Clozapine and Tardive Dyskinesia

TO THE EDITOR: Clozapine is associated with low rates of extrapyramidal side effects and is thought to have a minimal risk of tardive dyskinesia. Furthermore, clozapine has been shown to significantly diminish dyskinetic movements in patients with tardive dyskinesia and is considered an effective treatment for it (1). Despite these observations suggesting clozapine's benefits, there have been several case reports of tardive dyskinesia associated with clozapine. Several reports (2–4) have involved patients who received previous treatment with typical antipsychotics. The following report describes clozapine-related tardive dyskinesia appearing after 10½ years of treatment with clozapine in a woman who had had minimal exposure to typical antipsychotics.

Ms. A was a 33-year-old woman with a 16-year history of paranoid schizophrenia characterized by persistent auditory hallucinations, persecutory delusions, and negative symptoms. Initially, she was treated with haloperidol, 5 to 10 mg/day, for approximately 1 year and was then switched to fluphenazine decanoate, 37.5 mg intramuscularly every 2 weeks for 1 year; both treatments led to minimal response. She was subsequently given clozapine for her treatment-resistant schizophrenia. After an initial dose of 400 mg/day, her clozapine dose was gradually increased over a 1-year period to 875 mg/day. She eventually experienced remission of her auditory hallucinations and had significant improvement of her persecutory delusions and negative symptoms.

An assessment with the Abnormal Involuntary Movement Scale (5), performed before Ms. A started taking clozapine, revealed no evidence of dyskinetic movements. After 10½ years of treatment with clozapine, Ms. A was first noted to have mild repetitive involuntary jaw and tongue movements; she was given vitamin E, 800 IU b.i.d. The abnormal movements continued and gradually worsened. Her dose of clozapine was gradually reduced from 875 to 625 mg/day over 12 months. Ms. A's psychiatric status remained stable, and the abnormal involuntary movements persisted unchanged.

This case suggests that long-term treatment with clozapine may be associated with tardive dyskinesia in an individual with minimal exposure to conventional antipsychotics. Since the patient had approximately 2 years of exposure to typical antipsychotics before starting to take clozapine, their contribution cannot be discounted. Given that the patient had no evidence of involuntary movements before clozapine treatment and that she received clozapine for approximately 10½ years before the onset of tardive dyskinesia, the impact of typical antipsychotics is likely to be minimal at most. It is possible that the patient's dyskinesia would have occurred spontaneously in the absence of antipsychotic exposure, but this is unlikely. In conclusion, clozapine and the other atypical antipsychotic drugs appear to have greatly reduced the liability for tardive dyskinesia, but it appears that they have not totally eliminated the risk.

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Safety of Quetiapine During Pregnancy

TO THE EDITOR: Tamás Tényi, M.D., Ph.D., et al. (1) were the first, to our knowledge, to report pregnancy in a woman receiving quetiapine. There is little information as yet concerning the safety of atypical antipsychotic drugs used in pregnancy. We report the case of a woman who was treated with risperidone then quetiapine throughout pregnancy without complications.

Ms. A, a 33-year-old woman, experienced a first episode of psychosis that was initially treated with risperidone, 4 mg/day. After 2 weeks, her medication was switched to quetiapine because of a combination of higher prolactin levels (1997 mU/liter; <550 is the normal maximum) and poor clinical response. Pregnancy was diagnosed during week 4 of the 39-week gestation, after 2 weeks of quetiapine treatment. Conception took place despite hyperprolactinemia.

A collaborative decision was reached to have Ms. A continue taking quetiapine throughout pregnancy because of the level of risk and family history of psychosis. We found no reports of complications during pregnancy or teratogenicity in the medical literature or manufacturer's database regarding quetiapine. Clinical improvement was monitored by using various clinical rating scales at baseline and at the 6-week, 3-month, and 9-month time points. Ms. A's scores on the Brief Psychiatric Rating Scale were 21, 0, 4, 0, and 1; her Global Assessment Scale (2) scores were 35, 84, 81, 91, and 89. Her side effects were negligible. Her initial maintenance dose of 300 mg/day was reduced to 200 mg/day at week 21. This dose remained stable until 4 weeks before Ms. A's estimated due date, when her quetiapine dose was reduced by 50 mg/day each week to enable breast-feeding after birth. Ms. A remained in remission throughout pregnancy and at week 39 gave birth to a healthy girl. The baby weighed 3.61 kg. Her Apgar score in the first minute was 8, and after 5 minutes, it was 9. No problems developed in the first month postpartum. There was no exacerbation of psychosis, and successful breast-feeding was initiated.

This case adds to the small database on the safety of administering atypical antipsychotic drugs at conception and throughout pregnancy. Given the low risk of extrapyramidal and sexual side effects with these drugs, it is likely that they will be used in younger, sexually active patient groups. This report and that of Dr. Tényi et al. on the safety of quetiapine during pregnancy are encouraging. More information is required regarding the long-term effects on children exposed to these drugs in utero. We concur with Dr. Tényi et al. (1) that a

cautious clinical approach should be adopted that weighs benefits and risks on a case-by-case basis.

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Quetiapine and Falsely Elevated Nortriptyline Level

To the Editor: Drug interference in laboratory assays is becoming more complicated as newer drugs are introduced. This is the first report, to our knowledge, of the atypical antipsychotic quetiapine causing falsely elevated serum levels of nortriptyline by standard immunoassay.

Ms. A was a 42-year-old woman with diagnoses of schizoaffective disorder and borderline personality disorder. She was hospitalized for acute exacerbation of schizoaffective disorder with psychosis, depression, and suicidal ideation. Quetiapine was added to her medication regimen (nortriptyline, 25 mg q.i.d.; levothyroxine, 0.1 mg/day; and lithium, 300 mg t.i.d.) and titrated up to 200 mg t.i.d. over several weeks.

Her serum nortriptyline level, measured at admission, was noted to be 34 ng/ml. Several weeks later, a repeat serum level was noted to be 487 ng/ml. Ms. A, however, exhibited no signs of acute toxicity. Discussion with the reference laboratory revealed that the supratherapeutic level had been ascertained by using standard immunoassay. Repeat analysis of her blood with high-performance liquid chromatography demonstrated a blood level of nortriptyline of 216 ng/ml. Although high, this level was more consistent with her drug dose and clinical picture.

Ms. A's original serum drug level was assessed by using the Tricyclic Antidepressants Assay (Abbott Laboratories, Abbott Park, Ill.), a fluorescence polarization immunoassay run on the TDx/TDxFlx analyzer (Abbott Laboratories). Based on the competitive binding principle, this assay uses antibodies that detect a wide variety of tricyclic compounds in serum and plasma. Quetiapine, structurally similar to the tricyclic antidepressants, has been noted to interfere with immunoassays for tricyclic antidepressants (1, 2). Repeat analysis of Ms. A's serum by using high-performance liquid chromatography demonstrated the presence of quetiapine and its metabolites. These were identified and differentiated from Ms. A's serum levels of nortriptyline and nortriptyline metabolites.

In summary, quetiapine can interfere with standard immunoassays for tricyclic compounds and indicate falsely elevated levels. It is advisable to alert the laboratories of patients taking quetiapine when serum tricyclic assays are performed. In these circumstances, high-performance liquid chromatography, rather than an immunoassay, is the test of choice.

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Comparative Effectiveness of Antipsychotic Drugs

To the Editor: Regarding the study by Jan Volavka, M.D., Ph.D., et al. (1), the authors should be commended for attempting to differentiate four different antipsychotics in a single trial. However, I believe that the conclusions reached in this study cannot be supported by the data. During the last 6 weeks of the trial, the dose was increased in all four treatment groups. Only the olanzapine group had greater efficacy as a result. Why was the dose increased in the other treatment groups if there was no further improvement? In the case of risperidone, this increase resulted in a mean dose of 11.6 mg/day. It has been well established that risperidone doses above 10 mg/day are less effective than lower doses (2). Thus, this study demonstrated that investigators are unable to optimize patient response using dose titration. An alternative design (e.g., with a fixed dose) should have been employed.

The authors made little justification for the choice of olanzapine dose. The current labeling for olanzapine states that its antipsychotic efficacy occurs between 10 and 15 mg/day and that doses above 10 mg/day are not more efficacious. Despite this, the labeling was ignored, and the authors chose a target dose of 20 mg/day. Why did the authors design a trial in which patients were targeted with olanzapine at twice the recommended dose? Furthermore, why were the patients allowed to have their doses titrated up to 40 mg/day of olanzapine—more than twice the known safety limit? Fortunately, there were no serious adverse events during the trial. Further studies are needed to demonstrate that higher doses of olanzapine may be warranted and are safe. This should have been stated in the text.

In addition to problems with efficacy, there is also the issue of potential unblinding of the trial due to lack of tolerability. The authors attempted to mask the expected extrapyramidal symptoms of haloperidol by giving their patients prophylactic benztropine. A benztropine placebo was given for the other antipsychotics, and actual benztropine was blindly used only if needed. The labeling for risperidone indicates there is a dose-related increase in extrapyramidal symptoms. This becomes significantly higher than with placebo in doses of more than 10 mg/day. In the present trial, 32% of the patients taking risperidone required benztropine, compared to 13% for both the olanzapine and clozapine patients. For a rater observing extrapyramidal symptoms, the a priori likelihood that the patient was taking risperidone was significantly higher; as a result, it is conceivable that the blinding may have been compromised and the scoring biased.

In summary, by arbitrarily picking doses outside currently approved drug labeling, using a dose titration scheme that

was unable to detect the maximally effective dose, and failing to adequately mask extrapyramidal symptoms, the authors designed a study that could not possibly have reached a conclusion as to which antipsychotic drug was superior to haloperidol. It is unfortunate that this trial belongs to the growing category of studies in which a flawed design yields uninterpretable results.

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RICHARD C. MEIBACH, PH.D.
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TO THE EDITOR: We read with interest the study by Dr. Volavka and colleagues comparing three second-generation antipsychotics and haloperidol in patients with chronic schizophrenia. In this study, olanzapine was randomly assigned to a second cohort of patients after the study had been in progress for 15 months. The result of the combined cohorts was that olanzapine had the largest effect size for total scores on the Positive and Negative Syndrome Scale.

The authors found no cohort effect. For their statistical analysis, they assumed that if a cohort effect were present, the three first-cohort medications (i.e., haloperidol, risperidone, and clozapine) should have all fared better in the second cohort. We question this assumption. If the second cohort consisted of patients with a better prognosis for second-generation antipsychotics, we would have expected the following: haloperidol should not have been effective in either cohort because both cohorts were selected to be resistant to neuroleptics, clozapine should have performed well in both cohorts, and risperidone should have been inferior to clozapine in the first cohort (1) and comparable in the second cohort (2, 3). The reported results fit these assumptions fairly well. Haloperidol was indeed ineffective in both cohorts. Clozapine did moderately well in both cohorts, with scores on the Positive and Negative Syndrome Scale increasing only a small amount in the second cohort (6.48 versus 7.05, respectively). The risperidone group's improvement scores increased from –0.03 in the first cohort (N=25) to 7.93 in the second cohort (N=16). The latter appears comparable to the improvement with olanzapine (9.1, N=39). In summary, the cohort results appear too different to be validly combined.

Other analyses in this article seem to favor olanzapine. The authors reported that two patients had seizures while taking risperidone, but none had seizures while taking olanzapine. However, the authors did not note the discordance of the results for their small group of patients with seizure rates in the premarketing trials of these antipsychotics. According to the package inserts, there was a higher rate of seizures with olanzapine than with risperidone (0.9% and 0.3%, respectively). Two patients developed neutropenia with risperidone, and the authors cited a published report of another instance. They did not mention that olanzapine is associated with at least 10 cases, which we found in a PUBMED search.

Finally, the article's abstract stated—without qualification—that improvements in negative symptom scores "were superior" with clozapine and olanzapine. The supporting evidence seems weak at best. Negative symptom scores on the Positive and Negative Syndrome Scale decreased from 21.7 at baseline to 20.1 after 14 weeks of olanzapine, including 6 weeks at the top dose of 30 mg/day. The risperidone patients' negative symptoms did not improve at 8 mg/day nor at the 11.6-mg/day dose taken between weeks 8 and 14. But risperidone might have equaled or exceeded the tiny improvement produced by olanzapine had the dose been kept at 8 mg/day or reduced during weeks 8–14. Notwithstanding the authors' two citations (one unpublished), suggesting that 8 mg/day of risperidone may be better than 4 mg/day, most data and expert opinions indicate better results with risperidone doses below 8 mg/day (4–8; Marder and Meibach, 1994). For a more balanced and appropriately cautious interpretation of the data in this study, this deserved acknowledgment.

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TO THE EDITOR: Caution is needed when interpreting the results of the study by Dr. Volavka et al. The article and the accompanying editorial (1) acknowledged that the cohort effect cannot be ruled out, the dose of risperidone was too high, and 18% of the funding was obtained from Eli Lilly and Company. The olanzapine arm of the study was included 15 months after the study had started; there was no quetiapine arm, although both drugs became available around the same time. Use of haloperidol in comparison with either loxapine or molindone as a comparator first-generation antipsychotic drug is questionable. Both offer certain advantages over other first-generation antipsychotics.

The authors' concept of suboptimal response is less rigorous than the more widely accepted criteria of Kane et al. for treatment resistance (2). The score on the Positive and Negative Syndrome Scale required for study entry was >60. These factors may have contributed to entry of treatment-responsive patients and those with milder illness.

High doses for haloperidol (mean=25.7 mg/day, SD=5.7; approximately 1720 chlorpromazine-equivalent units) during the second phase of variable dosing cannot be justified. Low doses (mean=3.4 mg/day, SD=2.3) of haloperidol are efficacious in patients with acute schizophrenia; higher doses cause a significant increase in extrapyramidal side effects (3). Positron emission tomography experiments performed by Farde et al. (4) suggested that there is sufficient dopamine D_2 receptor occupancy with doses of haloperidol as low as 4–6 mg/day. High doses of haloperidol in treatment-resistant patients with schizophrenia do not provide any advantage based on D_2 receptor occupancy (5).

The advantages of atypical antipsychotics in terms of efficacy and dropouts disappear when doses below 12 mg/day of haloperidol are used (6). The optimal dose for risperidone is 4 mg/day, and there is a therapeutic window: poor response results at higher doses (Love et al., 1999; Williams, 2001). No incremental clinical improvement in chronic psychosis is seen at doses above 375 mg/day in chlorpromazine-equivalent doses, although a significant increase in adverse reactions is observed (7).

The Clinical Antipsychotic Trials of Intervention Effectiveness study, sponsored by the National Institute of Mental Health, may offer some more insight; however, this study is also limited by including only one comparator from the first-generation drug category. No study on the comparative effectiveness of first-generation versus newer antipsychotics can be definitive without using loxapine or molindone in treatment arms.

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TO THE EDITOR: I congratulate Drs. Volavka and colleagues on the publication of their landmark study comparing the efficacy of the atypical antipsychotics clozapine, risperidone, olanzapine, and haloperidol in patients with suboptimal response to conventional antipsychotics. The key feature of this study to a clinician like myself is that for the first time "apples and apples" were compared in a design that was hypothesis, not marketing, driven. All of the agents were compared with similar measures of efficacy and side effects. The medication doses used were similar to those used in clinical practice settings for patients with chronic illness in the schizophrenia spectrum. The commonly mentioned mean dose of 4.6 mg/day of risperidone does not work well in this group of patients. This study clearly tells us that in order to achieve therapeutic efficacy as determined by objective rating criteria, higher doses need to be used, as evident in the case of both risperidone and olanzapine, and that it can be done safely while managing neuroleptic-induced parkinsonism. This favors antipsychotic monotherapy in a subset of patients. In clinical practice, however, patients take combinations of antipsychotics in suboptimal doses without any support from the literature. Combination therapy is also costlier than monotherapy.

This study must have been difficult to conduct, and I am curious to know what extra steps the investigators took—if any—to maintain the blind with clozapine, because it causes extreme dry mouth, hypotension, sedation, and drooling. Data pertaining to neuroleptic-induced parkinsonism were reported: 30% of the risperidone group needed antiparkinsonian medication, while the percents were relatively low in the clozapine and olanzapine groups. Was there any differential in the rates of tardive dyskinesia even though the study duration was only 14 weeks? It would also be interesting to know if there was any difference in suicide attempts or completed suicides among patients in the various medication groups. Could the authors also comment on glucose or lipid abnormalities in the groups?

This study is an excellent example of a fruitful partnership between industry and federal funding, with scientific interests and patient care given their due.

SANJAY GUPTA, M.D.
Olean, N.Y.

TO THE EDITOR: This double-blind study enrolled 157 patients with chronic schizophrenia and schizoaffective disorder and compared the efficacy and the safety of three atypical antipsychotics (clozapine, olanzapine, and risperidone) with one another and with haloperidol. The analysis of the results was based on two statistical approaches: 1) analysis of covariance for determining change over time in symptom scores, with baseline severity as a covariate, and 2) random regression with hierarchical linear modeling. As the authors stated in their section on Statistical Analyses, after a preliminary analysis of the results, "Hierarchical linear modeling analysis was adopted as the primary statistic for our study" (p. 257) and

was in fact used to test the significance of differences in symptom severity.

In our view, this approach is incorrect. The traditional method of conducting clinical trials requires the investigators to predetermine both the endpoints and the analyses and to carry out the statistical analyses originally planned regardless of what happens with random assignment of subjects. So the sequence in design and performance of the trial that we expected was the following: 1) performance and completion of the study and 2) execution of the analyses initially planned by the protocol (and possibly a third phase in which other analyses were carried out after the realization that random assignment to groups was unsuccessful in some respects).

On the contrary, the sequence of work by Dr. Volavka et al. was the following: 1) performance and completion of the study, 2) preliminary analysis to determined what happened with randomly assigned groups, and 3) determination of the most convenient analysis in light of the results provided by the preliminary analysis. Of course, phase 3 can be criticized because it is clearly biased.

We appreciate that the article was very honest on this point because it stated that the analysis was chosen after observation of the results. However, if the analysis is conducted with this open method, the double-blind design makes little sense, and more important, the results of the study become less reliable.

ANDREA MESSORI, M.D.
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Dr. Volavka and Colleagues Reply

TO THE EDITOR: We appreciate the opportunity to discuss our results. First we address the concerns about the risperidone doses we used. Dr. Meibach suggests that "It has been well established that risperidone doses above 10 mg/day are less effective than lower doses," referring us to his publication (Marder and Meibach, 1994). However, that statement is not supported by their data. Their dose of 16 mg/day of risperidone was more effective than 2 mg/day or 10 mg/day; 6 mg/day was "as effective as 16 mg" (p. 825).

Drs. Osser and Akhter suggest that "most data and expert opinions indicate better results with risperidone doses below 8 mg/day" than with higher doses. To support their statement, they cite five articles presenting original data. Except for the report by Marder and Meibach (1994), the articles present no data on doses ≥8 mg/day; thus, higher doses are not compared with the lower ones in these articles (Ho et al., 1999; Lane et al., 2000; Conley et al., 2001; and Love et al., 1999). Therefore, they cannot provide empirical support for Drs. Osser and Akhter's statement. A records review (Love et al., 1999) found that patients receiving 2–4 mg/day of risperidone were more likely to be discharged than those taking 6 mg/day. However, the patients' doses were determined by clinical judgment, and thus the more seriously ill patients (who were therefore less likely to be discharged) were more likely to receive the higher dose.

Would the efficacy of risperidone have been better had we used lower doses? We address this issue indirectly. Blood samples for the determination of antipsychotic plasma levels were drawn at several time points. Our validated assay of risperidone and 9-hydroxyrisperidone (in progress) is expected to yield results comparable to those obtained by others (1). Similar to others (1), we summed the levels of risperidone and 9-hydroxyrisperidone, creating a variable we labeled RISSUM. Since plasma levels of RISSUM are known to correlate with risperidone dose, the clinical outcome in patients with low levels of RISSUM may yield insights about what would happen had we used lower risperidone doses in our study. At the end of the 8-week fixed-dose period, RISSUM values were available for 36 patients. The median RISSUM value was 42.5 ng/ml. (Incidentally, in patients treated with 6 mg/day of risperidone, the average RISSUM value reported by others was 47.9 ng/ml [1]). At 8 weeks, the average improvement in total score on the Positive and Negative Syndrome Scale for the subgroup of 18 patients whose RISSUM values exceeded the median was 5.39 points (SD=16.89). The analogous number for the 18 patients scoring below the median was 2.85 points (SD=18.81). The difference was not statistically significant, but the response tended to be better with higher plasma levels. This suggests that lower doses would not have been more effective in this group.

That said, we recognize that many clinicians feel that our target risperidone dose (8 mg/day) was too high. We would have avoided that criticism—and perhaps reduced some side effects—by using 6 mg/day instead. We did not do that for the reasons explained in the article. Although empirical evidence suggests that our efficacy results would not have differed substantially, the lower dose would have been closer to current mainstream prescription patterns, thus making the study appear more relevant for many clinicians. Finally, as we stated in the article, the dose of risperidone in the variable-dose period of the study was probably too high. Dr. Meibach is concerned about the high doses of olanzapine we used; however, doses above 20 mg/day are commonly used in clinical practice (2).

Dr. Adityanjee feels that our average dose of haloperidol in the variable-dosing phase, 27.5 mg/day, "cannot be justified." However, the average haloperidol dose was 28 mg/day in a large, well-respected study of patients with treatment-resistant schizophrenia (3). To support his feelings about our dosing, Dr. Adityanjee refers us to two articles that included first-episode patients (McEvoy et al., 1991; Farde et al., 1992). It is well known that such patients require (and tolerate) much lower doses than those who are in the later stages of schizophrenia, such as our patients. Another study (Wolkin et al., 1989) showed that the average dose of 55 mg/day of haloperidol did not yield any advantage in comparison with 39 mg/day; these doses were too high to be relevant here. The conclusion drawn from a meta-analysis (Geddes et al., 2000) was that the efficacy of haloperidol is better when doses below 12 mg/day are used, but that conclusion is invalid since studies using doses governed by clinical judgment were included (e.g., reference 3). In such studies, doctors who see a poor response sometimes increase the dose, but this change may not improve efficacy (4). Thus, the high dose may be a consequence—rather than a cause—of poor response.

Another concern pertains to potential unblinding of raters for the Positive and Negative Syndrome Scale due to the raters observing extrapyramidal symptoms; in Dr. Meibach's view, the presence of extrapyramidal symptoms might give the rater a hint that the patient was randomly assigned to risperidone. However, the extrapyramidal symptom ratings, completed on the same day as the Positive and Negative

Syndrome Scale, showed a substantial overlap between risperidone and other treatments (Table 2 in our article). This overlap would have prevented the use of extrapyramidal symptoms to correctly guess the patients' treatment assignment.

Drs. Osser and Akhter speculate that the cohort of patients enrolled after the olanzapine arm began had a better prognosis and that this was manifested by the improvements with risperidone in that cohort. However, there was only a small difference between the cohorts among clozapine patients. This argues against a cohort effect. Such effect, if present, would have resulted in an increase of the improvement rate with clozapine that would have been similar in size to that observed with risperidone. To support their speculations, Drs. Osser and Akhter quote three articles, all of which compared clozapine and risperidone in patients with treatment-resistant schizophrenia. In one of them (Azorin et al., 2001), clozapine was found superior to risperidone. The other two articles showed no difference, probably because of ineffective doses of clozapine (Bondolfi et al., 1998) or because the study group was too small (Wahlbeck et al., 2000). It is not clear how these articles could support Drs. Osser and Akhter's speculation. Nevertheless, we admit that we cannot prove that there was no cohort effect.

Drs. Osser and Akhter mention that two patients receiving risperidone developed seizures and suggest that we should have discussed that finding. However, there were no seizures in the patients taking risperidone; a correction of this error in our article was published in the December 2002 issue of the *Journal* (p. 2132). Finally, Drs. Osser and Akhter note the modest size of the observed improvements. We agree.

Regarding Dr. Gupta's question on rater blinding for the clozapine patients, the raters of the Positive and Negative Syndrome Scale did not ask the patients about salivation problems, and the patients generally did not spontaneously complain about this. There were no suicides or suicide attempts during the study. There was no significant difference among the treatments in the effects on dyskinesias (as assessed with the Extrapyramidal Symptom Rating Scale). A report on glucose and lipid abnormalities was published in the *Journal* (5).

Dr. Messori takes us to task for what she sees as our failure to "carry out the statistical analyses originally planned regardless of what happens with random assignment of subjects." However, this dogma is not universally accepted. Feinstein, an outstanding biostatistician, explained that the random selection process "does not protect against inadvertent fortuitous distortion or 'the luck of the draw.'" Therefore, after the group is drawn, the investigator "will want to have a method of checking what has happened, and, if substantial distortion occurred despite all the precautions, he [or she] will want to be able to eliminate or adjust for the effects of distortion" (6, pp. 608–609).

The data-analytic cycle consists of two components: model selection and model checking (7). Investigators should implement model-checking procedures to see if their models are internally consistent with the data. "What we should not do is to accept a class of models a priori, put the data through a standard package and accept the output as an appropriate analysis….We believe strongly that editors and referees should not accept articles, and regulators should not accept submissions, unless the authors can show that they have checked their models" (7, p. 2318).

Contrary to Dr. Messori's claim, our analytical method was not selected in an open-ended manner; it was specified a priori as one of the two methods to be used. Consequently, her alarming suggestion that the double-blind design makes little sense given our analytical approach is not warranted.

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Neuroactive Steroid Levels in Patients With Panic Disorder

TO THE EDITOR: I find the article by Andreas Ströhle, M.D., et al. (1) very puzzling. The authors studied seven women and three men with panic disorder and examined them in relation to 10 age- and sex-matched comparison subjects. The steroid levels were given as the mean and SD in nanomoles per liter, with the sexes combined.

We were not told in what phase of the menstrual cycle the women were studied; one must assume, since the SDs for the steroids were relatively small—implying that the values for men and women were similar—that the women must have been studied in the follicular phase of their cycles. Or perhaps some of them were postmenopausal, since the age range was quite wide (37.2 years, SD=10.2).

However, the levels of progesterone for the comparison subjects (24.1 nmol/liter, SD=2.6), and, indeed, for all the subjects, are clearly in the luteal range!—far above the well-estab-

lished value of about 1 nmol/liter in men, in postmenopausal women, and in women in the follicular phase of the cycle (2–4). Luteal levels range from 6 to 64 nmol/liter. The research method used was gas chromatography/mass spectrometry; one was referred to a previous article by the same group (5). In that article, the mean level of progesterone in eight healthy comparison men was 7.2 nmol/ml, while the mean level of allopregnanolone was about 4 nmol/liter. The authors' levels of these two steroids are thus inconsistent with their own previous data.

Their progesterone values are in serious disagreement with well-established data, obtained mostly through radioimmunoassay. Their values for almost all of the steroids measured are much higher than those found by a colleague and me by using a combination of high-performance liquid chromatography and radioimmunoassay (6). While gas chromatography/mass spectrometry holds great promise for providing more sensitive methods for detection of neuroactive steroids, which are present in very low concentrations in the blood, one cannot ignore the large differences in the results obtained to date that have not been explained.

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Dr. Ströhle and Colleagues Reply

TO THE EDITOR: We thank Dr. Pearson Murphy for her comments on our recent article on neuroactive steroids in patients with panic disorder before and during paroxetine treatment. Because our article was published as a Brief Report, we had to be as brief as possible with regard to the description of our methods. Two of the seven women in both groups were postmenopausal. We agree that the reported progesterone levels of about 20 nmol/liter are too high for this study group, and we therefore have reanalyzed our gas chromatography/mass spectrometry data. In doing so, we found that when switching from steroid analysis by gas chromatography/mass spectrometry from the electron impact mode that was employed in our previous study of depression (1998) to the negative chemical ionization mode, we made a mistake with the calculation of progesterone concentrations. In our article, we reported on calculations based on m/z 178 and m/z 197, which represent both progesterone and pregnenolone (which partially coelute), instead of m/z 197, which represents progesterone only. This explains why the progesterone values reported were too high. We now have recalculated the progesterone levels using m/z 197. The corrected mean progesterone concentrations were 2.9 nmol/liter (SD=0.2) for the comparison subjects and 3.1 nmol/liter (SD=0.2) for the patients with panic disorder before paroxetine treatment. During paroxetine treatment of the patients with panic disorder, progesterone concentrations were between 2.6 nmol/liter (SD=0.2) and 2.9 nmol/liter (SD=0.3). The other steroid concentrations reported are correct. We seriously apologize for this error and thank Dr. Pearson Murphy for bringing up this issue, which enables us to provide the correct progesterone data. The slight differences between the correct progesterone data and those reported in our previous article regarding depression (1998) are probably due to the fact that in the meantime we changed both our gas chromatography/mass spectrometry instrument and our mode of steroid analysis.

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Summer Birth and Deficit Schizophrenia

TO THE EDITOR: Brian Kirkpatrick, M.D., and co-authors (1) reported interesting findings that are in line with previous findings reported by the same research group. Taken together, these findings fit the suggestion that the deficit type of schizophrenia is associated with summer birth and has an etiopathophysiology separate from that of other types of schizophrenia. However, a problem with these findings is that they have not yet been replicated by others (e.g., 2, 3). On the occasion of the article by Dr. Kirkpatrick et al., we analyzed our own data from a follow-up study on schizophrenia with respect to the topic addressed by Dr. Kirkpatrick et al. (For a description of the study design, see reference 4.)

At the 15-year follow-up evaluation, we found that 50% of the patients had a deficit syndrome according to the criteria proposed by Dr. Kirkpatrick et al. As did Dr. Kirkpatrick et al. (1), we used four definitions of summer birth: May to August (definition 1), June to August (definition 2), June to July (definition 3), and July to August (definition 4). We analyzed the association between each of the four definitions of summer birth and the deficit type of schizophrenia. Logistic regression analyses revealed that none of the four definitions was predictive for that type of schizophrenia. The odds ratios and confidence intervals (CIs) were as follows—definition 1: odds ratio=1.41, 95% CI=0.44–4.51 (Wald χ^2=0.34, df=1, p=0.56); definition 2: odds ratio=1.99, 95% CI=0.51–7.71 (Wald χ^2=0.99, df=1, p=0.32); definition 3: odds ratio=1.39, 95% CI=0.28–6.83 (Wald χ^2=0.16, df=1, p=0.67); definition 4: odds ratio=1.81, 95% CI=0.38–8.38; (Wald χ^2=0.57, df=1, p=0.45). These findings are comparable with those obtained in two independent previous studies by our research group (5, 6), nei-

ther of which could demonstrate that there is an association between summer birth and the deficit type of schizophrenia. In conclusion and with regard to the fact that the association between summer birth and the deficit type of schizophrenia has only been shown by the studies of one research group but was not shown by the present analyses or by other previous studies (2, 3), the evidence concerning this association is still far from definitive.

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Dr. Kirkpatrick and Colleagues Reply

TO THE EDITOR: We appreciate the interest of Dr. Bottlender and colleagues in our recent article. They cite three published studies that, in their view, fail to replicate the association between deficit schizophrenia and summer birth (Dollfus et al. 1999; Rodrigo et al. 1991; Bottlender and Möller, 2000). However, there are several issues that undermine the value of these studies as either refutations or confirmations of the previous findings. The first is that these studies did not use population-based samples and, therefore, are not appropriate for epidemiological research. Moreover, in two of these studies (Rodrigo et al. and Bottlender and Möller), the investigators did not attempt to distinguish deficit and nondeficit groups, as the aims of the studies were quite different. One study (Rodrigo et al.) compared patients born between December 1 and March 31 to those born between April 1 and November 30; these dates are not relevant to a replication of the summer birth effect.

Dr. Bottlender and colleagues also present a new analysis in their letter; the data appear to come from an extension of a previous study (Bottlender and Möller, 2000; Bottlender et al., Eur Psychiatry, in press). Unfortunately, this analysis does not provide more information on the summer birth effect. First, the study group does not appear to be population based (Bottlender and Möller, 2000), so it is not appropriate for discussion of this epidemiological issue. Second, their statement that "it can be assumed that most patients with a residual type of schizophrenia…would also fulfill the criteria for a deficit syndrome" (Bottlender and Möller) is puzzling, as their own data demonstrate that such is not the case. When they state that "50% of the patients had a deficit syndrome according to the criteria proposed by Dr. Kirkpatrick et al.," it is not clear whether they are referring to use of the Schedule for the Deficit Syndrome (1) or the Proxy for the Deficit Syndrome (2). In either case, the 50% prevalence of deficit schizophrenia makes it clear that their deficit and nondeficit groups did not resemble those in previous studies of deficit schizophrenia and summer birth, as the prevalence of the deficit group is about 20%–25% among study groups with chronic schizophrenia and 15%–20% in first-episode, population-based samples (3, unpublished report by E. Messias et al.). As a consequence, there are many false positive diagnoses of deficit schizophrenia in their study. There may be many false negative diagnoses as well, but the information needed to make that judgment is not available to us, as we were not provided with clinical and demographic comparisons of the deficit and nondeficit groups. The appropriate use of the Proxy for the Deficit Syndrome, and especially validity testing for groups defined by it, have been described previously (2, 4–8, unpublished report by Messias et al.).

The Proxy for the Deficit Syndrome is a special case of the more general issue of intergroup reliability for the deficit/nondeficit categorization (9). Dr. Bottlender and colleagues are certainly correct in their view that it would be desirable for other research groups to investigate the summer birth risk factor. However, without population-based samples and deficit and nondeficit groups that are similar to those in the published studies, it will not be possible to refute or confirm the existence of the summer birth risk factor.

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Psychiatry and Neurology

To the Editor: I read with interest the editorial by Stuart C. Yudofsky, M.D., and Robert E. Hales, M.D. (1). I was encouraged by their attention to the overlap between psychiatry and neurology and the arbitrary line of distinction that is drawn between these two fields. I agree that the developing field of neuropsychiatry provides us an opportunity for addressing this issue and that these areas are theoretically related and should be conceptualized in a theoretically integrated framework.

However, I disagree with their main conclusion that psychiatry and neurology should be integrated into a single specialty of neuropsychiatry. The reasons for this are merely practical. Specialties in medicine are based not only on theoretical but also practical reasons. Accordingly, physicians who treat patients with brain disorders typically are interested only in treating a subset of patients with these disorders using a subset of the available treatment options. For this reason, we currently have the specialties of psychiatry, neurology, and neurosurgery. It is a rare physician who chooses to specialize in more than one of these areas, with the obvious extensive training requirements. Given the advances made in the understanding of brain disorders, this need to specialize in a subset of brain disorders probably will become more important—not less.

Therefore, I predict that, eventually, neuropsychiatry will develop as an area of specialty between neurology and psychiatry. It will include disorders such as schizophrenia, dementia, mental retardation, and Parkinson's disease. Psychiatry will attract physicians who are more interested in psychodynamics and treating patients with psychotherapy, social interventions, and integration of medication and psychosocial treatments. The lines between these areas will be flexible ones. Specialists in brain disorders will have an integrated model within which they can understand their patients, practice their specialties, and communicate with other specialists.

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To the Editor: The proposal in the editorial by Drs. Yudofsky and Hales gives me pause. What is the difference between this proposal and the ones made by others (1, 2)? If the answer is that they continue to include the psychodynamic, interpersonal, and other psychosocial perspectives, do they propose a continuation of psychotherapy training in residency training programs? If not, how are these perspectives to be transmitted? What about retraining for current physicians?

The point about two medical specialties treating disorders of the central nervous system is inaccurate. There are currently four such specialties, the other two being neurosurgery and physical medicine and rehabilitation. Just as the last two distinguish themselves by their treatment modalities, not by their disease entities, so psychiatry and neurology distinguish themselves by their differing treatment targets: the former addressing difficulties in affect, cognition, perception, and behavior and the latter targeting difficulties in movement, sensation, and equilibrium.

Have Drs. Yudofsky and Hales asked neurologists if they wish to attend to problems with affect, cognition, and behavior? Do they or other psychiatrists wish to attend to problems of the senses or extremities or the peripheral nervous system that are remote from their customary clinical problems?

As a child psychiatrist, I can state that the clinical problems we treat are less well defined as neuropsychiatric illnesses, so the argument for merging pediatric neurology and psychiatry is less cogent (3). For example, the hallmarks for defining depression in adults (changes in the hypothalamic-pituitary-adrenal axis, monoamine depletion, altered sleep architecture, increased limbic blood flow, modified periventricular structure, response to pharmacological agents) are equivocal in children, despite the descriptive criteria for the illness being the same.

Finally, even if neurology and psychiatry are merged into a single medical specialty, there is still reason to consider some boundaries. In obstetrics and gynecology, a patient who is in the postpartum may not be in the same hospital unit as a woman with metastatic cervical cancer. Similarly, a patient who is beginning to walk after a stroke, even though he or she may have mood symptoms, may not be best served on a unit with an agitated patient who has schizophrenia and mild motor symptoms. The arguments made by Drs. Yudofsky and Hales are valid, but these issues need to be taken into account.

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Drs. Yudofsky and Hales Reply

To the Editor: We thank Drs. Ross and Cooper for their replies to our editorial and understand full well that the issues they raise would be shared by many other of our thoughtful and concerned colleagues in psychiatry and neurology.

Dr. Ross's assertion that "physicians who treat patients with brain disorders are typically interested only in treating a subset of patients with these disorders using a subset of the available treatment options" and Dr. Cooper's questions, "Have Drs. Yudofsky and Hales asked neurologists if they wish to attend to problems with affect, cognition, and behavior? Do they or other psychiatrists wish to attend to problems of the senses or extremities or the peripheral nervous system that are remote from their customary clinical problems?" high-

light precisely why we believe the fields of psychiatry and neurology should move more closely together under the conceptual scaffolding of neuropsychiatry.

Let us consider the example of a neurologist's treatment of a 17-year-old boy with grand mal seizures. Without an intensive emphasis in his or her residency education on the psychosocial aspects of care, the neurology practitioner might regard the localization of the underlying lesion in the patient's brain and prescribing the appropriate anticonvulsant as adequate treatment. However, what about the young man's complex emotional and behavioral sequelae to having had a grand mal seizure—with incontinence—in front of his entire 11th-grade class, and how will he respond to no longer being able to drive a car like the rest of his peers? Our experience from having spent significant parts of our careers in hospitals that specialize in the care of patients with neurological and neurosurgical disorders is that such a patient would most likely be discharged without full consideration of these issues or without a referral to a psychiatrist—often with dire consequences for the recovery of the patient. In our editorial, we referenced the unfortunate history and attendant damage to our patients and to the field of psychiatry when the neurobiological aspects of causality and treatment of people with mental illness have been neglected by psychiatrists.

Perhaps the following comparison will help Drs. Ross and Cooper understand better the point that we endeavored to make in our editorial. It has been suggested by others, using hauntingly similar arguments to those posited by Drs. Ross and Cooper, that psychopharmacology and psychotherapy should become separate subspecialties of psychiatry approved by the American Board of Psychiatry and Neurology. We are sure that Drs. Ross and Cooper would agree with us that this is a dangerous idea and that these therapeutic (and somewhat theoretical) realms have been and should remain fundamental to the education and clinical repertoire of every psychiatrist. Similarly, in the mid-19th century, psychiatry and neurology were much more closely aligned (1). We maintain the firm conviction, as delineated in our editorial, that the subsequent separation of neurology and psychiatry into discrete specialties has tenuous conceptual validity and deleterious consequences for the patients served by both fields.

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Genetic Linkage in Schizophrenia

TO THE EDITOR: I would like to comment on the article by Lynn E. DeLisi, M.D., et al. (1) presenting a genome-wide scan for linkage to chromosomal regions in individuals with schizophrenia or schizoaffective disorder. The article refutes previous linkage studies for schizophrenia, noting that "no linkage appears to be consistently replicable across large studies" (p. 803). Additionally, the authors questioned whether "the genetic contribution to this disorder is detectable by these strategies" (p. 803). Another recent article demonstrated that genome-wide scans are very prone to false positive results (2). Perhaps these two articles can put to rest the vicious cycle of genome-wide scans refuting previous linkage findings while creating more false positives to be refuted by the next genome-wide scan (although the authors leave that cycle intact). At the very least, I suggest that any such studies in the future include the use of a comparison group to compare the number of false positives within that study group.

At what point is it safe to say that no such linkages are likely to be found for schizophrenia or other mental disorders? The authors' suggestion that the genetic contribution of schizophrenia may be "epigenetic, i.e., related to gene expression rather than sequence variation" (p. 803) is intriguing, but I think it also opens the door for another possibility. Perhaps schizophrenia and other mental disorders, even though shown to be heritable in twin studies, are not actually genetic. This, of course, is paradoxical and would require a paradigm shift in our understanding of mental illness and genetics. But the fact of the matter is that the evidence is pointing in that direction, despite what our current scientific bias leads us to believe. The mind is a complex thing, and our attempts to reduce it to genetic loci or epigenetic expression is surely an oversimplification, if not a complete misrepresentation.

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STEPHEN J. PITTELLI, M.D.
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TO THE EDITOR: Dr. DeLisi et al. reported the results of a genome-wide scan for linkage in 382 sibling pairs with schizophrenia or schizoaffective disorder. The results of this study emphasized the weakness and fragility of linkage reports on schizophrenia: no linkage appears to be consistently replicable across studies. Thus, the authors questioned whether the genetic contribution to schizophrenia may be epigenetic in nature and whether genetic mapping strategies can detect the underlying genes.

Recently, in fact, I proposed (1, 2) that epimutations (heritable defects in gene expression that do not involve changes in DNA sequence), rather than genetic mutations (heritable changes in DNA sequence of genes), underlie primary (idiopathic) mental disorders such as schizophrenia and that, hence, epigenetic strategies are needed to identify their underlying genes. I gave the following lines of evidence:

1. Among all animals, epigenetic mechanisms in gene expression play the greatest role in humans, and among all organs, they play the greatest role in the development of the brain.

2. Epigenetic mechanisms in gene expression played a major role in the evolution of human mental functions and abilities.

3. Epigenetic mechanisms in gene expression were the link in the transition from genetic inheritance to cultural inheritance (a genetic-based inheritance system involving the stor-

age and transmission of information by the brain through communication, imitation, teaching, and learning) during the evolution of heredity.

Unlike in the case of primary mental disorders, genetic mapping strategies have been successful with regard to the neuropsychiatric disorders: susceptibility genes underlying diseases such as Alzheimer's disease and Huntington's disease have been identified. The reasons for this discrepancy that I suggested were that 1) the neuropsychiatric disorders have simpler modes of inheritance (in many, if not all, cases) than the primary mental disorders and, hence, there are likely to be fewer epigenetic mechanisms in the expression of genes underlying neuropsychiatric disorders, and 2) since neuropsychiatric disorders involve fewer psychosocial factors than the primary mental disorders in their pathogenesis, neuropsychiatric disorders are likely to involve fewer epigenetic mechanisms in the expression of their underlying genes (since it is known that epigenetic mechanisms in gene expression involve environmental inputs).

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TO THE EDITOR: After not finding a susceptibility gene for schizophrenia, Dr. DeLisi et al. suggested that schizophrenia could result from variation in gene expression. They also recommended that investigators who choose candidate genes for schizophrenia take under consideration various defects observed in schizophrenia. I wish to add three additional recommendations.

First, successful identification of candidate genes for schizophrenia may be enhanced if the higher urban prevalence of schizophrenia is considered. Second, a variation of genetic expression could result from a pathological mechanism known as translational pathophysiology (1). Abnormalities of protein translation could allow genetic, infectious, and nutritional pathways to affect brain development. Third, investigators might consider that a schizophrenia gene enhances survival during prenatal growth.

Translational pathophysiology could result in both enhanced survival and schizophrenia if a gene that provides resistance to an infectious agent through translational interference is expressed during fetal growth and inhibits both viral and host proteins. I hypothesized this Darwinian approach in merging the literature on the flavivirus resistance gene with the geographies of schizophrenia and flaviviruses (2). In this context, the genetic resistance of certain mice to typhoid fever may also have application to schizophrenia. A critical genetic control of typhoid resistance is the natural resistance-associated macrophage protein 1 (NRAMP 1) (3). This gene enhances expression of several proteins, is expressed in neurons, and is associated with behavioral and immune responses to stress (4, 5). The human homologue maps to chromosome 2q35 (3), a location also linked to susceptibility to rheumatoid arthritis (4). Given the controversial hypothesis that persons with schizophrenia are resistant to rheumatoid arthritis, it is noteworthy that chromosome 2 was one of the few chromosomes in which Dr. DeLisi et al. found positive linkages.

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Drs. DeLisi and Crow Reply

TO THE EDITOR: We are grateful that the manuscript we co-authored has provoked some response and thought from others. In the face of the inconsistencies of linkage studies, Dr. Pittelli draws attention to the susceptibility of genome scans to false positive findings and suggests that schizophrenia and other mental disorders, even though shown to be heritable in twin studies, are not actually genetic and says that "the mind is a complex thing." While we think that the twin and adoption study evidence cannot be discarded, we have some sympathy with this opinion if it refers to the gene sequence rather than its expression. In this case, the proposal is consistent with our suggestion that the variation is "epigenetic," i.e., related to methylation of the gene sequence, a suggestion that is similar to Dr. Peedicayil's concept of an epimutation. The problem in testing this possibility is that of identifying a gene sequence or sequences (in the absence of linkage) the epigenetic status of which can be investigated.

However, we see no merit in Dr. Brown's proposal that psychosis represents an anomaly of expression of a protein that protects against infection and other stresses (a hypothesis that resembles that of Huxley et al. [1]) because there is no evidence that patients with psychosis have this advantage, and we see no support in the literature for the particular genetic candidate that Dr. Brown suggests.

Over the past decade or more, the use of new molecular genetic linkage strategies have resulted in many positive reports emerging in the search for genes for schizophrenia and with results on only very small numbers of families. Sherrington et al. (2) in 1988 claimed a locus on proximal chromosome 5q that was never replicated. Pulver and colleagues (3–5) reported at various times positive linkages of schizophrenia to chromosomes 3, 8, 13, and 22. Still others reported additional linkages on chromosomes 1q, 2p, 2q, 4p, 6p, 6q, 10p, 15q, 18p, and X (reviewed in reference 6). In brief, almost every chromosomal arm has been reported to have a linkage to schizo-

phrenia. Thus, if we place our study in context with past literature, although we find a significantly positive lod score on both chromosomes 2p and 10p, we fail to find the several other "positives" previously reported in our group of 382 sibling pairs. Thus, when Dr. Brown writes that our linkage on chromosome 2 is consistent with a gene for resistance to infection, his argument is clearly very weak from this angle as well. Moreover, Dr. Brown indicates that its location on chromosome 2q35 suggests this relationship is based on our linkage to chromosome 2p-q. However, chromosome 2 is one of the largest chromosomes, and the linkage we report is not at all linked to the region for the NRAMP1 gene but is several centimorgan map distances away. More important is the fact that Dr. Brown's hypothesis does not explain any of the facts we know about schizophrenia today—i.e., that it is likely a developmental structural brain disorder, that it has an onset in early adulthood and continues through much of the lifetime of the affected individual thereafter, and that it has sex differences in age at onset, outcome, and symptoms. These clues need to be considered in the formulation of any hypothesis about the pathophysiology of this disorder.

While reports exist now of candidate genes that resulted from reports of linkage on chromosomes 6p (7), 8p (8), and 13q (9), these genes have not yet been determined to show specific modification in multiple members with schizophrenia within families. Another possible gene (protocadherin X-Y) proposed by one of us (10) has the unique advantage of explaining several of the facts just mentioned about schizophrenia. This gene is located on a recently evolved region of the X and Y chromosomes. On the basis of a combination of evidence from individuals with sex chromosome anomalies and the uniquely human aspects of schizophrenia, it has been proposed as a candidate gene. Since this gene is located in a region that has homologous genes on both X and Y chromosomes, even with an assumed sequence variation in the gene, linkage studies that rely on assumptions of standard autosomal or X-lined inheritance may not detect it. If epigenetic modification of the gene is the crucial event leading to schizophrenia, it is also possible that linkage studies will not detect it. This region thus is being further pursued closely in our families with schizophrenia to determine whether either or both situations are present, i.e., a sequence variation or abnormal methylation in one of the exons or the promotor of the gene.

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