sity produced by MOC32 from the mean fluorescence intensity produced by the D8/17-specific monoclonal antibody. At the reanalysis of our published data, there appeared to be an unexpected, close correlation between the mean fluorescence intensity produced by the control IgM, MOC32, and that by the D8/17-specific IgM, both in the 33 tic disorder patients (Pearson's r=0.730, df=31, p<0.001), the 20 healthy comparison subjects (r=0.839, df=18, p<0.001) and in the group as a whole (r=0.753, df=51, p<0.001). Also, the median mean fluorescence intensity produced by MOC32 appeared to be significantly (Mann-Whitney U=125.0, df=51, p<0.001) higher in the 33 tic disorder patients (median=13.3 arbitrary units) than in the 20 healthy comparison subjects (median=8.9), as was the case with the median mean fluorescence intensity produced by the D8/17-specific antibody (median: patients=23.9, comparison subjects=13.4; Mann-Whitney U=89.5, df=51, p<0.001). These results could suggest that, at least in part, we did not detect D8/17 overexpression on B cells in tic disorder patients in relation to healthy comparison subjects but, rather, increased expression of receptors for the constant parts of IgM molecules (Fc-μ) on B cells, so explaining the increased binding of both the D8/17-specific monoclonal antibody and the control monoclonal antibody (MOC32). This may be due to a more general state of immune activation. Thus, these results may suggest that tic disorder patients do not express a specific, possibly genetic, susceptibility marker for experiencing autoimmune sequelae in the aftermath of streptococcal infections, but at best, show evidence of increased immune activity. Perhaps, previous positive reports were due to a nonspecific increase of the number of Fc-μ receptors on B cells, a possibility that certainly deserves further study.

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Depression and the Decision to Abort

TO THE EDITOR: We recently completed a study examining the impact of depression and antidepressants on obstetrical outcome (1). This study was approved by UCLA's institutional review board, and written informed consent was obtained from all subjects. Although not a primary outcome variable, we found that 46 women with a history of depression had a significantly higher mean number of prior therapeutic (elective) abortions than 16 women without a history of depression (mean=0.78, SD=1.11, versus mean=0.31, SD=0.60, respectively) (robust t=2.11, Satterthwaite df=48.9, p=0.04; Poisson regression χ^2=4.63, df=1, p=0.03). The mean number of prior pregnancies and spontaneous abortions did not differ. Upon closer inspection of the literature, we observed that in two other studies of antidepressants and obstetrical outcome in which abortion-related statistics were reported (2, 3), similar findings were presented but not discussed. Chambers et al. (2) found that spontaneous abortion rates were comparable but that elective abortion rates were significantly higher in fluoxetine-treated pregnant women (9.6%) in relation to comparison subjects (2.7%) (p=0.002). Kulin et al. (2) found that women who took selective serotonin reuptake inhibitors during pregnancy had similar rates of prior spontaneous abortions but higher rates of prior elective abortions in relation to comparison subjects (24% versus 13%, p=0.03). While the reason for these differences is unclear, the consistency of the finding is concerning and merits attention.

We speculate that either 1) depression in the first trimester can adversely affect a woman's view about whether to continue with the pregnancy, and she may choose to have an abortion while in a depressed state; 2) concerns regarding the effects of the pharmacological treatment of depression on the developing fetus may compel her to have an abortion, despite a desire to keep the pregnancy; or 3) concerns about first-trimester antidepressant exposure may lead a physician to discuss the option of abortion with a pregnant woman with first trimester antidepressant exposure. Our study cannot discern which of these factors, or others, played a role in the decision by women to undergo an abortion. Causality cannot be confirmed, and one must also consider that having an abortion may contribute to the onset of depression. However, the process by which women with a history of significant depression make abortion decisions and the role of the psychiatrist working with the obstetrician during pregnancy requires further understanding. If a woman in a depressed state decides to have an abortion, the need for treatment is that much more imperative, especially if her capacity to make such a decision is compromised in this depressed phase.

Given the interest in pregnancy outcome in women with depression and antidepressant exposure and the significant contributions of major depression to disease disability in women of childbearing age, prospective studies are warranted that examine the reasons for the association between depression and abortion decisions.

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The Relevance of Epigenomics to Psychiatry

TO THE EDITOR: I read with interest the overview article by Kathleen Ries Merikangas, Ph.D., and Neil Risch, Ph.D. (1), in the special issue of the *Journal* commemorating the 50th an-

niversary of the discovery of the DNA double helix. In this article, the authors discussed how the complexities of mental disorders, such as the lack of validity of the classification of these disorders and the complex pattern of their transmission, may have contributed to the difficulties in the identification of their underlying genes by genetic mapping studies such as linkage analysis and association studies. They suggested the use of endophenotypes for the classification of mental disorders and the various tools of genetic epidemiology in future linkage and association studies in order to overcome these sources of complexity in these disorders.

Drs. Merikangas and Risch mentioned epigenetic factors as one of the causes of complex transmission of mental disorders. However, I feel they did not pay due attention to the potential importance of epigenetic factors in mental disorders. Over the past few years, various lines of evidence have been presented that suggest that epigenetic factors, such as epimutations, underlie the primary (idiopathic) mental disorders, such as schizophrenia and bipolar disorder, and that these factors may be the reason for the difficulties that have been encountered in identifying the genes underlying these disorders by genetic mapping studies (2, 3).

Epigenetics refers to the study of nonmutational phenomena, such as DNA methylation and modifications of histones (DNA packaging proteins) in chromatin that modify the expression of genes. Interest in epigenetics has led to the counterpart of genomics: epigenomics, the systematic mapping of epigenetic variation across the genome (4, 5). This is the mission of the Human Epigenome Consortium, which is cataloguing the genomic positions of distinct DNA methylation variants (5).

Recently, I outlined various epigenetic strategies, such as the study of the DNA methylation patterns of genes and the modifications of histones in chromatin in patients with primary mental disorders that may help identify the underlying genes (6). This area of research is being actively pursued, and potentially significant results are beginning to emerge (5). Thus, in the future, epigenomics, in addition to genomics, may prove to be of crucial relevance to psychiatry.

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Ziprasidone and Mania

TO THE EDITOR: I read with interest the article by Paul E. Keck, Jr., M.D., and colleagues (1) that reported that treatment of bipolar patients with ziprasidone was efficacious and relatively safe. However, I was concerned about the use of a significant amount of benzodiazepines in this study. The authors reported that overall, the use of benzodiazepines was similar between patients treated with ziprasidone and those treated with placebo. However, if ziprasidone was robustly effective for acute mania or acute instability of mood, one would have expected that it would be associated with a decreased need for use of benzodiazepines.

A more specific concern was that long-acting benzodiazepines were used to treat insomnia in a substantial percentage of patients in both study groups. At study endpoint, the authors reported that for patients treated with ziprasidone, 20 were treated with temazepam, and three were treated with diazepam. In comparison, for patients treated with placebo, seven were treated with temazepam, and one was treated with diazepam. Therefore, at study endpoint, of the 75 ziprasidone-treated patients, 23 (31%) were treated with a long-acting benzodiazepine, and of the 31 placebo-treated patients, eight (26%) were treated with a long-acting benzodiazepine.

Thus, it is of concern that a substantial percentage of ziprasidone-treated patients required benzodiazepines for the treatment of insomnia and that this percentage was not significantly lower than that for placebo-treated patients. Furthermore, the steady-state half-lives of these benzodiazepines and their metabolites are considerable: 14 hours for temazepam and 42 hours for diazepam (2). Using the general guideline that it takes about four half-lives for a drug to clear the body, these patients would have had clinically significant blood levels of these drugs during the day after evening administration. These levels could have affected several measures of efficacy and side effects. For example, they could have improved efficacy by reducing symptoms of mania or mood instability. And they could have caused side effects, for example, daytime sedation, which was a significant problem in the ziprasidone-treated group. Also, they could have reduced other potential side effects, including akathisia, acute dystonia, or parkinsonism. For these reasons, other studies will avoid sedative-hypnotics at bedtime or perhaps use a much shorter-acting agent, such as chloral hydrate.

Finally, the authors reported that the use of anticholinergic medication to treat parkinsonism or propranolol to treat akathisia was recorded, but they did not report the results. Was there significantly greater use of these medications in the ziprasidone-treated patients? If so, it would indicate that acute-onset movement disorders were a clinically significant effect of ziprasidone in contrast to the authors' conclusion to the contrary.

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