Transfusion-Associated Malaria

To the Editor: A recent article by Zucker (1) described two cases of malaria that were probably transfusion associated. A case of transfusion-associated malaria in which the source *was* identified was reported in San Francisco in 1991. The case was in an elderly man in whom malaria infection developed after coronary bypass surgery.

The patient was born in China and immigrated to the United States in 1940. His only travel outside the United States was a trip to Hong Kong in 1951 for 6 months. The patient's wife was born in China and had malaria in 1941 during World War II. She received no treatment at that time or at any other time. She came to the United States in 1960 and has not left the country since.

The patient had six donors, five of whom had no history of malaria, and had negative serologic test results for all four malaria species. Both the patient and his wife had blood smears positive for *P. malariae*. The patient's wife had positive serologic test results for *P. vivax* and *P. ovale* (1:64), for *P. falciparum* (1:258), and for *P. malariae* (1:1024).

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1. Zucker J. Changing patterns of autochthonous malaria transmission in the United States: A review of current outbreaks. Emerging Infectious Diseases 1996: 2:37-43.

Reply to F. Taylor: Dr. Taylor's letter calls attention to the small but important number of induced malaria cases that occur in the United States. From 1957 to 1994, 101 such cases were reported to the Centers for Disease Control and Prevention (CDC); these (including the 1990 case described by Dr. Taylor [1]) are reviewed annually and reported by CDC (2). The occasional occurrence of induced malaria further emphasizes the importance of including malaria in the differential diagnosis of fevers of unknown origin, even in patients who have not traveled to countries where malaria is endemic. Preventing induced malaria requires screening potential blood, tissue, and organ donors and deferring those with a history of malaria or travel to malarious areas. Furthermore, timely surveillance must be maintained to detect induced cases promptly, identify infected blood donors, and prevent additional cases.

The case described by Dr. Taylor was not included in "Changing patterns of autochthonous malaria transmission in the United States: a review of recent outbreaks" (3) because it was a case of induced rather than autochthonous malaria. Each reported malaria case is classified according to standardized terminology (4). *Imported* malaria (which accounts for most cases in this country) is acquired outside the United States and its territories. Malaria acquired within the United States is rare and occurs by one of three mechanisms: *Autochthonous* malaria is acquired through the bite of an infective mosquito. *Congenital* malaria is acquired when a child is infected in utero. *Induced* malaria is transmitted by mechanical means such as transfusion of blood or blood products, organ transplant, deliberate infection for malariotherapy, or contaminated needles or injection equipment. Congenital and induced cases were not included in this review.

When an investigation fails to identify the source of transmission and a case cannot be epidemiologically linked to another case of malaria, the case is classified as *cryptic*. Most cryptic cases are believed to be autochthonous, and there is often evidence to suggest mosquito-borne transmission, even when the source of infection remains unidentified. For this reason, most cryptic cases were included in this review of autochthonous malaria. The two exceptions noted in the article were excluded because both patients had recent histories of blood transfusion, suggesting that their infections were induced.

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An Outbreak of Hemolytic Uremic Syndrome due to *Escherichia coli* O157:H-: Or Was It?

To the Editor: Since the first reported outbreaks of hemolytic uremic syndrome (HUS) and related conditions more than 10 years ago (1), outbreaks of HUS due to *Escherichia coli* O157 have been reported from many parts of the world, particularly North America and Europe. While most of these reports have incriminated the motile strains of serotype O157:H7, nonmotile serotypes (e.g., O157:H-) have also been associated with HUS; these two serotypes are most commonly associated with both outbreaks and sporadic cases of HUS and related conditions. Over the last decade, a number of techniques for the rapid identification of these organisms have been developed. Of these, the use of sorbitol-MacConkey agar (2) has perhaps been the most valuable. This technique is based on the fact that these organisms rarely ferment sorbitol on primary isolation, while most other *E. coli* usually ferment this substrate. We believe that outbreaks due to other enterohemorrhagic *E. coli* may have been attributed to serogroup O157 because of the limited technology used in investigating these outbreaks.

No outbreaks of HUS due to serogroup O157 have occurred in Australia despite sporadic cases of HUS caused by such strains. Other serogroups (particularly serotype O111:H-) have been associated with most cases of HUS and related conditions in Australia (3). No outbreak of HUS had been reported in Australia until January 1995, when an outbreak associated with the consumption of contaminated mettwurst (fermented sausage) was reported from South Australia (4). Twenty-three children with HUS were hospitalized. Most required hemodialysis; one died. Verocytotoxigenic strains of *E. coli* O111 producing Shiga-like toxin (SLT) I and II were isolated from 19 patients and from samples of mettwurst. In addition, strains of *E. coli* O157:H- that produced SLT-I and SLT-II were isolated from three of the patients and the mettwurst. These strains did not ferment sorbitol on the sorbitol-MacConkey agar, which facilitated their isolation. The predominant O111 strains were sorbitol-positive, unlike the O111 strains, recently described as being sorbitol-negative (5). Symptoms of the patients from whom the O157:H- strains were isolated, in addition to *E. coli* O111:H-, were not significantly different from those of the patients whose specimens yielded only *E. coli* O111:H-. In addition to O111 (and O157), other serotypes of enterohemorrhagic *E. coli*, including strains of serogroup O23, O26, and O91, were isolated from the patients. However, antibodies to O111 were detected in nearly all patients, which indicates the serogroup's leading role in the outbreak. The isolation of serogroup O157 is comparatively easy; therefore, it is less likely that these strains would have been missed, than it is that O111 and other serotypes would have been. Even though a negative finding can never be considered conclusive, we consider the inability to isolate serogroup O157 more conclusive than the same result for other serotypes. It has frequently been suggested that the O157 serogroup is cleared from the patient relatively rapidly, which makes its isolation difficult or impossible. We found a similar situation with other enterohemorrhagic *E. coli* serotypes. The fact that most patients elicited an O111 antibody response (and no anti-O157) almost certainly proves this serotype's causal role in this outbreak.

The laboratory in South Australia was particularly well disposed to deal with such an outbreak because some of its ongoing research programs included studies on aspects of enterohemorrhagic *E. coli* and related organisms. The most sophisticated molecular biologic techniques were immediately available to investigate the outbreak accurately and confirm epidemiologic leads regarding a common source. Polymerase chain reaction (PCR) played a major role not only in identifying SLT-I, SLT-II, and SLT-I and SLT-II producing bacteria in the stool of patients, but also in identifying the suspected source (mettwurst). In addition, PCR, utilizing sequences specific for the O111 serogroup, enabled this serogroup to be rapidly identified in patients' feces samples and suspected source material. Without this technology, the outbreak would not have been contained so rapidly. On the other hand, if the laboratory had to rely on conventional microbiologic culture procedures, including sorbitol-MacConkey agar, strains of serogroup O157 would have been identified from three patients, as well as from the epidemiologically incriminated mettwurst. The laboratory would not have found the O111 strains because they all fermented sorbitol readily and would have been discarded as normal flora as would the other enterohemorrhagic *E. coli* serotypes. The outbreak would have been reported as another O157 outbreak, from which only about 15% of the patients yielded the incriminating strains. This outbreak could be recognized as one caused by a number of different enterohemorrhagic *E. coli* serotypes, of which serotypes O111:H- and O157:H- were the most prominent.

Other serotypes, however, such as O23, O26, and O91, were also present. With the widespread nature of verocytotoxigenic strain of different serotypes as has been reported from many environmental studies, it is not surprising that a product, such as mettwurst, which is made from meats from various sources, would contain a number of these potential pathogens.

A large number of E. *coli* serotypes can be verocytotoxigenic and, in a few cases, outbreaks due to such strains have been reported. Most notable have been reports from Italy of outbreaks due to enterohemorrhagic *E. coli* O111 (6); however, the impression is that these are the exception and that the most prominent serotype is O157:H7. Some of the reported outbreaks due to O157 strains may in fact have been due to other serotypes and the O157 strains were only present in comparatively small numbers; however, because of the ease with which these strains can be identified using sorbitol-MacConkey agar, they were believed responsible for the outbreaks. For example, in Argentina, *E. coli* O157:H7 was found in only one (2%) of 51 children with HUS (7) and in the Netherlands, only 5 (19%) of 26 HUS patients yielded *E. coli* O157:H7 (8). In a 10-year, retrospective, population-based study of HUS, this serotype was isolated in 13 (46%) of 28 patients (9), and in their review, Su and Brandt (10) put an overall figure of 46% to 58% as the incidence range of E. *coli* O157:H7 infection in cases of HUS. Finding SLT sequences in a fecal specimen by PCR, or free fecal toxins in many patients of an outbreak while isolating strains of O157 from only a few, does not exclude the presence of other serotypes, but culture methods now available would rarely pick these up. Thus there is ample room to speculate that approximately half the cases of HUS may be caused by serogroups other than O157 and, by inference, at least half the outbreaks may be wrongly attributed to this serogroup. We recognize that enterohemorrhagic *E. coli* O157 have become extraordinarily widespread throughout the world since their first description (1); this does not mean that other serotypes are not also causing infections, either alone, in conjunction with O157, or even with other known or unknown enteric infections. It is important to be aware of the existence of these other serotypes and be vigilant for them. The isolation and characterization of strains of serogroup O157 from patients with HUS is certainly noteworthy, but so is the finding of O111 or any other serogroup. Serogroup O111 has amply demonstrated the ability to cause extensive outbreaks (6). Even though many laboratories are becoming aware of the importance of testing for serogroup O157:H7, we think that testing for this serotype only is a disservice; simple culture techniques can identify this serogroup, but always at the risk of missing other serogroups. The development of simple methods to detect all enterohemorrhagic *E. coli* is now required.

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The Dilemma of Xenotransplantation

To the Editor: I read with considerable interest Robert E. Michler's commentary on xenotransplantation (1).

From my point of view, that of a basic virologist, the dilemma is not to know in what "foreseeable future, clinical xenotransplantation may achieve its targeted goal of extended graft survival," but what deadly emerging infectious disease, most probably viral in nature, would arise in a recipient of a baboon or chimpanzee heart. While we face the terrific threat of AIDS, which clearly emerged from Africa and non-human primates 40 to 50 years ago, we are preparing a new infectious "Chernobyl."

Monkeys and apes harbor approximately 50 simian viruses; some of them pose a serious threat to humans, especially the heavily immunosuppressed. Recently, an outbreak of encephalitis related to a new type of reovirus (2) occurred among baboons from a colony used in human organ transplants. Moreover, once unknown or unrecognized simian viruses, like HIV, may be efficient invaders of the entire earth's population.

Xenotransplantation does not simply pose an ethical problem; it concerns the survival of the human species, an endangered species if transplant practitioners continue their course. Ronald Montalero, a virologist, was right when he said "unknown viruses were always a major concern in xenotransplants" (2). A moratorium on these procedures seems the best solution until all simian pathogens are identified and the risks they pose to humans are clearly established.

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The Thucydides Syndrome: Ebola Déjà Vu? (or Ebola Reemergent?)

To the Editor: The plague of Athens (430-427/425 B.C.) persists as one of the great medical mysteries of antiquity (1-5). Sometimes termed "the Thucydides syndrome" for the evocative narrative provided by that contemporary observer (6, 7), the plague of Athens has been the subject of conjecture for centuries. In an unprecedented, devastating 3-year appearance, the disease marked the end of the Age of Pericles in Athens and, as much as the war with Sparta, it may have hastened the end of the Golden Age of Greece (3). Understood by Thucydides to have its origin "in Ethiopia beyond Egypt, it next descended into Egypt and Libya" and then "suddenly fell upon" Athens' walled port Piraeus and then the city itself; there it ravaged the densely packed wartime populace of citizens, allies, and refugees. Thucydides, himself a surviving victim, notes that the year had been "especially free of disease" and describes the following major findings: After its "abrupt onset, persons in good health were seized first with strong fevers, redness and burning of the eyes, and the inside of the mouth, both the throat and tongue, immediately was bloody-looking and expelled an unusually foul breath. Following these came sneezing, hoarseness . . . a powerful cough . . . and every kind of bilious vomiting . . . and in most cases an empty heaving ensued that produced a strong spasm that ended quickly or lasted quite a while." The flesh, although neither especially hot nor pale, was "reddish, livid, and budding out in small blisters and ulcers." Subject to unquenchable thirst, victims suffered such high temperatures as to reject even the lightest coverings. Most perished "on the ninth or seventh day . . . with some strength still left or many later died of weakness once the sickness passed down into the bowels, where the ulceration became violent and extreme diarrhea simultaneously laid hold (2.49)." Those who survived became immune, but those who vainly attended or even visited the sick fell victim (2.51).

By comparison, a modern case definition of Ebola virus infection notes sudden onset, fever, headache, and pharyngitis, followed by cough, vomiting, diarrhea, maculopapular rash, and hemorrhagic diathesis, with a case-fatality rate of 50% to 90%, death typically occurring in the second week of the disease. Disease among healthcare providers and care givers has been a prominent feature (8, 9). In a review of the 1995 Ebola outbreak in Zaire, the Centers for Disease

Control and Prevention reports that the most frequent initial symptoms were fever (94%), diarrhea (80%), and severe weakness (74%), with dysphagia and clinical signs of bleeding also frequently present. Symptomatic hiccups was also reported in 15% of patients (10).

During the plague of Athens, Thucydides may have made the same unusual clinical observation. The phrase *lugx kene*, which we have translated as "empty heaving," lacks an exact parallel in the ancient Greek corpus (5). Alone, *lugx*, means either "hiccups" or "retching" and is infrequently used, even by the medical writers. Although contexts usually dictate "retching," we note unambiguous "hiccups" in Plato's Symposium (185C). In his thorough commentary on the Thucydides passage, the classicist D. L. Page remarks: "Hiccoughs is misleading, unless it is enlarged to include retching." Regarding "empty, unproductive retching [he] has noted no exact parallel . . . in the [writings of the] doctors, but . . . tenesmus comes very close to it" (5). A CD-ROM search of Mandell, Bennett, and Dolin discloses no reference to either "hiccups" or "singultus" in the description of any disease entity (6).

The profile of the ancient disease is remarkably similar to that of the recent outbreaks in Sudan and Zaire and offers another solution to Thucydides' ancient puzzle. A Nilotic source for a pathogen in the Piraeus, the busy maritime hub of the Delian League (Athens' de facto Aegean empire), is clearly plausible. PCR examination of contemporaneous skeletal and archaeozoological remains might test this hypothesis against the 29 or more prior theories.

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