

mental health is needed so that appropriate interventions may be implemented at individual, family, and societal levels.

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## Highly Pathogenic Avian Flu, Japan

**To the Editor:** More than 15,000 chickens on an egg farm in Yamaguchi Prefecture (Chugoku area) have died since the end of 2003. A highly pathogenic avian influenza virus, which had not appeared in Japan for 79 years, was detected in the dead chickens. Of the 34,600 chickens on the farm, dozens to hundreds have died daily since December 28. Moreover, the deaths have increased during 2004. The Ministry of Agriculture, Forestry, and Fisheries ascertained that the same H5N1 avian influenza virus had caused the bird flu epidemic that started in 1997 in East Asia, including Hong Kong, Vietnam, and South Korea. The H5N1 type is a virulent pathogen that can also infect humans as demonstrated by the >20 deaths in Hong Kong, Vietnam, and Thailand. After the influenza infection was confirmed, the ministry immediately ordered the hennery to recall all

eggs that had been shipped. The hennery was then disinfected, and non-workers were restricted from entering. Yamaguchi Prefecture also restricted transfer of the chickens and eggs within a 30-km radius of the infected hennery. The hennery was the first facility infected in Japan. Since mid-February, an additional three outbreaks have occurred (one in Ohita Prefecture in Kyushu Island and two in Kyoto Prefecture in the Kansai Area). In a big poultry farm in Kyoto, 40,000 deaths of chickens, caused by H5N1, were confirmed. The H5N1 virus was also detected by polymerase chain reaction in crows found dead near the chickens in Kyoto. All four sites with infected chickens are in western Japan.

Modern stock raising that involves breeding a large number of domestic animals and fowl in high density has become a risk factor for large-scale outbreaks. The globalization of the marketplace and easy mobility of people and goods have facilitated the spread of many pathogens. Avirulent pathogens that mutate easily may acquire stronger infectious and toxic properties as confirmed in the influenza pandemic of 1918 (1).

Several possibilities exist for the appearance of avian influenza virus in Japan. First, migratory birds from disease-epidemic areas might be the primary vectors of the virus. Yamaguchi Prefecture is located 200 km south-east of South Cholla Province, South Korea, where avian influenza is epidemic. The two areas are close enough for wild birds to cross the Korean Strait. Ito et al. reported that avirulent viruses found in wild waterfowl and bearing the consensus avirulence type sequence R-E-T-R have the potential to become pathogenic when present in chickens (2). Thus, migratory birds that are asymptomatic carriers may cross the Korean Strait harboring the H5N1-type virulent viruses generated in Korea. Alternatively, people, cars, and feed grains instead

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.

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## 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-