Occasional Notes

A Mysterious Death

PRESENTATION OF CASE

A 32-year-old man presented with fever and pain in the right upper quadrant. The patient had been well until the day after a night of heavy alcohol consumption (12 pints of wine[1,2]), when fatigue and generalized aches developed. The following evening, he consumed a similar quantity of wine and had sharp pain in the right upper quadrant of such severity that he cried out.[3] The pain resolved quickly, but the area remained tender to palpation. He later had chills, sweats, and fever, which continued into the next day.

The patient bathed in cool water and after three days began to feel better. The fever returned, however, and was accompanied by rigors, anorexia, and fatigue, which worsened over the next two days. He was evaluated on the sixth day of his illness and treated with cool baths and chest compresses. On the eighth day of illness, he had an extremely high fever, was unable to speak, and could make only slight movements of his eyes and hands.

One year earlier, the patient had suffered penetrating trauma to the right chest, complicated by hemopneumothorax.[4] He had also received penetrating wounds in his thigh and shank[5] and a closed head injury.[6] Several years earlier, he had contracted an illness characterized by fatigue and fever after bathing in the river Cydnus, in Cilicia.[7]

The patient was a native of northern Greece and was active in military service. He had traveled extensively through Asia Minor and the Middle East and to the Indian frontier. He had been married twice and was bisexual. A homosexual partner had recently died from a febrile illness.[8] The patient did not use tobacco; he intermittently drank large amounts of alcohol. The patient's mother and half-brother were alive and well. His father had been murdered.

Physical examination revealed a well-developed man in acute distress. He was diaphoretic and febrile and had slow, deep respirations. He responded to questions only with slight movements of his eyes and hands. His abdomen was supple and was not tender on palpation. There was no rash or icterus. Severe, generalized, symmetric weakness was present. A healed, ragged wound was noted in the right chest.

On the 11th day of illness, the patient began to breathe shallowly, became comatose, and died. Several days elapsed before the body could be prepared for burial. During this time, signs of postmortem putrefaction were notably absent.[9]

DIFFERENTIAL DIAGNOSIS

Dr. David W. Oldach: This is an extraordinary case in many respects: a 32-year-old war veteran, his male lover recently dead after a febrile illness, drinks 12 pints of wine, has a febrile illness with severe abdominal pain, and dies as a result, with no signs of decay for several days. His medical care was equally remarkable, apparently limited to the administration of cool baths and compresses for a fatal febrile illness. The physical examination, notable for its brevity, appears to have relied exclusively on touch and observation. One is forced to conclude that this patient died at a great distance from any modern medical facility.

The patient's illness appears to have been precipitated by a night of heavy alcohol consumption, raising the question of direct ethanol toxicity. Alcoholic hepatitis can result in pain in the right upper quadrant and fulminant liver failure, leading to coma and death. Fever is observed in up to 50 percent of patients and may be caused by hepatic necrosis alone.[10] However, patients with alcoholic hepatitis are likely to have icterus, signs of profound malnutrition, and evidence of chronic liver disease on physical examination, none of which were described in this case. Consumption of alcohol can also induce acute necrotizing pancreatitis, which frequently presents with severe abdominal pain and often results in death due to sepsis.[11] However, the illness described in this patient, which was heralded by fever and transient abdominal pain and marked by deterioration over a period of 11 days, is uncharacteristic of acute (septic) necrotizing pancreatitis. Let us therefore consider what else might have been in the wine.

Methanol is a natural fermentation product, which may reach concentrations as high as 300 mg per liter in wines.[12] Methanol's metabolic pathway, through formaldehyde to formate, is of interest when one considers the curious absence of postmortem decay in this patient. After a latent period of 6 to 30 hours, acute methanol intoxication is manifested as progressive metabolic acidosis due to the accumulation of formic acid, with attendant optic and retinal neuropathy.[13,14] Peripheral neuropathy may also occur, and this might explain the patient's profound generalized weakness. However, fever and abdominal pain would not be expected with methanol intoxication, and the patient did not have the visual symptoms or ophthalmologic findings (i.e., optic-disk hyperemia) that are characteristic of this disorder. Thus, although the possible embalming effect of formaldehyde is an intriguing explanation of the unexpected postmortem course, I believe methanol intoxication is an unlikely cause of death.

Any discussion of the toxic effects of alcohol must

include the consideration of lead, a cause of illness since antiquity.[15,16] Some believe that widespread use of lead water pipes and lead-based pottery glazes resulted in epidemic lead poisoning in ancient Rome, perhaps even contributing to the fall of that great civilization.[17] In modern times, lead exposure has more often been linked to occupational or environmental sources, although a dramatic association was found between lead poisoning and the consumption of moonshine distilled in automobile radiators.[18] Acute lead intoxication is a cause of severe gastrointestinal symptoms (colic), fatigue, paralysis, and encephalopathy.[19] Thus, one might speculate that homemade wine, stored in pottery with a lead-based glaze, was the key to this patient's illness. However, the presence of fever as a cardinal feature of the illness argues against the diagnosis of acute lead intoxication.

What else might have been in the wine? If foul play was involved, arsenic, a favored tool of professional and amateur assassins for millennia, must be considered. The toxicity of arsenical compounds is related to their ability to uncouple oxidative phosphorylation. Trivalent arsenic (As^{3+}) binds sulfhydryl groups and, in this manner, inhibits pyruvate dehydrogenase, whereas pentavalent arsenic (As^{5+}) resembles phosphate chemically and may thus disrupt glyceraldehyde phosphate dehydrogenase.[20]

Medicinal use of arsenic dates back to Hippocrates, who recommended it as a treatment for ulcers.[21] In more modern times (1787), Dr. Thomas Fowler extolled the use of arsenic for "the cure of agues, remitting fevers, and periodic headaches," a practice that persisted into the 20th century with the use of salvarsan (arsphenamine) in the treatment of syphilis.[22] Accidental contamination of wine with arsenic has been reported,[23] but trace amounts consumed in this manner would be more likely to result in chronic manifestations of arsenic intoxication, such as hyperkeratosis and white transverse nail-bed lines (Mees' lines), with possible chronic vasospasm leading to gangrene of the legs and feet (blackfoot disease).[24,25] The ingestion of large quantities of arsenic can cause extensive transmural inflammation of enteric mucosa, severe abdominal pain, hemorrhagic gastroenteritis, and hepatic necrosis.[26] Systemic endothelial injury can develop, with capillary leak, pulmonary edema, hypotension, and shock. If these events are not fatal, a progressive neuropathy, which may be indistinguishable from the Guillain–Barré syndrome, may yet claim the patient's life. This scenario mirrors our patient's illness in certain respects and must therefore be given serious consideration.

Cholecystitis and cholangitis may both present with fever, abdominal pain, and delirium, particularly if perforation and bile leak occur. Obstruction of the biliary tree due to tumor, stones, or parasitic infection are all plausible, although tumor and stones are less likely than infection in a 32-year-old man. Yellow fever and, in rare cases, fulminant hepatitis A or B may progress rapidly to coma and death. The absence of icterus in this case largely eliminates these possibilities. Pain in the right upper quadrant can be induced by diaphragmatic pleural irritation due to empyema or lower-lobe pneumonia. The history of a penetrating chest wound with hemopneumothorax raises the possibility of a recrudescent empyema. The abrupt onset and severity of the patient's abdominal pain, however, are more consistent with the perforation of an abdominal viscus. Given the heavy alcohol consumption, a perforated gastric or duodenal ulcer that caused progressive peritonitis is worthy of consideration. However, for reasons that I will now elaborate, I believe distal small-bowel disease is more likely in this case.

In an analysis of the clinical course of 500 untreated cases of typhoid fever, Osler reported abdominal pain and tenderness in 60 percent.[27] The symptoms derived from both abdominal and pleural complications, including intestinal perforation, which characteristically resulted in the sudden onset of severe abdominal pain. The pain was most often paroxysmal in character and localized to the right of the midline in the hypogastric region. As generalized peritonitis ensued, clammy perspiration, quickening of a thready and weak pulse, and facies hippocratica (a drawn, pale appearance indicating impending death) were observed. The course was almost invariably fatal. Osler also described the development of acute ascending paralysis (which he called poliomyelitis and which we might characterize as the Guillain–Barré syndrome) as a complication of the infection. Thus, untreated typhoid fever complicated by bowel perforation could explain the continuous fever and acute severe abdominal pain in this patient, as well as the recent death of his lover due to febrile illness (a possible source of the patient's infection), with a progressive neurologic disorder (the Guillain–Barré syndrome) responsible for the generalized weakness, coma, and death.

Any untreated infection of the distal gastrointestinal tract complicated by bowel perforation with peritonitis could account for the clinical outcome described in this patient. *Campylobacter jejuni* infection may lead to bowel perforation, although not frequently, and is strongly associated with the development of the Guillain–Barré syndrome.[28] However, a characteristic feature of *C. jejuni* infection is diarrhea, which was not present in this patient. Diarrhea is not a ubiquitous symptom in patients with typhoid fever and, in some studies, it has been reported in less than half the patients.[29]

The patient was a native of northern Greece and had had an earlier illness characterized by fever and fatigue. Malaria is, or was, endemic in this area. Although acute abdominal pain is not a typical feature

Figure 1. Detail from a Roman Mosaic Illustration of Alexander at the Battle of Issus (Museo Archeologico Nazionale, Naples, Italy). Reprinted with permission from Scala/Art Resource, New York.

of *Plasmodium falciparum* infection, it can occur. This presentation, termed "algid malaria" by Osler, develops because of intestinal ischemia due to thrombosis of mesenteric arteries.[27] Superimposed cerebral malaria might likewise have been responsible for the progressive neurologic deterioration in our patient. Without detailed data on the course of his temperature, the results of laboratory tests, and examination of a peripheral-blood smear, differentiating between malaria and enteric fever is difficult. However, abdominal pain is much more common in patients with typhoid fever than in those with malaria.

Brucellosis, also known as Malta fever, is another disease found in the Mediterranean region that warrants brief consideration. In a study of 109 previously healthy soldiers hospitalized with Malta fever, Bruce reported a fatal outcome in only 4.[30] Abdominal pain was not a characteristic feature of the illness, nor, evidently, was death, even among patients who did not receive specific antimicrobial therapy.

How, then, do we make sense of this case? Why are we given such limited information from the physical examination? Why did this patient receive such ineffective care? How do we explain the mysterious statement that the body showed no signs of decay for several days after death? This patient received little in the way of modern medical care, I believe, because he lived at a time when such care was unavailable. Who traveled extensively, at war, through Asia Minor, the Middle East, and India? What same person lost his father through homicide and died at the age of 32? The answer, of course, is Alexander the Great (Fig. 1).

What happened to this great man, and what are we to make of the claim that his body failed to decompose after death? It is likely that the deification of Alexander by those who survived him resulted in the creation of a legend of physical incorruptibility. However, there may be scientific merit to a claim so easily discounted as myth. If ascending paralysis developed during the course of Alexander's fatal febrile illness (presumably typhoid fever), this paralysis may have given the impression of death before it actually occurred.

DR. DAVID W. OLDACH'S DIAGNOSIS

Salmonella typhi enteritis, complicated by bowel perforation and ascending paralysis.

HISTORICAL DISCUSSION

DR. EUGENE N. BORZA: According to an ancient story, when the news of Alexander's death reached Athens, a prominent orator shouted at the Athenian assembly, "What? Alexander dead? Impossible! The world would reek of his corpse!" This is a nice synopsis of what was thought of Alexander in his life-

time — that he was larger than life. This Alexander of legend has been an enduring theme in European and Asian art, history, and folklore. A few facts: by 18 years of age, Alexander was a proven military commander; at 20, he was king of the Macedonians; at 22, he crossed from Europe to Asia. By the age of 26, he had forced the capitulation of the largest empire the world had yet seen. At 30, he reached the edge of the known world (from the European perspective) at the Indian frontier, and he was dead before his 33rd birthday.

Any explanation of Alexander's death is complicated by the uneven quality of information that survives from antiquity. The single outstanding problem with this case is that the earliest surviving account of Alexander — in *Historical Library,* by Diodorus of Sicily — was written some three centuries after his death, and the best account — the *Anabasis of Alexander,* by Arrian — was written two centuries later. Many authors wrote about Alexander in the period between his death, on June 10, 323 B.C., and the earliest of the surviving accounts from the Roman period, but very little of that literature has survived.

Alexander became a legendary figure shortly after his death. The legend arose, in part, because Alexander was the subject of school exercises. A question such as this might be posed: "Alexander approached Babylon. The Magi greeted him and said, 'Alexander, we have a prophecy: If you enter Babylon, you will never leave alive.' What would you have done had you been Alexander?" The students would be asked to write essays on the subject, knowing that Alexander died at Babylon several months after his entry into the city. The essays would be debated as part of the rhetorical training so important for admission to public life and careers in law. Such essays have become part of the general literature about Alexander and may be imbedded in the surviving accounts of his last days and final illness.

Information about Alexander's death may also be tainted by propaganda. It was not uncommon for those who wrote about unpopular historical figures to claim that they died slowly of agonizing diseases. For example, the Roman dictator Sulla was said to have been eaten alive by worms and other vermin. He was thus punished by writers after his death in ways that would have been impossible while he was alive. (Sulla probably died quickly of a massive hemorrhage, according to recent studies.) Is the poisoning plot to which the death of Alexander is attributed connected to such propaganda? Classical scholars have written at length on the subject, and whether or not Alexander was poisoned, I would have been surprised if a story of poisoning had not been told.[31,32] The king had motivated and capable enemies, and there were masters of the art of poisoning in Macedonia. Ancient sources relate the story that a potion was transported 1200 miles from Macedonia to Babylon, where it was put in the king's drink. The acceptance of a poisoning plot by both ancient and modern writers results in part from the difficulty of dealing with the death of a famous young person. Had Alexander died gloriously in battle, there would have been no problem, but he died slowly of an unknown ailment.

What was in Alexander's wine? What wine? Whose wine? Did warriors carry wine with them on expeditions? Military exigencies dictated a limited transport capacity: one carried water. Macedonian soldiers went for long periods without consuming wine, but when it was available locally (in Europe, Asia Minor, and Mesopotamia), they drank heavily.[33] The Greeks traditionally mixed their wine with water, but the Macedonians drank their wine in a manner described by the Greeks as *akratos* (unmixed). Our ancient sources on Alexander describe great symposia and mention heavy drinking at these events, and although it is certain that Alexander was an occasional heavy drinker, it is difficult to know whether he was disabled as the result of alcoholism.

Until the 1920s, Macedonia was considered to be the most malarious region in the nontropical world.[34,35] There are two varieties of anopheles mosquitoes in Macedonia, stream breeders and marsh breeders, both of which transmit malaria. The malarial season was thus prolonged throughout much of the year. The swampy area from Thessaloniki to the central Macedonian plain was drained by engineers in the 1920s and 1930s, but evidence from ancient writers, modern accounts, and comparative environmental studies indicate that malaria was endemic to the region until recently. Several years before his death, Alexander had an illness marked by a high fever.[36] He was at Tarsus, in southern Turkey, on his way east, at the time. He bathed in a river there, just as he bathed in the Euphrates River during his last few days, and both regions were noted for being malarious.

Whatever the nature of Alexander's disease, it may have been exacerbated by his prolonged and intense grief over the death of his companion Hephaestion in the summer of 324 B.C. One modern author has described it thus: "The violence and extravagance of the king's grief went beyond all normal bounds. . . ."[37] Alexander was disconsolate. He grieved deeply for months, and one wonders what effect this prolonged emotional anguish had on his health (Reames-Zimmerman J: personal communication). The king sought relief from his grief by engaging in an intense program of local campaigns, but it became clear by the spring of 323 B.C. that he was in a declining state of health. He became progressively weaker and finally died on June 10.

Alexander's corpse was prepared for interment and embalmed in Babylon. The funeral procession, en route to Macedonia, was hijacked, and the corpse

was taken to Alexandria and placed in a glass sarcophagus, where it remained on view for the next five and a half centuries. What happened to Alexander's corpse after this is unclear. In modern Alexandria, in the Mosque of the Nebi Daniel, there is a subterranean crypt that is cruciform in shape; it is part of the foundation of an early Christian church. There is a legend that the church was built over Alexander's mausoleum, and according to newspaper accounts in the late 19th century, a workman repairing the foundation gazed on the remains of Alexander's crypt. The possibility that one might gain permission to excavate this site in search of the remains of an ancient Macedonian king is remote, and Alexander's death today remains a mystery.

DAVID W. OLDACH, M.D.
ROBERT E. RICHARD, M.D., PH.D.
University of Maryland School of Medicine
Baltimore, MD 21201

EUGENE N. BORZA, PH.D.
Pennsylvania State University
University Park, PA 16802

R. MICHAEL BENITEZ, M.D.
University of Maryland School of Medicine
Baltimore, MD 21201

Address reprint requests to Dr. Benitez at 22 S. Greene St., Rm. S3B06, Baltimore, MD 21201.

Supported in part by an unrestricted continuing educational grant from Bayer Pharmaceuticals and by a grant from the Department of Veterans Affairs.

This case discussion was originally presented in an open forum sponsored by the University of Maryland and the Baltimore Veterans Affairs Medical Center as part of a series of historical clinicopathological conferences. Others have reviewed the death of Alexander before us, including Coulomb,[38] who disputed the malaria theory, Bosworth,[1] Ashton and Parkinson,[3] Engels,[39] and more recently, Sbarounis,[40] who suggested a diagnosis of acute pancreatitis. Our case history was based principally on the works of Plutarch and Arrian, and we believe a historical analysis was invaluable in evaluating the strengths and weaknesses of these sources, as well as giving a broader perspective to our medical discussion.

We are indebted to Philip A. Machowiak, M.D., for his creativity in this project and his encouragement and advice in the preparation of the manuscript.

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5. Plutarch. Lives: Alexander. Cambridge, Mass.: Harvard University Press, 1994:XLIV.3-XLV.3.
6. *Idem.* Lives: Alexander. Cambridge, Mass.: Harvard University Press, 1994:XVI.4-XVI.7.
7. *Idem.* Lives: Alexander. Cambridge, Mass.: Harvard University Press, 1994:XIX.2-XIX.5. Parmenio wrote to Alexander to warn him about Philip, a physician Parmenio thought had been bribed by Darius to kill Alexander. Philip gave Alexander a potion to "cure" his illness, after which "he fell into a swoon, had scarce any sense or pulse left," but recovered swiftly.
8. *Idem.* Lives: Alexander. Cambridge, Mass.: Harvard University Press, 1994:LXXII.1-LXXII.3. According to Plutarch, Hephaestion fell sick with a fever and subsequently "ate a boiled fowl for his dinner, and drank a huge cooler of wine, fell sick, and in a little while died." Arrian relates a similar story (*Anabasis of Alexander* VII.13.5-VII.13.14), although he states that Hephaestion's illness lasted seven days.
9. *Idem.* Lives: Alexander. Cambridge, Mass.: Harvard University Press, 1994:LXXVII.1-LXXVII.5. "His body, although it lay without special care in places that were moist and stifling, showed no sign of such a destructive influence, but remained pure and fresh." Plutarch offers this as evidence that Alexander was not poisoned.
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