Correspondence

Cat Got Your Tongue?

To the Editor—A 69-year-old woman with a history of seizures, which were well controlled with sodium valproate, and depression presented with acute onset of a painful swollen tongue that resulted in dysphagia, dysphonia, and drooling of saliva. She had not begun treatment with any new medications and was not using an angiotensin-converting enzyme inhibitor. There was no history of recent dental problems, and her only other medication was dothiepin.

On examination, her temperature was 37.6°C. There was gross swelling of the floor of the mouth and tongue, with no erythema. There was no exudate from the submandibular gland duct. The epiglottis and larynx were normal when visualized by direct laryngoscopy. Her neck was tender to palpation in the submental and submandibular regions, but there was no lymphadenopathy. There was no rash or stridor, and chest auscultation revealed normal vesicular breath sounds without any wheeze. The patient was treated with nebulized adrenaline, intravenous dexamethasone, and meropenem.

The C-reactive protein level was elevated to 142 mg/L (normal, <6 mg/L), and there was a neutrophilia with a marked left shift. CT of the neck revealed some patchy hypodensity in the inferior half of the tongue, which was consistent with edema/inflammatory change. Artifact from amalgam fillings obscured the superior half of the tongue. The salivary glands had a normal appearance, and there was no retropharyngeal or prevertebral collection. The nasopharynx, oropharynx, and laryngopharynx were patent, with no airway compromise.

Two sets of blood culture samples taken at admission to the hospital grew *Pasteurella multocida*. Subsequent history revealed that the patient had a cat in her home, but she could not recall a recent bite or scratch. Antibiotic treatment was changed to intravenous ampicillin and then oral amoxycillin, and the patient made a good recovery.

P. multocida is a small, gram-negative coccobacillus that colonizes the nasopharynx and gastrointestinal tracts of many animals [1]. Most human *P. multocida* infections are caused by dog and cat bites. These bites may result in various clinical syndromes, including cellulitis, subcutaneous abscesses, osteomyelitis, septic arthritis, pneumonia, meningitis, endocarditis, intra-abdominal infection, and septicemia [1]. With regard to upper respiratory tract infection, *P multocida* has been associated with sinusitis, otitis media, mastoiditis, tonsillitis, peritonsillar abscess, and epiglottitis [1–3]. This is, to our knowledge, the first reported case of *P. multocida* bacteremia manifesting with glossitis.

The earliest written example of the phrase "cat got your tongue" in the *Oxford English Dictionary* is from 1911; the expression is used when addressing someone who is refusing to speak [4]. Several other theories about the origins of this phrase exist: (1) in the Middle East, liars, as punishment, had their tongues removed and fed to the king's cats; (2) during the Middle Ages, it was thought that, if you saw a witch, her cat would steal or control your tongue such that you could not report the sighting; and (3) the fear of being whipped by the cat o'nine tails would paralyze the victim into silence [5].

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Drug Interactions between Warfarin and Efavirenz or Lopinavir-Ritonavir in Clinical Treatment

To the Editor—Warfarin undergoes liver metabolism by CYP2C9 [1], which is an isoenzyme of cytochrome P450 whose activity could be affected by antiretrovirals. The effect of coadministration in HIV-positive patients has been reported only for nevirapine, which has been shown to decrease warfarin concentration, probably via CYP2C9 induction [2]; no clinical data are yet available for other antiretrovirals. We describe 2 cases concerning coadministration of warfarin with efavirenz or lopinavir-ritonavir.

Case 1 occurred in a 34-year-old black

woman who was receiving stable antiretroviral therapy with didanosine, lamivudine, and efavirenz and who developed an extensive deep vein thrombosis of the right leg with involvement of inferior cave and right iliac veins. The patient underwent placement of a vena cava filter and anticoagulant treatment. After 12 days, the patient was discharged from the hospital with a prescription for warfarin (mean daily dose, 5 mg); she had an international normalized ratio (INR) within the optimal range (2–3) and a platelet count of 432,000 platelets/μL. The patient was readmitted to the hospital 22 days after discharge because of macrohematuria associated with an INR of 7, a platelet count of 58,000 platelets/μL, and normal renal function, without clinical or other pharmacological factors known to increase warfarin activity. The patients most recent INR measurement, obtained 3 days before, had shown an INR of 2.7, and the patient denied overdosing. After admission, warfarin treatment was transiently discontinued, vitamin K supplementation was initiated, bleeding rapidly ceased, and the patient's INR normalized. The patient's 12-h efavirenz concentration in plasma was 3125 ng/mL. The patient was finally discharged with a normalized platelet count and a mean daily dose of warfarin of 1.25 mg (one-fourth of the initial dose).

Case 2 occurred in a 66-year-old white man who underwent mitral valve replacement due to *Streptococcus viridans* endocarditis after stopping a previously effective HAART regimen that had included zidovudine, lamivudine, and lopinavir-ritonavir (400 mg/100 mg administered twice per day). The patient was discharged from the hospital with a warfarin daily dose ranging between 3.75 mg and 5 mg to maintain an INR within the optimal range (2–3.5). Two months later, the previous HAART regimen was reintroduced. After several days, a progressive increase in warfarin dosing up to 10 mg daily was needed to maintain an INR within the optimal range. Lopinavir plasma trough concentration was 4580 ng/mL. After 2 years, when the patient's treatment regimen was simplified to zidovudine-lamivudine-abacavir plus tenofovir, the warfarin dosage was decreased to 3.75–5 mg daily.

These are, to our knowledge, the first clinical reports on coadministration of warfarin with efavirenz or lopinavir-ritonavir. In both cases, the need for warfarin dose adjustments was probably attributable to the opposite effects of these 2 drugs on CYP2C9.

Efavirenz was reported to be a moderate inhibitor in vitro of such isoenzymes, potentially increasing the levels and/or effects of CYP2C9 substrates [3]. For instance, efavirenz was shown to increase phenytoin concentrations, because this anticonvulsant is known to be primarily metabolized by CYP 2C9 and 2C19 [4]. In our case, in which no explanations other than drug interaction were found for the increase in warfarin activity, the magnitude of interaction was impressive, leading to warfarin overdosing. Although concomitant transient thrombocytemia (probably attributable to previous use of heparin) had probably facilitated bleeding, a marked increase in INR is, per se, considered to indicate a high risk of hemorrhage [5]. Therefore, clinicians should be aware of such possible occurrences in their patients.

On the other hand, ritonavir is known to be an inducer of CYP2C9 [6]. The effect of lopinavir-ritonavir (400 mg/100 mg twice daily) on the metabolism of S-warfarin (administered in a 10-mg single dose) was studied in a group of 7 healthy volunteers, resulting in a 22% decrease in the warfarin area under the curve [7]. In our patient, lopinavir-ritonavir treatment was confirmed to decrease warfarin activity, but the magnitude of the interaction was higher than expected, requiring a doubling of the warfarin dose. This case highlights that data regarding drug interactions obtained from single-dose studies involving healthy volunteers could not exactly predict the extent of such interactions at the steady-state concentration in patients.

In conclusion, the clinical cases reported here showed clinically significant drug interactions when efavirenz or lopinavir-ritonavir were concomitantly administered with warfarin, suggesting the need for careful clinical monitoring and warfarin dose adjustment.

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Mycobacterium avium Subspecies *paratuberculosis* Bacteremia in Type 1 Diabetes Mellitus: An Infectious Trigger?

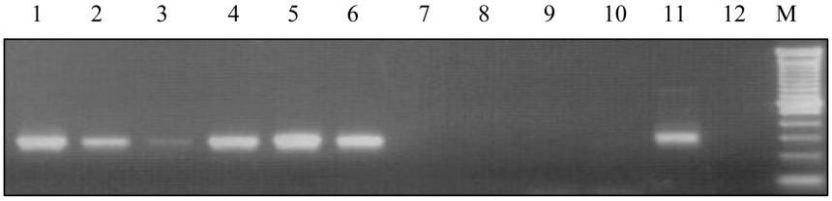

Figure 1. Representative PCR results showing amplification (or otherwise) of 298-bp genomic fragment corresponding to IS900 in diabetic patients *(lanes 1–8). Lanes 9* and *10,* Control subjects without type 1 diabetes mellitus. *Lanes 11* and *12, Mycobacterium avium* subspecies *paratuberculosis*–positive and *M. avium* subspecies *paratuberculosis*–negative control subjects, respectively. M, molecular marker (100-bp ladder).

To the Editor—*Mycobacterium avium* subspecies *paratuberculosis* (MAP) is the established cause of paratuberculosis in ruminants (i.e., Johne disease). The bacterium is shed in the milk of infected cows and survives pasteurization. Recently, an association between MAP and Crohn disease has been suggested, wherein MAP has been found to persist in a cell wall–deficient form, escaping clearance by the host immune system [1, 2].

Type 1 (insulin-dependent) diabetes mellitus (T1DM) reflects the interactions of polygenic traits with ill-defined environmental factors, and it is unknown what initiates and maintains autoimmunity to self-antigens expressed in the pancreatic islets of Langerhans [3]. Consumption of cow's milk early in life has been a recognized risk factor in the development of this disease, and environmental microorganisms are thought to trigger autoimmune responses in genetically susceptible individuals [4]. MAP bacilli have recently been hypothesized to trigger molecular mimicry and killing of pancreatic islet cells by the immune system.

We attempted to test the association of MAP with T1DM in an area of endemicity, such as Sardinia, by testing patients with T1DM for the presence of MAP bacilli in peripheral blood. A total of 96 participants, composed of 46 patients with T1DM and 50 healthy control subjects, were tested for the presence of MAP-specific IS900 signature (figure 1) using total DNA extracted from PBMCs. Informed consent from patients, as well as other necessary clearances, were procured before blood samples were obtained. PCR was performed to detect MAP DNA, as described elsewhere [2]. IS900 fragment identity was confirmed by sequencing (GenBank accession group 1517012) and by BLAST analysis against sequences in the National Center for Biotechnology Information database [5].

A total of 29 (63%) of 46 blood samples from diabetic patients were found to be positive for MAP, whereas only 8 (16%) of the 50 samples from healthy control subjects were positive for MAP. Although a majority of diabetic patients with positive PCR results had a family history of diabetes or other genetic and/or autoimmune disorders, 14 diabetic individuals with positive PCR results did not have any history of diabetes or other autoimmune diseases in their families. Although the differences in the outcome of PCR positivity were statistically validated and found to be significant ($\chi^2 = 10.07$; $P \leq .01$), it is our understanding that MAP-positive control subjects might possibly be representing either the genetic resistance or the asymptomatic forms of variable duration that generally precede the clinical presentation of T1DM.

Genetic evidence suggests that there are specific states of immune dysfunction that promote both T1DM and mycobacterial infection [6, 7]. Deficiency of vitamin D has been implicated as a risk factor for T1DM. Interestingly, vitamin D is also implicated in limiting mycobacterial infection by upregulating expression of an antimicrobial peptide [8].

The island of Sardinia has a high incidence of Crohn disease and other autoimmune diseases, such as T1DM, with a very high prevalence of MAP in Sardinian patients with Crohn disease [2, 3]. Because MAP is present in almost one-half of the sheep herds tested in Sardinia, it is probably endemically contaminating water, milk, and animal feed [9].

Finding evidence of MAP bacteremia in patients with T1DM is a novel observation that might provide an important foundation in establishing an infectious etiology for T1DM. These results also might possibly have implications for countries that have the greatest livestock populations and high incidence of MAP concurrent with the highest numbers of patients with T1DM. Although it is tempting to suggest that MAP could be a potential cause of autoimmune responses associated with T1DM in Sardinia, we believe that a large-scale study involving patients from different genetic and geographic backgrounds might further validate our findings.

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Untangling the Immunological Implications of Nadir on CD4+ Cell Recovery during Suppressive Highly Active Antiretroviral Therapy

To the Editor—Moore et al. [1] recently described a significant difference in $CD4^+$ cell recovery following HIV RNA suppression among patients receiving HAART according to nadir $CD4^+$ cell count, with individuals whose nadir $CD4^+$ cell counts were <200 cells/μL not achieving a protective $CD4^+$ cell count.

A lack of $CD4^+$ cell rescue despite complete HAART-driven viremia suppression represents an everyday dilemma for HIV/AIDS clinicians [2]. Invariably, $CD4^+$ cell count nadir proved to be a major and reliable determinant of suboptimal $CD4^+$ cell recovery and clinical outcome [1–8]. However, the mere quantification of $CD4^+$ cell count nadir fails to qualitatively estimate the ultimate immunological mechanism(s) hindering $CD4^+$ cell rescue. Only by detailing the immunological holes in nadir-driven T cell homeostasis will it be possible to devise the most efficacious treatment approach.

By limiting immune recovery assessment to total $CD4^+$ cell count in a large patient cohort, Moore et al. [1], although gaining statistical power, miss an insight into the immunological role of $CD4^+$ cell count nadir. On the contrary, we feel that stringently focused studies are needed that address the time course of specific immune pathways by nadir $CD4^+$ cell count strata. It would be interesting to know whether the authors have found distinct dynamics in immunephenotype and other immunologic parameters according to $CD4^+$ cell count ranges.

Given their major regulatory role in T cell homeostasis, common γ-chain cytokines, including IL-2, IL-7, IL-15, and IL-21 [9], might be ideal markers of the direction of immune recovery. Thus, although Moore et al. [1] recommend HAART initiation at a $CD4^+$ cell count >350 cells/μL for the most robust immune recovery, we advocate a broad immunologic investigation of regulatory cytokine networks to obtain an indication of pretherapy immune damage and $CD4^+$ cell rescue potential, as well as possible clinical relapses.

As an example of the exploitation of γ-chain cytokine kinetics, we would like to share our experience with the IL-7 and IL-7R system [10] in a cohort of 18 antiretroviral-naive, HIV-positive patients with advanced infection (nadir $CD4^+$ cell count, <150 cells/μL) whom we observed prospectively for the first 12 months of HAART. These patients displayed different virological and immunological responses to HAART: 12 patients had concordant responses (HIV RNA level, $\leq$50 copies/mL; $CD4^+$ cell count, $\geq$200 cells/μL), and 6 patients had discordant responses (HIV RNA level, $\leq$50 copies/mL; $CD4^+$ cell count, $\leq$200 cells/μL). Despite having a higher median baseline plasma IL-7 level than that for patients with concordant responses, patients with discordant responses had a tendency toward reduced $CD4^+$ cell count and lower IL-7Rα availability, which, by indicating free IL-7 mainly resulting from receptor downmodulation rather than compensatory production, also rules out a functional potential on T cell homeostasis. In fact, during HAART, despite a progressive reduction in IL-7, only patients with concordant responses displayed a substantial increase in $CD4^+$ cell and IL-7Rα expression. These findings, by clearly pointing to opposite IL-7 and IL-7R dynamics, also indicate that a lack of IL-7 and IL-7R regulatory control over $CD4^+$ cell homeostasis could be the basis of discordant responses, which cautions against IL-7–based treatment.

In conclusion, it is time to investigate the early integration of classic quantitative determinations of $CD4^+$ cell count nadir proposed by Moore et al. [1] with additional qualitative measures of $CD4^+$ cell count nadir–associated immune imbalances. The effort should be to highlight the immunological role of $CD4^+$ cell count nadir, not only as a quantitative reflection of T cell depletion, but mainly as evidence of more-complex T cell qualitative impairment. The intriguing hypothesis that a lack of IL-7– and IL-7R–mediated regulatory function is behind discordant responses in antiretroviral-naive patients with advanced infection clearly indicates the complexity of the immunopathogenetic mechanisms of $CD4^+$ cell immune recovery. The possibility of monitoring major T cell homeostasis regulators, such as γ-chain cytokines, by possibly disclosing upstream breakdown offers the appealing prospect of targeted immune interventions.

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Cholera or Choleric?

To the Editor—The cover of the 1 September 2007 issue of *Clinical Infectious Diseases* shows a 14th-century painting based on an 11th-century Arabic book that was described as an illustration of a treatment of cholera. However, there is no evidence that the disease that we now call cholera, caused by *Vibrio cholerae*, existed in Europe or Arabia at those times. The first evidence of the presence of this disease spreading westward outside the Indian subcontinent arose in the early 19th century [1].

Prior to the emergence of what we now know as cholera, the term "cholera" was sometimes applied to what were then considered to be various disorders traceable to disturbances of bile, including a "choleric" or angry disposition [2]. It appears to be likely that the cover illustration was intended to show treatment of that disorder, because the patient appears to be agitated, with breasts exposed, and seems to be biting a towel. There is no sign of the diarrhea, vomiting, dehydration, or collapse that are associated with what we now know as cholera.

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Interstrain Antigenic Variability of Mumps Viruses

To the Editor—We would like to congratulate Peltola et al. [1] on their excellent review. As the authors emphasize, protection from clinical disease is not perfect, even after 2 doses of mumps component vaccine; both primary and secondary vaccine failure were discussed as potential reasons. Another possibility for lack of protection after mumps vaccination (and wild-type virus infection) is the existence of heterologous mumps viruses that may escape immune protection because of interstrain antigenic variability [2, 3]. Here, we report 3 such laboratory-confirmed cases of symptomatic mumps virus infection in patients with documented pre-existing immunity.

The first case occurred in a 12-year-old girl who had received 2 mumps vaccinations (with Jeryl-Lynn vaccine strain in both July 1990 and April 1997) and presented with a lymphadenitis colli. At that time, antimumps IgG antibodies were determined in a serum specimen (IgG antibody concentration, 1400 IU/mL; IgM antibody negative). Two weeks later, bilateral parotid swelling appeared; a second ELISA performed in the same laboratory revealed a 17-fold increase in antimumps IgG antibody concentration to 24,000 IU/mL (IgM antibody negative).

The second case occurred in a 9-year-old boy who had received 2 documented mumps vaccinations (with Rubini vaccine strain in July 1995 and with Jeryl-Lynn vaccine strain in March 2000) and presented with acute bilateral parotid swelling; his antimumps IgG antibody concentration was 2900 IU/mL (IgM antibody negative). Four weeks later, convalescent-phase serologic examination revealed a

5.5-fold increase in antimumps IgG antibody concentration to 16,000 IU/mL.

The third case occurred in a 30-year-old male pediatric resident with no history of mumps vaccination who had mumps disease during childhood. He had an antimumps IgG antibody concentration of 33 IU/mL in a serum sample obtained for screening for newly employed health care workers at our institution. One year later, the patient developed acute bilateral parotid swelling. Examination of a serum sample obtained at that time revealed an 8.5-fold increase in IgG antibody concentration to 277 IU/mL; this sample was tested together with the previous sample and was antimumps IgM antibody negative. Neutralizing assays confirmed reinfection, despite pre-existing neutralizing antimumps serum antibodies. Ten days later, the patient's 26-year-old female partner (with no history of mumps disease or vaccination) developed a primary mumps infection (IgM antibody positive). These cases illustrate that symptomatic mumps reinfection may occur in the presence of pre-existing specific mumps virus serum antibodies.

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Prevention of Traveler's Diarrhea: A Call to Reconvene

To the Editor—More than 40 years have passed since the initial reports of traveler's diarrhea (TD), and much has been learned about the epidemiology of this illness, which is most often attributed to colonization of the intestinal track with pathogenic bacteria of a broad variety [1, 2]. Although our understanding has improved and effective treatment has been made available, individuals are still traveling from developed countries to lesser developed countries, and ~1 of 3 will experience an acute illness; some of these individuals will be incapacitated, but most will improve within a few days [3].

In addition, >50 years ago, the initial descriptions of postinfectious functional bowel disorders were reported [4, 5], and in the past decade, a proliferation of studies summarized in 2 recent systematic reviews have concluded that ~1 of 10 people who develop TD will acquire postinfectious irritable bowel syndrome (PI-IBS), despite normal preexisting bowel habits [6, 7]. Although PI-IBS is perhaps not as debilitating as less frequent sequelae of reactive arthritis [8], Guillain Barré syndrome [9], or inflammatory bowel disease [10], the attributable burden of PI-IBS is measurable. A quick calculation reveals that, among the 100 million travelers each year from industrialized countries who are at intermediate to high risk of diarrhea, ~30 million will develop TD, and 3 million new cases of PI-IBS will arise [11]. PI-IBS has been reported to persist in 57% of patients 6 years after its onset in one study, and postinfectious functional bowel disorders (predominantly PI-IBS) persisted in 76% of patients 5 years after its onset in another study [12, 13]. These illnesses not only decrease the quality of life of those afflicted, but the economic impact is considerable. In a review of 18 economic studies conducted in the United States and the United Kingdom, the direct cost per patient-year was estimated to be US$348–$8750 (in 2002), the annual number of lost days of work was 9–22 days, and the indirect cost per patient-year was estimated to be $355–$3344 [14]. Unquestionably, this represents significant social and economic impact.

In addition to travel-related PI-IBS, the fraction of cases of IBS secondary to domestically acquired foodborne illness needs to be considered. IBS is the most common chronic medical illness, seen in up to 15% of the US population and accounting for nearly one-third of all costs in gastroenterology as a result of investigation, management, and work loss among those seeking care [15–17]. Although the attributable fraction of IBS cases caused by domestic foodborne illness is unknown, it is likely to be large, given the frequency of these illnesses [18]. Thus, the traditional thought of foodborne illness as a self-limited condition also needs serious reconsideration and should inform future food security policy decisions.

Finally, shortly after the first reports of TD 40 years ago, reports of studies evaluating agents for use in prophylaxis followed. A number of effective regimens have been described; however, widespread use of prophylaxis, particularly antimicrobial agents, has been discouraged—a position formalized in a 1985 National Institutes of Health consensus meeting that has been unchallenged [19]. We feel that PI-IBS is a development that challenges this consensus.

The balance of chemoprophylaxis risk, compared with the consequences of TD and sequelae, needs reassessment. Although certain questions remain regarding the natural history of PI-IBS, effective treatment, and consequences of chemoprophylaxis, it is time that the questions regarding what can be done to prevent TD

and who could benefit from preventive interventions are reconsidered.

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