of migratory birds could carry the virulent viruses. To identify the source of infection, the genetic sequence of the virus will be compared with the sequences of viruses acquired in other epidemic areas.

The avian influenza virus did not originally infect other animals, including humans. The virus in Japan had different DNA sequencing from the viruses responsible for human deaths in Hong Kong and Vietnam. However, mutations of the virus in pigs as a result of hybridization are possible, since both avian and human influenza viruses can infect pigs. According to the Food and Agriculture Organization of the United Nations, the H5N1-type virus was detected in pigs raised on farms that also raise chickens infected with the virus in Vietnam. Thus, a new virus that can infect other animals may emerge. In fact, a clouded leopard died of avian influenza in Thailand.

The worst scenario would be that the new virus could be spread from person to person. An avian influenza vaccine is not available in Japan. Because a vaccine may not be developed quickly enough, this new influenza might become pandemic. Therefore, to prevent the virus from infecting humans, bird-to-bird transmission must be stopped.

Kazuo Inoue*

*University of Tokyo, Tokyo, Japan

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Address for correspondence: Kazuo Inoue, Department of Public Health, Graduate School of Medicine, the University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033 Japan; fax: 81-3-3816-4751; email: inouek@m.u-tokyo.ac.jp

Alexander the Great and West Nile Virus Encephalitis

To the Editor: Marr and Calisher suggest the cause of Alexander the Great's death in Babylon in 323 B.C. was West Nile encephalitis (1). They were intrigued by the fact that as Alexander entered Babylon, ravens fell dead from the sky. The authors postulated the ravens might have had West Nile encephalitis, and because of the endemicity of mosquitoes in ancient Babylon, Alexander could have died of West Nile encephalitis. The authors are to be complimented on coming up with a novel explanation for his death, but this explanation has several problems (2,3).

Determining the exact cause of Alexander's death is impossible. Classical scholars are hampered by difficulties with translations from ancient Greek texts as well as differences in terms used by Plutarch in his description of Alexander's demise. We are left with a description that is incomplete, but nevertheless contains cardinal features of his terminal illness (4–6). In infectious disease practice, a syndromic diagnosis is the basis of the clinical approach. Astute infectious disease clinicians must discern between consistent and characteristic features in syndromic diagnosis. In addition to characteristic clinical features, syndromic diagnosis also depends on time relationships of clinical features. That splenomegaly is a feature of Epstein-Barr virus infectious mononucleosis is important, but equally as important is the late rather than early appearance of splenomegaly in the illness. A laundry list of features associated with various infectious diseases tells only part of the story and is diagnostically unhelpful unless placed in the proper time sequence.

In the authors' table, the clinical symptoms associated with Alexander's final days are listed (1). In my review of translations of ancient sources, chills are never mentioned as accompanying Alexander's slowly rising fever. After a steadily increasing fever, Alexander first became weak, then lethargic, and finally died after a 2-week febrile illness. These features and time course are inconsistent with various explanations that have been given for Alexander's death, i.e., influenza, poliomyelitis, alcoholic liver disease, malaria, schistosomiasis, leptospirosis, and poisoning (6–8).

The death of Alexander was certainly caused by an infectious disease and not poisoning or alcoholic liver disease. Although Alexander had an appetite for alcohol, his terminal illness is inconsistent with liver failure attributable to alcoholic cirrhosis or delirium tremens. Poisoning, which has been postulated by some, is not a reasonable diagnostic possibility either, since toxins or poisons are not accompanied by fever. Therefore, we are left with an infectious disease that was endemic in ancient Babylon and was fatal after approximately 2 weeks. The infectious disease that resulted in Alexander's demise was characterized by a slow but relentless increase in temperature during 2 weeks, unaccompanied by chills or drenching sweats. While remaining mentally alert, he drifted into an apathetic state, according to Alexander's Royal Diaries. Details of his death do not provide additional details other than he was febrile, weak, and gradu-

ally became lethargic, lapsed into coma, and died. Are the features of his illness and temporal sequence of events characteristic of West Nile encephalitis (9)?

West Nile encephalitis is a mosquito-borne infectious disease that may have been endemic in ancient Babylon. Ravens could have had West Nile encephalitis, and if West Nile encephalitis was present at the time, certainly it was transmitted to animals as well as humans. No one would argue with the possibility of West Nile encephalitis in the ancient Middle East; however, proving that West Nile encephalitis explains Alexander's death is more difficult. West Nile encephalitis begins acutely, with initial signs and symptoms of mental confusion and muscle weakness. Fevers are not usually the most conspicuous feature of West Nile encephalitis, and in most cases the fever does not usually increase or last more than a 2-week period. Other forms of viral encephalitis, including West Nile encephalitis, all begin with an abrupt change in mental status, e.g., encephalitis, at the outset of the illness. The patient's mental status may change over time, but encephalitic symptoms are present initially. This symptom is a characteristic feature of viral encephalitis, whether it is due to West Nile encephalitis or western equine encephalitis, Venezuelan equine encephalitis, St. Louis encephalitis, or Japanese encephalitis. Even non–arthropod-borne causes of viral encephalitis, e.g., herpes simplex virus I encephalitis, occurs with encephalitis as an initial, not terminal feature.

Alexander's final illness is more characteristic of typhoid fever than West Nile encephalitis. On Alexander's return to Babylon, he was confronted by many portents and omens and correctly assumed that they were a forewarning of his death. Not only were ravens falling from the sky, but the birds that were sacrificed to foretell the future were devoid of a liver lobe, which was thought by the ancients to be an ominous sign. A docile animal in the royal menagerie, in a violent outburst, kicked the royal lion to death. A mysterious person entered the royal chamber and sat on Alexander's throne bypassing the household guards. He claimed that he was divinely sent. West Nile encephalitis could explain these unusual phenomena.

However, the time course and characteristic clinical features of West Nile encephalitis are inconsistent with the cause of Alexander the Great's death (10). On the basis of characteristic features and time course of the illness, typhoid fever is the most likely explanation for Alexander the Great's death. The ravens in this case were the red herrings.

Burke A. Cunha*†

*Winthrop-University Hospital, Mineola, New York, USA; and †SUNY School of Medicine, Stony Brook, New York, USA

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Address for correspondence: Burke A. Cunha, Infectious Disease Division, Winthrop-University Hospital, Mineola, NY 11501, USA; fax: 516-663-2753; email: rholobig@winthrop.org

To the Editor: We wish to commend Marr and Calisher for their brilliant presentation of the West Nile virus (WNV) hypothesis to explain the death of Alexander the Great (1). Having recently proposed typhoid fever as the cause of Alexander's demise (2), we read their paper with particular interest. While we could argue the finer points of the WNV and typhoid hypotheses in explaining limited available clinical data, or perhaps debate the capacity of encephalitic ravens to perform the aerial acrobatics described by Plutarch, many of these considerations were thoughtfully anticipated by the authors. Instead, we have taken the opportunity to "Brush Up Our Plutarch." Reading widely through his essays, we have come to fear that Marr and Calisher, perhaps unaware of the magnitude of Plutarch's obsession with avian augeries, have been led down a feathered path. In story, after story, after story, birds portend.

Our source material was the Dryden translation, Volumes I and II, of Plutarch's Lives (3). We were immediately struck by the opening paragraph of his essay on Alexander, where he writes, "my design is not to write histories," and "I must be allowed to give my more particular attention to the marks and indications of the souls of men" (4). And so, the great writer served notice; particular details, especially where the material might lend insight into a man's character, were subject to a creative process that he himself could not

describe as "history."

When approaching the time of Caesar's assassination, Plutarch wrote, "…many strange prodigies and apparitions are said to have been observed shortly before this event… the wild birds which perched in the forum" (5). As Cicero fled Antony's death sentence, Plutarch wrote, "…a flight of crows rose with a great noise, and made towards Cicero's vessel, as it rowed to land, and lighting on both sides of the yard, some croaked, others pecked the ends of the ropes" (6). On the founding of Rome, he wrote, "...concluding at last to decide the contest by a divination from a flight of birds… Remus, they say, saw six vultures, and Romulus double that number… Hence it is that the Romans, in their divinations from birds, chiefly regard the vulture" (7). (For Remus, who died shortly thereafter, this appears to have been a less propitious sighting.)

When writing on the lost grave of Theseus, Plutarch wrote, "…he, by chance, spied an eagle upon a rising ground pecking with her beak and tearing up the earth with her talons" (8).

On the defeat of the Persian armada at Salamis, he wrote, "...an owl was seen flying to the right hand of the fleet, which came and sat upon the top of the mast" (9). These examples, to which we could add others, should suffice to make our point.

Yet, we do not seek to diminish the contribution of Marr and Calisher. Plutarch, renown for his expositions on notable men, sought in doing so to identify elements of greatness. In this vein, we note the qualities that these three fine writers share. Truly, all are erudite. All share a remarkable awareness of the importance of birds. For this, both as physicians and as birders, we applaud them. In this age of emerging infections, including WNV and avian influenza viruses, we ignore bird health at our peril. We thank the doctors for this reminder and have increased our vigilance. We recommend, however, a grain of salt with Plutarch.

David Oldach,*†
R. Michael Benitez,*†
and Philip A. Mackowiak*†

*VA Maryland Health Care System, Baltimore, Maryland, USA; and †University of Maryland School of Medicine, Baltimore, Maryland, USA

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Address for correspondence: David Oldach, University of Maryland, School of Medicine, Room 552, Institute of Human Virology, 725 W. Lombard Street, Baltimore, MD 21201, USA; fax: 410-706-1992; email: oldach@umbi.umd.edu

To the Editor: The article by Marr and Calisher (1) concerning the causes of the death of Alexander the Great triggered our curiosity about the possibility of supporting this hypothesis by determining the evolutionary time of West Nile virus (WNV). WNV is a member of the *Culex*-transmitted clade of flavivirus (which also includes Japanese encephalitis virus, St. Louis encephalitis virus, and Murray Valley encephalitis virus) whose reservoir is birds (1). Like most of the RNA viruses, flaviviruses are characterized by a high degree of genomic variability (2,3). Strains of WNV currently are divided into two distinct lineages on a molecular basis: one with a worldwide distribution and the other, which includes the prototypic strain isolated in Uganda in 1937 that is only found in sub-Saharan Africa and Madagascar.

To estimate the time of divergence among the different WNV strains, we conducted a phylogenetic analysis of a number of WNV sequences available in GenBank using a maximum likelihood (ML) method that makes it possible to estimate the branch lengths of a phylogeny with dated isolates under the SRDT (single rate dated tip) model (4). In particular, we retrieved sequences included in the envelope (E) gene of 38 WNV isolates: 18 lineage 1 strains representative of all of the proposed type 1 subtypes, including one Kunjin virus isolate (5), and 20 lineage 2 strains, including the original 1937 isolate from Uganda (6,7). The date of isolation was available for all of the viruses for which sequences where considered.

The 227-bp sequences were aligned with ClustalW (Thompson 1994), and distance-based unweighted pair group method with arithmatic mean (UPGMA) and ML methods were used to make the analysis. The distance matrix and the ML trees were obtained using the PAUP* program (version 4.0b10, Swafford 2001). The

Kimura's two-parameters model of nucleotide substitution was used with γ-distributed rates. The substitution model, α shape, Ti/Tv ratio and base frequencies were estimated using Modeltest version 3.06 (8). The trees were obtained by means of a DR heuristic search and were rooted by using Japanese encephalitis virus as the outgroup. The trees were used to estimate branch lengths in accordance with the single rate dated tips (SRDT) model using the Tipdate program implemented in PAML version 3.13 (9). A likelihood ratio test (LRT) was used to examine the fit of each model to the data.

The high mean divergence between the two lineages (0.891 [SE 0.294] substitutions/site) was a good reason for analyzing them separately. The mean distance between the lineage 2 strains was 8.3 times shorter than that between the lineage 1 strains (0.018 [SE 0.05] sub/site vs. 0.154 [SE 0.036] sub/site). Analysis of the goodness-of-fit of the models showed that the likelihood of the SRDT and DR models was similar for lineage 2 (2Δ lnL 26.04, degrees of freedom-df: 17-$p > 0.05$ LRT), whereas DR was significantly better than SRDT for lineage 1 (2Δ lnL = 47.08, df = 15-$p < 0.001$ LRT).

The substitution rates estimated with the SRDT model were very similar in the two lineages (1.25×10^{-4} [$\pm 7.07 \times 10^{-6}$] in lineage 1, and 1.20×10^{-4} [$\pm 7.03 \times 10^{-5}$] in lineage 2). On the basis of these substitution rates, the most recent common ancestor (MRCA) for lineage 1 can be dated back 1,159 years ago (95% confidence interval [CI] 1,043–1,274, i.e., between 729 and 961 AD) and the MRCA for lineage 2 back to 208 years ago (95% CI 105–311; i.e., between 1,693 and 1,899 AD) (Figure).

Our calculated substitution rates are very close to those reported for other RNA viruses, including some flaviviruses. A phylogenetic study of the entire E gene of various flaviviruses (3) estimated a rate of 7.5×10^{-5} nonsynonymous nucleotide substitutions/site/year, and the divergence times estimated on this basis showed that the *Flavivirus* genus is relatively young (<10,000 years). As suggested by the phylogenetic trees, the divergence of the three groups of *Flavivirus* (mosquito-borne, tick-borne, and no known vector viruses) is the earliest event in their evolution and dates back to no more than 5,000 years ago (2), and the divergence of the *Culex*-transmitted group (including WNV) and *Aedes*-transmitted flaviviruses (including dengue and yellow fever viruses) has been placed at approximately 3,200 years ago (3).

One possible limitation of our study is the fact that the goodness-of-fit of the DR model is better than that of the SRDT model for lineage 1. However, on the basis of the results of a simulation study, the estimated substitution rates should still be reliable indicators of the average rate of evolution and can be used to infer the divergence times correctly also in this case (10).

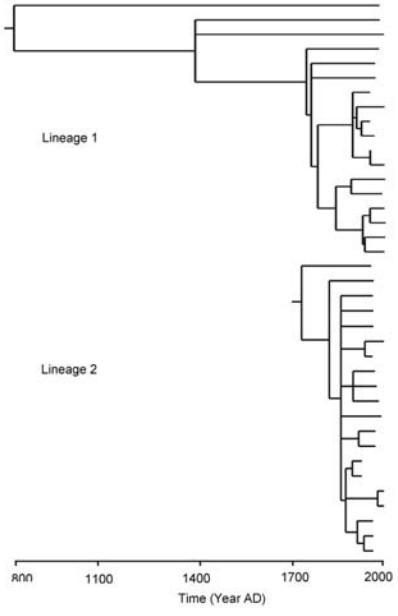

Figure. Maximum likelihood (ML) phylogenies constructed under SRDT model for lineages 1 and 2 of West Nile virus. Horizontal branch lengths are proportional to time.

In conclusion, our divergence time estimate suggests that WNV is a relatively young virus and reduces the probability of incidental infections of humans before 1,000 years ago. Encephalitis itself became a frequent complication of WNV fever in 1996 (11), which suggests the recent appearance of more pathogenic viral strains. Although the present spread of WNV lineage 1 may be compatible with its presence in the geographic area of ancient Babylon, the molecular dating of its origin acquits it of any responsibility for Alexander's death.

Massimo Galli,* Flavia Bernini,* and Gianguglielmo Zehender*

*Istituto di Malattie Infettive e Tropicali, Università degli Studi di Milano, Milan Italy

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Address for correspondence: Massimo Galli, University of Milano, L. Sacco Hospital Via GB Grassi, 74, Milano, Italy, 20157; fax: ++39023560805; email: massimo.galli@unimi.it

In reply: The response by Oldach et al. is wonderfully whimsical (a word that was unfortunately deleted from our manuscript by the EID reviewers). We do not think a witty response is indicated and cannot think of one anyway. We note, however, that both our paper (1) and the Oldach et al. response are examples of the serendipitous pleasures that can be brought to the literature by classical citations, and that all orthodox medical theories on historical causations should be periodically reexamined. Because we are the type who do not mind crawling around in dirty places, we consider computer-based epidemiology for the birds and are willing to eat *Corvus brachyrhynchos*.

We also thank Cunha for his exhaustive differential diagnosis. We felt we had to address all previously cited diagnoses as well as those not posited in the literature, even though, like Cunha, we did not think most of them were likely causes. We concur that most plant toxins do not induce fever, but some do contain anticholinergic alkaloids that may interfere with perspiration and elevate body temperature. (A most enjoyable recent book discusses a variety of poisons and their widespread use by the Greeks, Romans and Scythians [2]. The book illuminates the widespread use of poisons not only on persons but also as weapons in battle and sieges.) Since thermometers were not available at that time, it remains impossible to document this critical vital sign, but since poisoning was specifically mentioned by Plutarch, we felt we could not ignore this possibility. Who are we to ignore Plutarch?

We also agree that typhoid fever remains high on the list of probable causes, as Oldach eloquently argued 5 years ago (3). Although individual cases of this disease usually occur in a camp setting, one would expect reports of other similar cases (the same for malaria), which was apparently not the case. A singular case of West Nile encephalitis, however, is the rule, not the exception.

Cunha stresses the importance of "acute infectious diseases clinicians" arriving at a procrustean diagnosis. In our diagnosis, we chose to emphasize previously overlooked environmental and public health considerations, such as climatic conditions and the deaths of ravens. As stated earlier, we also had an ulterior motive in our writing: to continue the legacy of others in heuristic discussions of the classics (4). In that sense, we have achieved our goal. Cunha considers the diagnosis of West Nile encephalitis as a "red herring." We point out that *Clupeus harengus* was quite bountiful in ancient times (5), and at least some must have been erythematous.

As for the marvelous letter from Galli, Bernini, and Zehender, which minimizes Plutarch's assertions, we can only say that perspective is everything. That these investigators have gone to such lengths to investigate our "best guess" is reward enough for us. We attempted to show retrospectively, as all diagnoses must be done for dead patients, that to come to an Occamic conclusion, one should at least have a look beyond the obvious. Given the multitude of letters and messages we have received since the publication of our article, and given all the interviews we have given to newspapers, magazines, and other media, which always prefer a "hot" topic to an important one, we have been successful in promoting intellectual debate. We would be delighted to be proven right or wrong in our thesis**,** but we are not convinced that Galli et al. are correct in their estimation that West Nile virus did not exist at the time of the death of Alexander the Great. Various phylogenetic studies of flaviviruses (6–8) have discussed the time period when flaviviruses have emerged or diverged, with estimates based on nucleotide substitution rates. However, most groups seem to be retreating from their former definitive positions on this subject because of various technical discrepancies originating from assumptions made regarding the sequence dating methods themselves. Some investigators believe that such dating methods are unreliable for all but the most recent divergence events. At the very least, these methods remain controversial, as does the cause of death of Alexander the Great, who is, after all these years, still causing trouble.

John S. Marr*
and Charles H. Calisher†

*Virginia Health Department, Richmond, Virginia, USA; and †Colorado State University, Fort Collins, Colorado, USA

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Address for correspondence: John S. Marr, Office of Epidemiology, Virginia Health Department, Room 123, 1500 East Main Street, Richmond, Virginia 23218; fax: 804-786-1076; email: john.marr@vdh.virginia.gov

Syndromic Surveillance

To the Editor: As public health practitioners directly involved in constructing, maintaining, and interpreting syndromic disease surveillance systems, we offer the following comments on the Buehler et al. article, "Syndromic Surveillance and Bioterrorism-related Epidemics" (1). In general, this article was well-crafted. It reviewed the potential for syndromic surveillance to detect various diseases of bioterrorism, specifically an anthrax event based on the inhalational anthrax cases of 2001. However, the reader may conclude that hospital-based syndromic surveillance is potentially ineffective and unproven.

Buehler et al. describe how, within 18 hours, a presumptive diagnosis of anthrax would prompt a full-scale response. We think that functional syndromic surveillance can respond to the rapid onset of hospital-based disease. To isolate and positively identify *Bacillus anthracis* from a blood culture would take ≈48 hours. Syndromic surveillance should detect a large number of cases within 24 hours. A fully functional hospital syndromic surveillance system that uses automated analysis (such as the daily emergency department–based surveillance with SaTScan in New York City) should identify a substantial increase in a relevant syndrome within 12 to 24 hours after data submission (2). A continued daily rise in any disease category would most certainly set off alarms in a syndromic surveillance network. If active statewide laboratory surveillance is included in syndromic surveillance, such as the gram-positive rod surveillance conducted in Connecticut (3), this surveillance should rapidly detect even single cases of anthrax concurrent with the presumptive diagnosis within the hospital.

The authors also state that syndromic surveillance would not detect outbreaks too small to trigger statistical alarms. The combination of active and passive surveillance in the hospital admissions–based syndromic surveillance in Connecticut allows a number of syndromes to be tracked immediately upon notification; these syndromes include pneumonia and acute respiratory disease in healthcare workers admitted to a hospital, all disease clusters, and fever with rash illness. This system is very flexible, and active surveillance of other syndromes can be quickly instituted as required. This active surveillance component has been proven useful. The first 2 of Connecticut's 17 confirmed human cases of West Nile virus during 2002 were discovered in August when a health director, who regularly monitored the syndromic admissions data for the hospital in his municipality, requested immediate West Nile virus testing from the hospital's infection-control department when he received two late summer reports of neurologic illness.

Buehler et al. state that specificity for distinguishing bioterrorism-related epidemics from more ordinary illness may be low because the early symptoms of bioterrorism-related illness overlap with those of many common infections. Illness specificity can be modulated within a syndromic surveillance system by making changes in the definition of the information requested, the method of analysis used, or by incorporating varying amounts of active surveillance into a passive reporting system. In Connecticut, annual rates of hospital admissions for pneumonia and respiratory illness have significantly increased (>3 standard deviations) during winter months. These increases have corresponded temporally with peaks in laboratory-confirmed influenza reports and in our state-based and the national sentinel physician influenzalike illness reports. Similarly, in the military-based syndromic surveillance system, respiratory outbreaks are detected by monitoring routine outpatient visits and pharmacy prescriptions. Absolute numbers of visits, as well as percentage of visits, to primary care clinics for influenzalike illness provide up-to-date information on respiratory disease conditions at military installations in both active-duty personnel and family members.

Connecticut has added additional active surveillance categories to its syndromic surveillance for potential SARS cases by gathering extensive data on all healthcare providers hospitalized with respiratory illness. In the absence of an identified pathogen, the entire United States was conducting syndromic surveillance for SARS during the spring of 2003.

What are existing alternatives to rapid, patient-based reporting through syndromic surveillance for bioterrorism and emerging illness? Will individual physicians (i.e., the "astute clinicians") truly recognize an increase of nonspecific symptoms among their patients in time to warn public health authorities of an impending bioterrorism event? During the past 4 years in the U.S. military population, unless