TF. Efficacy of caspofungin alone in combination with voriconazole in a guinea pig model of invasive aspergillosis. Antimicrob Agents Chemother **2002**; 46:2564–8.
7. Sanchez-Portocarrero J, Perez-Cecilia E, Corral O, Romero-Vivas J, Picazo JJ. The central nervous system and infection by *Candida* species. Diagn Microbiol Infect Dis **2000**; 37:169–79.
8. Aaron L, Therby A, Viard JP, Lahoulou R, Dupont B. Successful medical treatment of *Candida albicans* in mechanical prosthetic valve endocarditis. Scand J Infect Dis **2003**; 35:351–2.
9. Melgar GR, Nasser RM, Gordon SM, et al. Fungal prosthetic valve endocarditis in 16 patients: an 11-year experience in a tertiary care hospital. Medicine **1997**; 76:94–103.

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Granulomatous Infections Due to Tumor Necrosis Factor Blockade: Correction

Sir—Since the publication of our manuscript, "Granulomatous Infectious Diseases Associated with Tumor Necrosis Factor antagonists" [1], we have learned that we inadvertently included foreign adverse event reports in our calculations. We regret this error. We also have been informed that Centocor has modified its method of calculating the total number of patients treated with infliximab (Remicade) in the United States, reducing slightly the estimate for the period of the report, from 233,000 patients to 197,000 patients. On the basis of these data, the rates of tuberculosis (TB) due to infliximab and etanercept use in the United States are 54 and 28 cases per 100,000 treated patients, respectively ($P < .0001$, by Poisson analysis [2]). Histoplasmosis, coccidioidomycosis, and listeriosis also occurred significantly more often with infliximab use. The corrected analysis appears in table 1.

Table 1. Granulomatous infections in US patients treated with infliximab or etanercept.

Infection	No. of patients (no. of patients per 100,000 patients treated), by drug		
	Infliximab[a]	Etanercept[b]	P[c]
Aspergillosis	17 (8.63)	7 (6.19)	.243
Candidiasis	20 (10.15)	6 (5.31)	.061
Bartonellosis	1 (0.51)	0 (0)	.563
Coccidioidomycosis	11 (5.58)	1 (0.88)	.013
Cryptococcosis	10 (5.08)	8 (7.08)	.179
Histoplasmosis	37 (18.78)	3 (2.65)	<.0001
Legionellosis	1 (0.51)	0 (0)	.563
Leprosy	1 (0.51)	0 (0)	.563
Listeriosis	17 (8.63)	1 (0.88)	.0006
Nontuberculous mycobacterioses	22 (11.17)	7 (6.19)	.066
Nocardiosis	7 (3.55)	1 (0.88)	.090
Pneumocystosis	1 (0.51)	0 (0)	.563
Salmonellosis	0 (0)	2 (1.77)	.031
Toxoplasmosis	4 (2.03)	0 (0)	.101
Tuberculosis	106 (53.81)	32 (28.32)	<.0001
Total	255 (129.44)	68 (60.18)	<.0001

[a] Rates were calculated on the basis of 197,000 patients treated with infliximab.
[b] Rates were calculated on the basis of 113,000 patients treated with etanercept.
[c] Significance was determined by Poisson analysis.

A major conclusion of our study [1] was that the risk of reactivation of TB was greater with infliximab than with etanercept. We postulated that these drugs had differential effects on preexisting granulomas that were based on differences in their mechanisms of action. Other conditions that impair mycobacterial immunity also increase the risk of disseminated or extrapulmonary disease and shorten the time to onset. Unlike incidence rates, these parameters are not readily compromised by incomplete reporting. We therefore sought to validate our analysis by examining time to onset of tuberculosis (TB) and extent of dissemination with use of the most recent data set released by the US Food and Drug Administration. This analysis was not restricted to cases reported in the United States.

Extrapulmonary disease was reported in 114 (26%) of 441 infliximab-associated cases, compared with 4 (10%) of 42 cases for etanercept ($P = .017$ by Poisson analysis). Meningeal disease was reported in 76 cases (17%), compared with 3 cases of disseminated disease (7%) ($P = .07$). Among patients receiving infliximab, 44% of TB cases occurred within the first 90 days of therapy, compared with 10% among patients receiving etanercept ($P < .001$). Country of origin and year of reporting did not affect this relationship. For example, 55% of infliximab-associated TB cases occurred within the first 90 days of therapy when the analysis was restricted to US cases occurring through the third quarter of 2002, compared with 11% of etanercept-associated TB cases.

The cumulative proportion of TB cases in relation to duration of anti-TNF therapy is shown in figure 1. The linearity of the etanercept curve is consistent with the occurrence of TB as a random event caused by acquisition of a new infection. In contrast, the clustering of cases in patients shortly after starting infliximab therapy is consistent with an etiology of reactivation, with the inflection of the slope after day 90 of therapy indicating a shift to new infection. On the basis of these observations, the rate of reactivation of TB during the first 90 days of treatment with

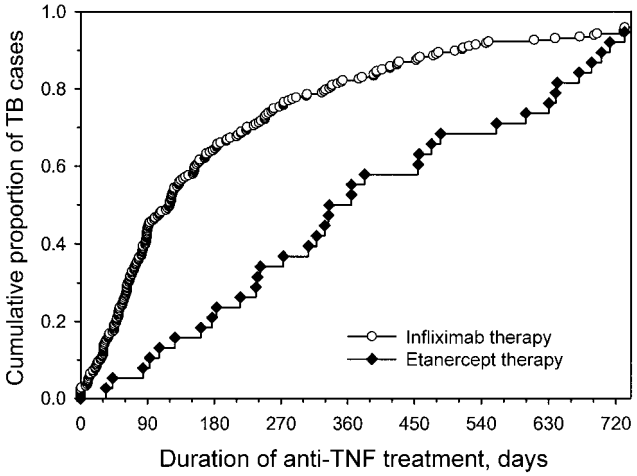

Figure 1. Cumulative proportion of tuberculosis (TB) cases in relation to start of anti-TNF treatment. Each symbol represents a case reported to the US Food and Drug Administration Adverse Event Reporting System from January 1998 through March 2003. The 2 curves differed by Kaplan-Meier analysis ($P = .00028$). The inflection in the curve at 90 days of infliximab therapy is consistent with a shift in etiology at that time from reactivation of disease to rapid progression of new infection.

infliximab was 95 cases per 100,000 person-years, compared with 11 cases per 100,000 person-years for etanercept. The overall TB incidence in the United States (reflecting both reactivation and progression of new infection) at the time of this study was 5.8 cases per 100,000 person-years [3]. Thus, despite the inherent shortcomings of postlicensing surveillance data, we believe that our conclusion—namely, that the risk of reactivation of TB is greater with infliximab therapy than with etanercept therapy—is correct.

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Conflict of interest. R.S.W. has served as a consultant for Amgen and is the recipient of a research grant from Wyeth. M.B. and J.W. are former employees of Zynx Health, a subsidiary of the Cerner Corporation. Zynx Health provides consulting services to biotechnology and pharmaceutical companies, including Amgen, which provided grant support for the original study [1]. D.B.: No conflict.

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References

1. Wallis RS, Broder MS, Wong JY, Hanson JY, Beenhouwer DO. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis **2004**; 38:1261–5.
2. Ott L. An introduction to statistical methods and data analysis. 3rd ed. Boston: PSW-Kent, **1988**:217–86.
3. Centers for Disease Control and Prevention. Reported tuberculosis in the United States, 2000. Atlanta GA: United States Department of Health and Human Services, **2001**. Available at: http://www.cdc.gov/nchstp/tb/surv/surv2000/default.htm. Accessed 31 August 2004.

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Inconsistencies in Reporting of Granulomatous Infectious Diseases Associated with Infliximab and Etanercept

Sir—The article by Wallis et al. [1], in which it is concluded that granulomatous infectious diseases occur more often in patients receiving infliximab, than in patients receiving etanercept, contains major inconsistencies that make the conclusions invalid. Table 1 of the article [1] purports to show the number of patients in the United States receiving infliximab or etanercept who had granulomatous infections reported to the US Food and Drug Administration (FDA) Adverse Event Reporting System (AERS). The authors overlooked, however, that this database includes not only voluntarily reported cases from the United States, but also cases reported worldwide. On the basis of our own analysis [2], as well as that of the FDA [3], approximately two-thirds of worldwide reported cases of tuberculosis (TB) in patients receiving infliximab are from outside the United States. Therefore, table 1 in the article [1] overstates the number of reported cases of TB in patients receiving infliximab in the United States by at least 3-fold. In contrast, because of limited use of etanercept outside of the United States, especially during the study period, the majority of TB cases reported in patients receiving etanercept are from the United States [4]. TB was the most frequently reported granulomatous infection for both patients receiving infliximab and those receiving etanercept, making the aggregate analyses reported by Wallis et al. [1] for all granulomatous infectious also erroneous. Furthermore, because the numerators are based on cases reported worldwide and the denominators pertain to cases reported in the United States only, the reporting rates in the report are erratic as well.

In the United States and most other countries, there are no regulations that require health care providers to report adverse events, and consequently, the data in spontaneous reporting systems, such as the FDA-AERS database, are generated in an uncontrolled and incomplete manner. A number of biases, usually unknown, can affect reporting [5, 6]. These biases might be different between products and, as the FDA has pointed out [6], require that extreme caution be exercised when comparing reporting rates; in fact, such com-