little as one cap of an appropriate species can be fatal. In ancient Rome, mushrooms (boleti) were a highly regarded delicacy. The favorites were *Amanita caesarea* and perennial truffles.

Mushroom poisoning (mycetismus) results commonly from accidental ingestion of members of the families *Amanita, Galerina, Cortinariu, Gyromitra, Clitocybe,* and *Inocybe* (19–21). The two most important members of the *Amanita* family in this regard are *Amanita phalloides* and *Amanita muscaria*. *Amanita phalloides* (Figure 2) contains highly toxic cyclopeptides, which inhibit ribonucleic acid polymerase (22), and causes abdominal pain, vomiting, and diarrhea 6 to 36 hours after ingestion. Although "temporary improvement" may follow, fulminant hepatic necrosis soon develops, leading to death in 2 to 7 days. Poisoning with this particular mushroom, therefore, would have been a less than ideal means of eliminating a Roman emperor. A swifter poison would have been chosen, lest Caesar lived long enough to exact retribution (23). *Amanita muscaria* contains a different kind of toxin; one that acts as a parasympathic stimulant. It causes lacrimation, vasodilatation, salivation, rhinorrhea, intractable diarrhea, severe abdominal pain, loss of sphincter control, wheezing, bradycardia, and hypotension. It may also cause death in as short a period as several hours (24). *Amanita muscaria*, however, contains only small amounts of muscarine (25,26), and would not likely have been fatal unless the adverse effects of muscarine were potentiated by some underlying disability. Muscarinic mushroom poisoning is most often the work of members of the *Inocybe* or *Clitocybe* family, which contain higher amounts of the toxin (21,25,27). *Gyrometra esculenta* contains a toxin that acts quickly and causes similar gastrointestinal symptoms. However, it also causes incoordination and headache.

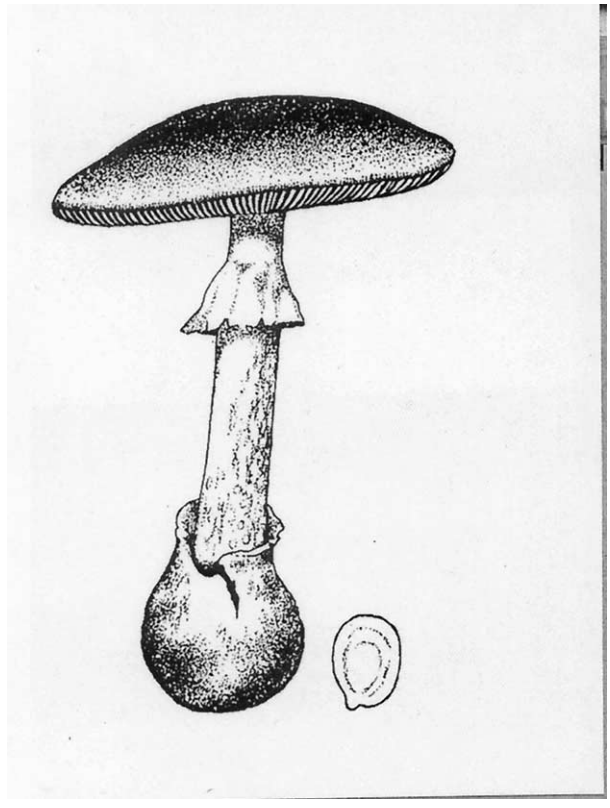

Figure 2. Sketch of the deadly mushroom, *Amanita phalloides*. This particular species typically has white lamellae (gills) and pilues (cap), with a veil surrounding the upper stalk and rounded volva (cup) underground. Reprinted with permission from Ellenhorn MJ, Schonwald S, Ordog G, Wasserberger J. *Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning*. 2nd ed. Baltimore, Maryland: Williams & Wilkins; 1997:1881.

One of Claudius' favorite foods, *Amanita caesarea*, was a favorite of Roman nobility (17,18). Others (18,23) have suggested that a dish of his favorite mushrooms was prepared for his final meal and then laced liberally with the juice of *Amanita phalloides*. The terminal events, however, occurred too rapidly to have been induced by *Amanita phalloides*. Therefore, it has been suggested that an additional poison was administered, most likely by Claudius' physician, Xenophon, on the feather he used to induce vomiting (23). This is certainly possible, although it might not have been necessary if muscarinic mushrooms had been used to poison the dish.

Muscarinic mushrooms would have been especially dangerous for Claudius, given his dystonia. Due to their cholinergic effects, muscarinic mushrooms might have accentuated Claudius' muscular contractions, and induced salivary hypersecretion, diarrhea, volume contraction, and confusion. The end result might then have been either massive pulmonary aspiration or a fatal "dystonic crisis" (28).

Dr. Valente's diagnoses: acquired (secondary) dystonia, probably congenital, and acute (fatal) cholinergic mushroom poisoning complicated by either dystonic crisis or pulmonary aspiration.

HISTORICAL DISCUSSION

Dr. Richard J. A. Talbert

In considering Claudius' illness, one must appreciate that such ancient testimony as survives is not based on careful, objective observation, or even derived from ancient medical experts. Rather, it consists of random, anecdotal reminiscences, typically recorded with the deliberate intent of finding fault or poking fun. Sympathy and respect for a person as physically and mentally challenged as Claudius would have been largely absent (5,29,30).

These considerations notwithstanding, it is clear, in my opinion, that Claudius' main physical problem was a movement disorder (1). He walked in a strange, uneven way, and could not always control the constant shaking of his head and hands. No doubt, it was this same disorder that affected his voice and speech unpredictably, so that on some occasions he is said to have spoken clearly and concisely, while on others confusedly and indistinctly.

Given the considerable disabilities due to Claudius' illness, it is impressive that he could have functioned as emperor, and for nearly 14 years, beginning at age 50, with no experience in affairs of state (5). How should we rate his performance? The answer to such a deceptively simple question depends on the criteria and the perspective used to evaluate him. Moreover, in selecting these criteria, three factors should be considered.

First, there was no position of 'emperor' as such during the time of Claudius. It was, in effect, a conspicuous and dominant status that Julius Caesar had created for himself as lifetime dictator, which was also why the senators (who controlled the old Republic that Caesar despised openly) assassinated him in 44 BC. After 14 more years of civil war, Caesar's heir and grandnephew, Augustus, achieved sole control of the empire. However, he chose deliberately to downplay his authority, insisting to the senate that he was merely 'Princeps,' or first citizen, and that the Republic was restored. This low-key, unostentatious style was consolidated by Augustus over what turned out to be a very long reign—a span of 44 years after the end of the civil wars. This same style was retained, albeit with less flair, by Augustus' stepson and successor, Tiberius, for another 23 years. It was Tiberius' successor, the 25-year-old Gaius Caligula, who chose to dispense with the Augustan political persona and, instead, to flaunt authority.

If there was something elusive and variable about the position of 'emperor,' the same must be said of the second factor we should consider—the nature and scope of the emperor's duties. The revived Republican administrative structure did not require involvement of an emperor in the daily functioning of either Rome or the Roman empire, nor was there a job description against which an emperor's performance might have been evaluated. If, like Tiberius, the emperor did not set foot in Rome for 10 years, he was under no obligation to do so, and yet, the city would continue to function. If, like Caligula and later Nero, he showed no interest in government and preferred to pursue other interests, again, the empire would go on. Of course, whatever an emperor chose to do would not necessarily prove to be popular with everyone, especially members of the upper classes. Although they comprised a small percentage of the empire's population, the upper classes were vital to an emperor's success, and their norms for acceptable behavior were strict.

Caligula was assassinated barely 4 years after becoming emperor because of his cruelty, extravagance, and capriciousness. His forays into foreign affairs had proved disastrous. By inviting the king of Mauretania to a meeting and then having him executed, he instigated a costly and counterproductive war with an ally of Rome. Moreover, he had inflamed his Jewish subjects, particularly in Alexandria (the second city of the empire after Rome), where he had supported the Greeks in their longstanding feud with Jewish inhabitants, allowing the conflict to reach the brink of a civil war. Meanwhile, he had also enraged the Jews of Palestine by ordering a statue of himself to be placed in the Temple in Jerusalem. Claudius, by contrast, offered a reassuring return to Augustan norms.

These were some of the challenges confronting Claudius on his accession, and, in my view, he should be recognized for having defused such crises promptly and effectively. He made it clear to the Greeks and Jews in Alexandria that he expected them to live together peacefully

again, and he sent a ship posthaste to Jerusalem, countermanding Caligula's order regarding the statue.

Third, we should consider the limited role of government in the Roman world; for example, issues that are of importance to most modern governments, such as education and health care, never gained the attention of the Roman authorities. Furthermore, the Romans and their subjects did not expect that their government would take the initiative to improve living conditions, which was instead the responsibility of the local communities. They might have appealed to a governor or the emperor in times of crisis, although neither was obliged to listen, let alone help. An emperor though might have interceded if a dispute had arisen between communities. At best, an emperor could try to ensure that the empire remained peaceful and stable. Even then, he had no great staff of civil servants at his disposal.

It was surely to Claudius' credit that he was, at the very least, a responsible emperor. He commissioned three major projects that were for the benefit of the public, rather than for his own personal gratification: a proper harbor for ships that provisioned Rome, two aqueducts to supply the city with fresh water, and drainage of the Fucine Lake in central Italy to increase the amount of arable land. However, Claudius sometimes struggled in vain; the drainage project, in particular, was far from successful.

It was a persistent striving for stability and fairness that I would suggest was Claudius' greatest strength as emperor. There is evidence too that he wished to extend the privilege of Roman citizenship to deserving noncitizens. On the not so favorable side, one might point to an undue reliance on freedmen assistants of questionable integrity. At the same time, it would have been difficult for him to have enlisted members of the upper classes as trusted assistants, who would not necessarily have proved to be less corrupt than the freedmen. Claudius' private life does, indeed, seem to have been untidy; for example, he did little to restrain his third wife, Messalina, and he chose Nero, the son (his stepson) of Agrippina, his last wife, as his successor instead of his own son, Britannicus—a decision that was in all likelihood his undoing.

We will never know if it was poison added by Agrippina that killed Claudius, or if it was "bad" mushrooms, or just old age and a bout of illness. Ancient tradition favors poison, but we have to recognize that this is simply history's standard explanation for deaths in the imperial family. The fact remains, however, that the timing of Claudius' death was highly advantageous to Agrippina and her son. Nero was then nearly 17 years old and married to Claudius' daughter, Octavia. Claudius' own son, Britannicus, who was 3 years younger, had not yet come of age. Furthermore, it is suspicious that Claudius' influential freedman, Narcissus, who hated Agrippina and favored Britannicus, was away from Rome at the time of Claudius' death, on a trip that had been suggested by Agrippina. Claudius' demise could still have been due to natural causes, but if so, its timing could not have better suited his wife's plan for the future.

COMMENT

Drs. Philip A. Mackowiak and Judith P. Hallett

The case history of Tiberius Claudius Drusus Nero Germanicus (10 BCE–54 CE), or Claudius, first conqueror of the British Isles, was largely recorded for posterity by three writers: Tacitus (56 CE–ca. 118 CE), Suetonius (ca. 70 CE–ca. 130 CE), and Cassius Dio (ca. 164 CE–after 229 CE). None was a physician. Each wrote his account many years after Claudius' death. Each, in words that Robert Graves attributes to Tacitus (31), recorded:

> a story that was the subject of every variety of misrepresentation, not only by those who then lived but likewise in succeeding times: so true is it that all transactions of preeminent importance are wrapt in doubt and obscurity; while some hold for certain facts the most precarious hearsays, others turn facts into falsehood; and both are exaggerated by posterity.

We are not nor will we ever be able to examine Claudius directly. He and all the Caesars were cremated. We are left to diagnose his illnesses using only the information that has been preserved in the writings of these ancient historians and other less extensive sources.

Dr. Valente has offered a new interpretation of their incomplete and, almost certainly, seriously flawed, clinical descriptions of this most complicated of the Julio-Claudians. Like other would-be diagnosticians since antiquity, he believes a poisonous mushroom was the proximate cause of death—in particular, one of the muscarinic variety. However, he suggests that Claudius' unique dystonia, his so-called "Claudian Complex," potentiated the muscarinic effects of the mushrooms and rendered fatal an assassination attempt that might otherwise have failed.

Mushroom poisoning has long been suspected as the cause of Claudius' death. In his *Roman History* (32), Cassius Dio reports that Nero quipped that his father "became a god by eating the food of the gods, a mushroom." Mushroom intoxication potentiated by an underlying secondary dystonia is a new idea. If Dr. Valente's hypothesis is correct, it reminds us that the outcome of an illness is dictated not only by its own virulence, but also by the special characteristics of the host that determine its capacity to resist the illness.

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