

### Desipramine Toxicity With Terbinafine

TO THE EDITOR: We report the following case to alert physicians to a possible interaction between desipramine, a tricyclic antidepressant, and a newer antifungal medication called terbinafine.

Mr. A, a 52-year old man with recurrent major depression of moderate severity and a baseline score of 27 on the Hamilton Depression Rating Scale 17-item version, responded to treatment with desipramine over a period of 2 months. In subsequent continuation treatment he remained stable while taking 350 mg/day with a serum level of 166 ng/ml (therapeutic range=125–250 ng/ml).

His primary care physician then started treating Mr. A with terbinafine for onychomycosis (a fungal nail infection). After 2 weeks of treatment, Mr. A began to notice increasing dizziness, which progressed to ataxia, incoordination, and difficulty swallowing. There were no specific cardiac-type symptoms, such as syncope or palpitations. In light of these new symptoms (after 3 weeks of treatment with terbinafine), Mr. A's desipramine level was rechecked and was found to be 580 ng/ml, even though his desipramine dose had remained unchanged.

Mr. A stopped taking desipramine for several days; after resolution of his somatic symptoms he was restarted on a dose of 50 mg/day. While Mr. A was taking 50 mg/day, his desipramine level was measured and found to be 174 ng/ml. Mr. A continued taking terbinafine during this time. When terbinafine was ultimately discontinued a couple of weeks later, his desipramine level was found to have fallen to 21 ng/ml, while he was taking the same 50-mg/day dose. The dose was gradually titrated back up to the initial amount of 350 mg/day of desipramine, which produced a serum level of 152 ng/ml.

On the basis of this clinical course of events we concluded that desipramine toxicity was secondary to an interaction resulting from the addition of terbinafine to the patient's desipramine treatment. Terbinafine is an allylamine antifungal agent used to treat dermatomycosis. This is the second case of which we are aware involving a toxic interaction between terbinafine and a tricyclic antidepressant (1). Up until now, terbinafine has been considered to be a weak inhibitor of the CYP2D6 system. However, evidence indicates that this is not the case (2).

With a 250-mg/day dose of terbinafine, the elimination half-life is 16 days; at a dose of 100 mg/day, the plasma half-life is 22 days (3). Therefore, there is a significant potential for interactions to occur with any of the CYP2D6 substrates, namely type I-C antiarrhythmic drugs, tricyclic antidepressants, neuroleptics, opiates, and beta-blockers.

Although tricyclic antidepressants are often the second- or third-line agents used to treat major depression, they are now a frequent choice in the management of chronic pain syndromes; therefore, it is important for physicians to be cognizant of this potential interaction.

#### References

1. van der Kuy PH, Hooymans PM: Nortriptyline intoxication induced by terbinafine. *Br Med J* 1998; 316:441
2. Abdel-Rahman SM, Gotschall RR, Kauffman RE, Leeder JS, Kearns GL: Investigation of terbinafine as a CYP2D6 inhibitor *in vivo*. *Clin Pharmacol Ther* 1999; 65:465–472

3. Gupta AK, Shear NH: Terbinafine: an update. *J Am Acad Dermatol* 1997; 37:979–988

JOHN P. O'REARDON, M.D.  
 JAMES M. HETZNECKER, M.D.  
 MOIRA A. RYNN, M.D.  
 CLAUDIA F. BALDASSANO, M.D.  
 MARTIN P. SZUBA, M.D.  
*Philadelphia, Pa.*

### Orlistat Misuse in Bulimia Nervosa

TO THE EDITOR: Orlistat is a novel anti-obesity drug that inhibits pancreatic lipases, thus reducing absorption of dietary fat (1). The recommended dose is 120 mg at each main meal that contains fat. Side effects include oily spotting of the rectum, flatulence, and fecal urgency. We describe a patient who used orlistat as a weight-loss behavior to compensate for binge eating.

Ms. A was a 49-year-old woman who came to our weight management program for extreme obesity (287 lb; body mass index=45 kg/m<sup>2</sup>). At this assessment, she met DSM-IV criteria for bulimia nervosa, purging type, and major depressive disorder, diagnosed by means of structured interview.

Ms. A's binge eating started at age 9 years; she weighed 140 lb at age 10. She continued binge eating and gaining weight throughout high school and college. At age 25, she was bingeing one or two times per day and weighed 206 lb. She took laxatives to relieve fullness one or two times a month but had no regular compensatory weight-loss behaviors.

Ms. A had tried nine weight-loss programs and two over-the-counter appetite suppressants in the past. One year before coming to our program, she began using orlistat, 120 mg t.i.d., as prescribed by her internist. Although she continued to binge four or five times per week, she lost 45 lb after 6 months. However, she stopped taking the drug because of financial difficulties and subsequently regained all of the weight within 4 months. Ms. A then began ordering orlistat through the Internet. To save money, she used the drug only during binges. When she came to our program 2 months later, she had lost 5 lb. However, Ms. A was bingeing four to seven times a week, using orlistat during every binge, having four to eight bowel movements per day with moderate to severe fecal urgency, experiencing oily rectal spotting, and having flatulence after every binge. She avoided most social situations because of the side effects. We suggested that the orlistat might be reinforcing Ms. A's binge eating and that it should be discontinued, but she responded that the drug had been helpful in preventing weight gain, and she was therefore reluctant to stop taking it.

To our knowledge, this is the first report of orlistat misuse in a person with an eating disorder. Although our patient's eating disorder initially met the provisional DSM-IV criteria for binge eating disorder, when she came to our program, we thought her orlistat misuse represented purging behavior and thus that her eating disorder met the DSM-IV criteria for bulimia nervosa, purging type (2). This case raises questions about the use of orlistat in persons with eating disorders. Although orlistat did help regulate this patient's obesity, it did not benefit her binge eating or depression. This case also

raises the importance of assessing psychiatric conditions (especially mood and eating disorders) in persons seeking treatment for weight loss.

#### References

1. Arterburn D, Noel PH: Extracts from "Clinical Evidence": obesity. *Br Med J* 2001; 322:1406-1409
2. Bulik CM, Sullivan PF, Kendler KS: An empirical study of the classification of eating disorders. *Am J Psychiatry* 2000; 157: 886-895

SHISHUKA MALHOTRA, M.D.  
SUSAN L. MCELROY, M.D.  
*Cincinnati, Ohio*

### Body Dysmorphic Disorder Triggered by Medical Illness?

TO THE EDITOR: Little is known about the causes and pathophysiology of body dysmorphic disorder. We report two cases of body dysmorphic disorder that followed a medical illness and suggest that the latter might play an active role as a trigger in the pathogenesis of the disorder.

Arnold was a 17-year-old boy who came to us with severe body dysmorphic disorder that had lasted 2 years. He had no psychiatric history until he developed Bell's palsy at the age of 15, after which he became socially isolated and self-absorbed, complaining of severe facial/skin deformities, despite resolution of the palsy. He spent long hours examining his face and picking at real or perceived lesions and discolorations. His symptoms were so severe that he attempted suicide and was hospitalized. Subsequently, he was referred to our clinic.

Mr. A was a 22-year-old man who came to our clinic with severe symptoms of body dysmorphic disorder related to his skin. His symptoms started immediately after he developed ulcerative colitis 18 months earlier. He believed that his skin was excessively dry and deformed and that people were commenting about his appearance. He spent hours checking his skin in the mirror. Mr. A became socially withdrawn, quit his job, and was homebound. Of interest, he reported a similar episode of body dysmorphic disorder when he was 16. This earlier illness resolved spontaneously after 6 months.

These cases suggest that a range of physical illnesses may act as a stimulus for the development and/or exacerbation of body dysmorphic disorder. To our knowledge, there is no literature connecting body dysmorphic disorder to a medical condition. However, there is a recent report (1) describing a similar link between a medical illness (malignancies) and obsessive-compulsive disorder (OCD). The latter has many features similar to body dysmorphic disorder, such as obsessive thoughts and repetitive behavior. Moreover, both disorders appear to preferentially respond to selective serotonin reuptake inhibitors, which suggests a common serotonin dysfunction (2). This neurochemical dysfunction might have been triggered by the inflammatory process in our patients. One possible pathophysiological mechanism for a biochemical link between these medical illnesses and the onset of body dysmorphic disorder or OCD may be through cytokines, which have been shown to be activated in inflammatory diseases and cancer and have been suggested to suppress serotonin synthesis (3). This report raises an interesting question about biological factors in the onset of body dysmorphic dis-

order. Further investigation to illuminate these factors is suggested.

#### References

1. Rajarethinam RP, Abelson JL, Himle JA: Acute onset and remission of obsessions and compulsions following medical illnesses and stress. *Depress Anxiety* 2000; 12:238-240
2. Philips KA, Dwight MM, McElroy SL: Efficacy and safety of fluvoxamine in body dysmorphic disorder. *J Clin Psychiatry* 1998; 59:165-171
3. Menkes DB, MacDonald JA: Interferons, serotonin and neurotoxicity. *Psychol Med* 2000; 30:259-268

VILMA GABBAY, M.D.  
MARY ALICE O'DOWD, M.D.  
ANDREA J. WEISS, M.D.  
GREGORY M. ASNIS, M.D.  
*New York, N.Y.*

### Olanzapine for Violent Schizophrenia and Klinefelter Syndrome

TO THE EDITOR: The frequency of psychiatric disorders in patients with Klinefelter syndrome could be higher than that in the general population (1). Among the personality features reported in men with the XXY karyotype of Klinefelter syndrome are passivity, weak concentration, emotional immaturity, shyness, and hypersensitivity (1). Some cases of Klinefelter syndrome with schizophrenia have been reported (2, 3), although aggressive behaviors in Klinefelter patients with schizophrenia have rarely been described.

Mr. A was a 21-year-old Caucasian man who was initially arrested for criminal violence against persons, including children. He was subsequently admitted to our psychiatric department without his consent. He fulfilled DSM-IV criteria for the paranoid type of schizophrenia, with transient persecutory delusional beliefs and auditory hallucinations. The results of a karyotype confirmed Klinefelter syndrome (karyotype 47, XXY). Throughout his hospitalization, Mr. A exhibited irritability, open hostility, and anger; he made frequent aggressive threats, impulsive physical attacks against individuals and objects, self-directed attacks, and assaults on mental health staff. He made three impulsive suicide attempts (twice trying to set himself on fire). His insight was poor. Mr. A was referred to our forensic psychiatric department four times, for a total duration of 6 years. An EEG showed nonspecific abnormalities localized to the temporal lobes (slow-wave activity). Mr. A never had the substance use disorders frequently associated with such violence.

During Mr. A's hospitalization, a variety of antipsychotic medications were used, including 150 mg of intramuscular fluphenazine decanoate every 2 weeks, 1000 mg/day of chlorpromazine, and 30 mg/day of haloperidol. Mr. A also received carbamazepine, 800 mg/day, and lorazepam, 5 mg/day, for 2 years. He was found to meet criteria for resistance to conventional antipsychotics; he had at least two periods of 6 weeks of treatment with antipsychotics from at least two chemical classes (chlorpromazine-equivalent doses higher than 1000 mg/day) without significant symptom improvement.

Mr. A's aggressive behaviors occurred persistently for 9 years and suddenly stopped after he starting olanzapine treatment, 20 mg/day. He showed a significant improvement in conceptual disorganization, hallucinatory behavior, violence, and unusual thoughts. His selective atten-

tion and insight were especially improved. To date, Mr. A's psychiatric symptoms have been controlled for 20 months with olanzapine.

To our knowledge, this is the first report of a violent patient with comorbid Klinefelter syndrome and schizophrenia. Two atypical antipsychotics, clozapine and olanzapine, are thought to have antiaggressive effects (4). This case suggests that olanzapine may be an effective treatment for hostile agitation, threatening, and assaultive violence in schizophrenia patients with Klinefelter syndrome.

#### References

1. Sorensen K, Nielsen J: Twenty psychotic males with Klinefelter's syndrome. *Acta Psychiatr Scand* 1977; 56:249–255
2. Nielsen J, Johnsen SG, Sorensen K: Follow-up 10 years later of 34 Klinefelter males with karyotype 47,XXY and 16 hypogonadal males with karyotype 46,XY. *Psychol Med* 1980; 10: 345–352
3. Pinabel F, Gorwood P, Ades J: The impact of oestradiol on ages at onset in schizophrenia reevaluated through Klinefelter syndrome (letter). *Schizophr Res* 1997; 23:269–270
4. Volavka J: The effects of clozapine on aggression and substance abuse in schizophrenic patients. *J Clin Psychiatry* 1999; 60(suppl 12):43–46

ALAIN DERVAUX, M.D.  
ERIC ARTIGES, M.D., PH.D.  
*Orsay, France*

### Clozapine and Pericarditis With Pericardial Effusion

TO THE EDITOR: We report the case of a patient receiving clozapine who developed pericarditis with pericardial effusion, which resolved when the drug was discontinued.

Mr. A, a 43-year-old unmarried white man with chronic paranoid schizophrenia that had been stabilized with clozapine for 7 years, developed pericardial effusion. More than 1 liter of fluid was removed by means of pericardiocentesis. The fluid gradually reaccumulated, as documented by serial ECGs. Because the treating psychiatrist and cardiologist considered clozapine possibly responsible for the effusion, a decision was made to substitute ziprasidone; when a therapeutic dose was reached, the clozapine (775 mg/day) would be slowly tapered and discontinued.

Three weeks later Mr. A came to our hospital emergency treatment center with shortness of breath and chest pain that had lasted for several weeks, along with a 15-lb weight gain. His medications included 750 mg/day of clozapine, 160 mg/day of ziprasidone, 240 mg/day of furosemide, and 60 mg/day of paroxetine; paroxetine had been taken for the past 18 months for depressive symptoms. An ECG revealed a sinus rhythm with a rate of 115 bpm and nonspecific T-wave abnormalities. A chest X-ray revealed a stable cardiomegaly.

A physical examination showed a morbidly obese man in no acute distress. His blood pressure was 130/70 mm Hg. His rate of respiration was 20 breaths per minute at rest, and his pulse was 110–120 bpm. His heart sounds were distant, but no rub was present. His lungs were clear to auscultation and percussion. An examination of his extremities revealed 1–2+ pitting edema bilaterally. An ECG showed considerable pericardial fluid, which was suggestive of cardiac tamponade. Mr. A was admitted for a sec-

ond pericardiocentesis, and 1.2 liters of serosanguineous fluid was withdrawn. The results of fluid analysis were unremarkable. At this point, clozapine was abruptly discontinued. At a 3-month follow-up, there was no reaccumulation of pericardial fluid.

Pericarditis may result from a transmural myocardial infarction, metastatic malignancies, uremia, collagen vascular diseases, radiation, or viral, bacterial, protozoal, or fungal infections. Drugs known to cause pericarditis include procainamide, hydralazine, and isoniazid. The inflammation caused by acute pericarditis often produces exudation of fluid into the pericardial space. Pericardial tamponade develops when fluid accumulates rapidly or the amount of fluid becomes so large that it compresses the heart and presents a life-threatening situation.

We are aware of two reported cases of pericarditis induced by clozapine (1, 2). In each instance, the pericardial effusion developed soon after initiation of treatment and resolved after drug discontinuation. In the first report (1), the pericardial effusion redeveloped when the patient was rechallenged with clozapine. In our patient, the pericardial effusion developed after he had been taking clozapine for 7 years. Of the many possible causes for a pericardial effusion, all were ruled out, with the possible exception of viral infection. The fact that pericardial fluid reaccumulated shortly after the first pericardiocentesis, while Mr. A continued taking clozapine, also suggests the possibility of clozapine-induced pericardial effusion. Because pericardial tamponade can be life threatening, it may be prudent to discontinue clozapine if a patient develops pericardial effusion.

#### References

1. Daly JM, Goldberg RJ, Braman SS: Polyserositis associated with clozapine treatment (letter). *Am J Psychiatry* 1992; 149:1274–1275
2. Catalano G, Catalano MC, Frankel Wetter RL: Clozapine induced polyserositis. *Clin Neuropharmacol* 1997; 20:352–356

AIDA MURKO, M.D.  
SARAH CLARKE, P.A.C.  
DONALD W. BLACK, M.D.  
*Iowa City, Iowa*

### Transcranial Magnetic Stimulation in Schizophrenia

TO THE EDITOR: Repetitive transcranial magnetic stimulation (rTMS) has been found to down-regulate serotonin 2 receptors in the frontal cortex (1) and increase the responsiveness of rats to dopaminergic stimulation (2), which suggests that rTMS may affect frontal cortex function and antagonize the dopaminergic-blocking adverse effects of typical antipsychotics in schizophrenia patients.

We investigated the effects of rTMS add-on treatment on the P300 event-related potential and hyperprolactinemia caused by typical antipsychotics. All subjects provided written informed consent. Five patients with chronic schizophrenia (two men and three women, mean age=33.2 years) treated with typical antipsychotics received 5 seconds of 10-Hz rTMS (20 times at 30-sec intervals) at the left dorsolateral prefrontal cortex for 5 consecutive days. Both P300 event-related potentials and serum prolactin levels were measured at baseline and 2 days after the last rTMS treatment. Ongoing antipsy-

chotic medication treatment was not altered during the study periods.

Generally, treatment was well tolerated, and no serious adverse effects were reported. Three patients reported improvement in their mood after rTMS; no exacerbation of psychotic symptoms was found. The prolactin levels of all five patients decreased 24.4%–49.4% from their respective baseline levels after rTMS treatment. The difference in the mean prolactin levels before and after rTMS was significant (Wilcoxon's signed-rank test:  $z=-2.02$ ,  $p<0.05$ , two-tailed). Amplitudes of P300 at the Fz site were also significantly elevated after rTMS treatment (paired  $t=-4.08$ ,  $df=4$ ,  $p<0.02$ , two-tailed) and elevated at marginal significance at the Cz site (paired  $t=-2.61$ ,  $df=4$ ,  $p<0.06$ , two-tailed).

Our finding is in contrast with the results of a previous study of normal volunteers in which rTMS did not change serum prolactin levels (3). This discrepancy may be due to differences in rTMS method (e.g., frequency, location) or the study group source; our patients had antipsychotic-induced hyperprolactinemia. rTMS might enhance dopaminergic function (2), which may antagonize hyperprolactinemia because of dopaminergic blocking by typical antipsychotics.

Event-related potentials are thought to reflect neuroelectric activity related to cognitive processes, such as the allocation of attention and short-term memory to auditory stimuli (4). Our results suggest that rTMS may be used as an add-on therapy in patients taking antipsychotics to improve cognitive function and antagonize the adverse effects of hyperprolactinemia.

#### References

1. Ben-Shachar D, Gazawi H, Riboyad-Levin J, Klein E: Chronic repetitive transcranial magnetic stimulation alters beta-adrenergic and 5-HT<sub>2</sub> receptor characteristics in rat brain. *Brain Res* 1999; 816:78–83
2. Zyss T, Mamczarz J, Roman A, Vetulani J: Comparison of effectiveness of two schedules of rapid transcranial magnetic stimulation on enhancement of responsiveness to apomorphine. *Pol J Pharmacol* 1999; 51:363–366
3. George MS, Wassermann EM, Williams WA, Steppel J, Pascual-Leone A, Basser P, Hallett M, Post RM: Changes in mood and hormone levels after rapid-rate transcranial magnetic stimulation (rTMS) of the prefrontal cortex. *J Neuropsychiatry Clin Neurosci* 1996; 8:172–180
4. Kok A: Event-related-potential (ERP) reflections of mental resources: a review and synthesis. *Biol Psychol* 1997; 45:19–56

HSEIH-CHIAO YU, M.D.  
KWONG-KUM LIAO, M.D.  
TA-JEN CHANG, M.D.  
SHIH-JEN TSAI, M.D.  
*Taipei, Taiwan (R.O.C.)*

#### Origins of Dreaming

TO THE EDITOR: Morton F. Reiser, M.D. (1), approached the topic of dreams in psychiatry by integrating the parallel findings of neurobiological, clinical, and psychoanalytical studies. He drew attention to the changes that have taken place in the regulation of wakefulness in the evolution from lower vertebrates to the mammalian species. In their explanation of the function of dream sleep, Crick and Mitchison (2) also drew attention to a change in brain organization in the evolutionary process. Because REM sleep appeared first in mam-

mals, they suggested that a new type of REM-facilitating circuitry developed that became a prerequisite for dream sleep and made possible the unloading of useless experiences from the brain during dreaming, thereby consolidating meaningful memory imprints.

There is also another evolutionary aspect of the step from lower species to mammals that has relevance for understanding the origins of dreaming. Simultaneous to brain development, a fundamental change also occurred in the infant-mother relationship. The survival of the infant became dependent on the continuity of the mother's feeding and the ensuing vital relationship. My colleagues and I (3) found that the feeding of the newborn is related to a significant increase in the amplitude of the infant's brain activity in occipital-temporal-parietal areas. This suggests parallel activation of the projection areas of several sensory modalities, which become linked to the primitive experience of satisfaction induced by feeding. The hypothesis of the effect of infant feeding on primitive mental imagery seems thus to have a neurophysiological basis.

After feeding, the human infant is likely to fall asleep. The amplitude increase in occipital-temporal-parietal areas during feeding may activate the cortical junction of these areas, which Dr. Reiser suggested plays a gateway role in dreaming. This is another example of concurrent neurophysiological and experiential events, in which perceptual and primitive emotional processes contribute to sleep and the induction of dreaming. Such a process, involving neurobiology and infant-mother interaction, also makes sense of the isomorphic features common to REM physiology and psychoanalytic dream theory (4).

The Crick-Mitchison hypothesis fits well with Freud's first postulate about the meaning of dreaming, namely, that dreams are guardians, i.e., preservers, of the restorative power of sleep but does not fit with the second postulate concerning the meaning of dream images. To understand the origin of the latter, it is necessary to also appreciate the evolutionary significance of the change in the infant-mother relationship and its impact on brain function.

#### References

1. Reiser MF: The dream in contemporary psychiatry. *Am J Psychiatry* 2001; 158:351–359
2. Crick F, Mitchison G: The function of dream sleep. *Nature* 1983; 304:111–114
3. Lehtonen J, Könönen M, Purhonen M, Partanen J, Saarikoski S, Launiala K: The effect of nursing on the brain activity of the newborn. *J Pediatr* 1998; 132:646–651
4. Lehtonen J: The relationship between neurophysiology and psychoanalysis in the light of dream research. *Perspect Biol Med* 1980; 23:415–423

JOHANNES LEHTONEN, M.D., PH.D.  
*Kuopio, Finland*

TO THE EDITOR: Dr. Reiser's article was a scholarly review that deserves appreciation as an effort to ally neuroscientists and psychoanalysts in an effort to solve the mind-brain problem (i.e., How does the brain produce the activity of the human mind?) through analysis of the dream. But the article troubles us because the two disciplines have been at odds for decades and have shown little interest in a common ground. We are neither neuroscientists nor psychoanalysts but are no strang-



ers to the ideas of both groups. Our view of Dr. Reiser's article has led us to the following conclusions and speculations:

1. When neuroscientists and psychoanalysts talk about "the dream," "affect," or "emotion," they are not talking about the same objects.

2. REM, while an interesting phenomenon and the subject of much excitement by neuroscientists, says little or nothing about the meaning of the dream.

3. Freud's notion of the dream as wish fulfillment is either incorrect or a gross simplification that fails to take into account alternative motives.

4. Dr. Reiser misspoke when he implied an identity between psychoanalysis and the mind. Surely the mind is much more. And he misspoke when he implied an identity between neuroscience and the brain.

5. In general, the history of psychiatry has not depended on the coalescence of diverse orthodoxies such as neuroscience and psychoanalysis.

6. Dr. Reiser's expressed hope for a breakthrough by means of positron emission tomography and computerized tomography scans seems in the nature of a Freudian wish.

7. We were disappointed that Dr. Reiser's review did not contain a single reference to the work of the great neurosurgeon/psychologist Wilder Penfield, director of the Montreal Neurological Institute in the 1930s.

Penfield showed that conscious brain-damaged subjects, when their brains were surgically exposed and tagged, reported dream-like experiences when their brains were stimulated by electrodes at different sites but *different* dream-like experiences when later their brains were stimulated at approximately identical sites. (Penfield must have understood that his electrodes may have sparked fewer or greater numbers of brain cells when he applied his electrodes to sites he had tagged.)

We owe a debt of gratitude to Dr. Reiser for raising the subject of the meaning of dreams, which remains one of the great mysteries of human activity, both functional and dysfunctional, but question his call for an alliance between such adversarial groups of scientists. We suspect that any major breakthrough in dreaming will come from a chance observation by a brilliant observer such as Penfield or Freud.

CARMEN VEIGA ZUK, M.D.  
GERALD H. ZUK, PH.D.  
*Santa Clarita, Calif.*

### Meta-Analysis and Psychiatric Genetics

TO THE EDITOR: In the article by Stephen V. Faraone, Ph.D., et al. (1), I find the use of meta-analysis to substantiate their claim perplexing. Meta-analysis may be a useful tool when examining studies with reasonably similar results, but using meta-analysis "to reconcile conflicting findings" (p. 1052) is a dubious endeavor. A significant majority of the studies in their meta-analysis either do not substantiate or contradict the claim that the 7-repeat allele of the dopamine D<sub>4</sub> receptor gene is seen in higher prevalence in individuals with attention deficit hyperactivity disorder (ADHD). I certainly agree that the authors' conclusion is "counterintuitive" (p. 1055). Notwithstanding that, I have a few criticisms of the meta-analysis itself.

1. While the authors ruled out the possibility that the results of an initial study (2) were false positive, using that same study in the meta-analysis along with attempts to replicate it is "stacking the deck." The prevalence of refuted initial false positives from molecular genetics studies of mental illnesses approaches 100% (3). Thus, this initial study should not be included in the meta-analysis (even if it is the most strongly positive study).

2. Despite the impressive mathematical demonstration of nonbias, I suggest there are a few potential areas of bias. First, Dr. Faraone included one of his own studies in the meta-analysis. Second, I can hardly imagine more biased groups to cull data from than "colleagues presenting such data at national meetings" and "the molecular genetics e-mail network" (1, p. 1053). Also, the authors stated, "Unfortunately, neither type of study has consistently confirmed the putative association between ADHD and the DRD4 7-repeat allele" (p. 1052). Unfortunate for whom?

3. Even if "it is reasonable to attribute differences among studies to chance fluctuations" (p. 1055), this does not account for the possibility that the studies regarding the D<sub>4</sub> receptor gene 7-repeat allele simply provided the most false positives in comparison with molecular genetic studies of ADHD as a whole. A controlled meta-analysis of all molecular genetic studies for ADHD would be interesting; a null hypothesis should first assume that no such genes exist and that all significant findings to date, both positive and negative, are the result of "chance fluctuations."

4. The argument that ADHD is "mediated by many genes acting in concert" (p. 1052) is rather circular in that it is based primarily on the complete failure of molecular genetic studies to find such genes and replicate those findings. Whether or not ADHD genes truly exist (individually or acting in concert) remains an unproven assumption.

To claim that there is a link between ADHD and the D<sub>4</sub> receptor gene 7-repeat allele "or some nearby gene" (p. 1052), a consistent replicable protocol must first be developed. A "small" association noted in a meta-analysis of conflicting studies does not meet the burden of proof.

### References

1. Faraone SV, Doyle AE, Mick E, Biederman J: Meta-analysis of the association between the 7-repeat allele of the dopamine D<sub>4</sub> receptor gene and attention deficit hyperactivity disorder. *Am J Psychiatry* 2001; 158:1052-1057
2. LaHoste GJ: Genetics of complex behavioral traits: obesity, dopamine, and mood. *Mol Psychiatry* 1996; 1:302
3. Faraone SV, Tsuang MT, Tsuang DW: *Genetics of Mental Disorders*. New York, Guilford, 1999

STEPHEN J. PITTELLI, M.D.  
*San Luis Obispo, Calif.*

### Drs. Faraone and Biederman Reply

TO THE EDITOR: Using meta-analysis, we showed a small but significant association between ADHD and the D<sub>4</sub> receptor gene. Dr. Pittelli's letter about our article highlights common misconceptions about meta-analysis and about psychiatric genetics.

He states that using meta-analysis to reconcile conflicting findings is dubious; that is not true. Meta-analysis provides a statistical framework for determining if a series of studies

does or does not support a hypothesis. It provides tests of heterogeneity, which determine if conflicting findings are statistically different, and tests of covariates, which determine if demographic, design, or other factors can account for conflicting findings. Thus, the method of meta-analysis is ideally suited for clarifying apparently inconsistent findings.

Our comments on Dr. Pittelli's numbered points are as follows:

1. We agree that meta-analysis can be misinterpreted if an original positive finding is included. Dr. Pittelli overlooked our Table 3, which showed that the meta-analysis was significant when this study was excluded.

2. There is no statistical basis for Dr. Pittelli's assertion that a meta-analysis is biased if it includes a study from the person who performed the meta-analysis. He also overlooked Table 4, which showed that the meta-analysis was significant after omission of our study. Dr. Pittelli claims that research presented at national conferences or solicited from the ADHD Molecular Genetics Network e-mail list is biased; this is incorrect. The main bias of concern to meta-analysis is that negative studies are published, not that conference reports are more positive than published studies. Dr. Pittelli asks why we think it unfortunate that studies of ADHD and the D<sub>4</sub> receptor gene have not consistently confirmed their association. It is unfortunate because the use of small study groups to detect small effects obscures findings and inhibits progress.

3. The claim that a meta-analysis of studies of ADHD and the D<sub>4</sub> receptor gene must include all other genes tested makes no sense. Studies of different genes test different hypotheses. Mixing apples and oranges does not clarify any statistical analysis.

4. Dr. Pittelli incorrectly claims that whether ADHD genes truly exist remains an unproven assumption. The twin literature about ADHD clearly indicates that ADHD is one of the most heritable of psychiatric disorders (1). Moreover, the genetics literature is consistent with a multigenic theory of ADHD (2), despite Dr. Pittelli's claim that such a theory is circular.

We never claimed that our meta-analysis proved the D<sub>4</sub> receptor gene to be a susceptibility gene for ADHD. We concluded that the extant data were strong enough to warrant further studies of the D<sub>4</sub> receptor gene and ADHD.

#### References

1. Faraone SV, Biederman J: Neurobiology of attention-deficit hyperactivity disorder. *Biol Psychiatry* 1998; 44:951-958
2. Faraone SV, Doyle AE: The nature and heritability of attention-deficit/hyperactivity disorder. *Child Adolesc Psychiatr Clin N Am* 2001; 10:299-316, viii-ix

STEPHEN V. FARAONE, PH.D.  
JOSEPH BIEDERMAN, M.D.  
*Boston, Mass.*

### Shakespeare and Successful Aging

TO THE EDITOR: We noted that at the end of the excellent article on successful aging by George E. Vaillant, M.D., and Kenneth J. Mukamal, M.D. (1), there is a minor error that our shared respect for the "Bard of Avon" will not let us pass unnoticed. The authors refer to Hamlet's great friend Horatio in paraphrasing a line that should be attributed to Cassius in addressing Brutus in *Julius Caesar*:

Men at some time are masters of their fates:  
The fault, dear Brutus, is not in our stars,  
But in ourselves, that we are underlings.

—*Julius Caesar*, Act I, scene ii

#### Reference

1. Vaillant GE, Mukamal K: Successful aging. *Am J Psychiatry* 2001; 158:839-847

ROBERT RUBEY, M.D.  
LAWRENCE LABBATE, M.D.  
*Charleston, S.C.*

### Drs. Vaillant and Mukamal Reply

Our faces are red, but our hearts are grateful for the correction of our error by Drs. Rubey and Labbate.

GEORGE E. VAILLANT, M.D.  
KENNETH J. MUKAMAL, M.D.  
*Boston, Mass.*

### Sweet Taste Preference and Alcohol Dependence

TO THE EDITOR: We applaud the article by Henry R. Kranzler, M.D., et al. (1) and concur that sweet taste preference, rather than being a marker for alcoholism risk or a generalized alteration in rewarding response to hedonic stimuli in those with alcohol dependence (2), instead reflects a chemosensory adjustment to the effect of alcohol on the olfactory system. Both acute alcohol intoxication (3) and chronic alcoholism (4) are associated with an impaired olfactory ability. Smell is approximately 90% of what is described as taste or flavor; hyposmic individuals perceive food as bland or tasteless (5). In order to compensate, spices and enhanced true taste (e.g., sugar) are added to food (6). Therefore, through a learned response paradigm, those who are alcohol dependent develop a preference for a higher concentration of sugars, even in the absence of other foods.

Alternatively, because of chronic excess daily use of sugars, they may induce an up-regulation of the sweet taste receptors, raising their sucrose threshold and their associated sucrose hedonic curve (7). Thus, preference for higher sucrose concentration in individuals dependent on alcohol may represent only a behavioral compensatory response for those with alcohol-induced olfactory loss and thus, as Dr. Kranzler et al. found, would not be useful as an indicator of risk for developing alcohol dependence.

#### References

1. Kranzler HR, Sandstrom KA, Van Kirk J: Sweet taste preference as a risk factor for alcohol dependence. *Am J Psychiatry* 2001; 158:813-815
2. Kampov-Polevoy A, Garbutt JC, Janowsky D: Evidence of preference for a high-concentration sucrose solution in alcoholic men. *Am J Psychiatry* 1997; 154:269-270
3. Hirsch AR, Russell GS: Effects of inebriation on olfaction (abstract). *Investigative Medicine* 1995; 43:422A
4. Mair RG, Doty RL, Kelly KM, Wilson CS, Langlais PJ, McEntee WJ, Vollmecke TA: Multimodal sensory discrimination deficits in Korsakoff's psychosis. *Neuropsychologia* 1986; 24:831-839
5. Hirsch AR: Olfaction in migraineurs. *Headache* 1992; 32:233-236

6. Ferris AM, Schlitzer JL, Schierberl MJ, Catalanotto FA, Gent J, Peterson MG, Bartoshuk LM, Cain WS, Goodspeed RB, Leonard G, Donaldson J: Anosmia and nutritional status. *Nutrition Res* 1985; 5:149–156
7. Contreras RJ: Gustatory mechanisms of a specific appetite, in *Neural Mechanisms in Taste*. Edited by Cagan RH. Boca Raton, Fla, CRC Press, 1989, pp 119–145

ALAN R. HIRSCH, M.D.  
*Chicago, Ill.*

TO THE EDITOR: Dr. Kranzler and colleagues asked 122 nonalcoholic subjects to rate a series of sucrose solutions. Comparing subjects with and without a paternal history of alcoholism, they found that subjects in both groups preferred a 0.42-mol sucrose solution. They therefore concluded that their results failed to support the hypothesis that a sweet preference is a marker of alcoholism risk.

I take issue with their logic. Since a paternal history of alcoholism is itself merely an indicator/marker of alcoholism risk, what Dr. Kranzler et al. actually showed is that a sweet preference does not characterize this indicator/marker of alcoholism risk. This is not the same as concluding that a sweet preference is not a marker of alcoholism risk.

CHITTARANJAN ANDRADE, M.D.  
*Bangalore, India*

### Ms. Sandstrom and Dr. Kranzler Reply

TO THE EDITOR: We thank Drs. Hirsch and Andrade for their thoughtful consideration of our report. Dr. Hirsch's suggestion that the sweet preference observed among alcoholics may represent an artifact of impaired olfaction is interesting and worthy of further consideration. Although reports showing greater sucrose preference in alcoholics have revealed no impairment in the capacity to discriminate among different sucrose concentrations, an impairment of olfaction could influence the hedonic value of the solution.

The results of our effort to avoid the confounding effects of alcoholism on taste preference by studying nonalcoholic children of alcoholic fathers has recently been replicated by other researchers (1). Nonetheless, we agree with Dr. Andrade's comment that the lack of an association between sweet preference and paternal history of alcoholism does not preclude an association between sweet preference and alcoholism risk. Since studies comparing nonalcoholic groups with and without paternal alcoholism do not directly measure alcoholism risk, the only study design that we believe fully addresses this question is a prospective, longitudinal one. However, such a study would be costly and time-consuming. In view of the recent report of an association between a family history of alcoholism and sweet preference among alcoholics (2), further studies of sweet preference among alcoholics (e.g., after variable periods of abstinence from alcohol) may clarify whether sweet preference is a valid phenotypic marker of alcoholism.

#### References

1. Scinska A, Bogucka-Bonikowska A, Koros E, Polanowska E, Habrat B, Kukwa A, Kostowski W, Bienkowski P: Taste responses in sons of male alcoholics. *Alcohol Alcohol* 2001; 36: 79–84
2. Kampov-Polevoy AB, Tsoi MV, Zvartau EE, Neznanov NG, Khalitov E: Sweet liking and family history of alcoholism in hospital-

ized alcoholic and non-alcoholic patients. *Alcohol Alcohol* 2001; 36:165–170

KRISTEN A. SANDSTROM, B.A.  
HENRY R. KRANZLER, M.D.  
*Farmington, Conn.*

### Amnesia and Neonaticide

TO THE EDITOR: In the study of neonaticide by Margaret G. Spinelli, M.D. (1), amnesia was reported by 14 (93%) of 15 murderers of newborns. Such a high prevalence of amnesia has never been described before in neonaticide, to our knowledge, and may reflect the use of the Dissociative Experiences Scale to systematically screen for dissociative phenomena. Alternatively, it is conceivable that presenting the accused with an extensive checklist of mental symptoms may inadvertently educate them about psychiatric symptoms that might provide an alibi or justification for their actions.

In an archival study of 53 murders of newborns committed in Rio de Janeiro, Brazil, between 1900 and 1995 (2), amnesia was the only psychiatric symptom observed; it was reported by 17 (32%) of the women. Among the 26 women indicted under the Brazilian 1890 infanticide statute (which granted to single women killing their newborns a considerably lighter punishment in the defense of their honor than to common murderers) only two (8%) reported amnesic symptoms. Among 27 women indicted under the Brazilian infanticide statute of 1940 (based on the concept that the influence of the puerperal state might trigger a brief psychotic episode and lead to the killing of the newborn), 15 (55%) reported amnesia. This statistically significant difference ( $\chi^2=11.82$ ,  $df=1$ ,  $p<0.001$ ) between the two groups led us to hypothesize that the 1940 statute's emphasis on the causal role of a putative psychiatric disorder may have prompted the accused to falsely acknowledge psychiatric symptoms in order to avoid being charged with homicide.

Since tests for malingering were not employed in Dr. Spinelli's study, it is difficult to ascertain the veracity of these reports of amnesia. We would be grateful if Dr. Spinelli could provide additional information about the nature and the timing of the dissociative symptoms. It would be important to know if the reports of amnesia were spontaneous or were elicited by the Dissociative Experiences Scale.

Murder of newborns represents a significant clinical, forensic, and moral problem. Solving the riddle of these amnesic symptoms is an important first step toward developing effective preventive measures and scientifically based legal approaches for women who killed their newborns.

#### References

1. Spinelli MG: A systematic investigation of 16 cases of neonaticide. *Am J Psychiatry* 2001; 158:811–813
2. Mendlowicz MV, Jean-Louis G, Gekker M, Rapaport MH: Neonaticide in the city of Rio de Janeiro: forensic and psycholegal perspectives. *J Forensic Sci* 1999; 44:741–745

MAURO V. MENDLOWICZ, M.D.  
MARK HYMAN RAPAPORT, M.D.  
LEONARDO FONTENELLE, M.D.  
GIRANDIN JEAN-LOUIS, PH.D.  
TALVANE M. DE MORAES, M.D.  
*Rio de Janeiro, Brazil*

## Dr. Spinelli Replies

TO THE EDITOR: Dr. Mendlowicz and colleagues describe findings derived from their “archival” study of neonaticide (1900–1995) “cases identified retrospectively through a search in the judicial files of the city of Rio de Janeiro” (Mendlowicz et al., 1999; reference 1). They hypothesize that the increase over time in reports of amnesia in their series was a result of a change in Brazil’s legislation, which provided mitigation for psychiatric symptoms in cases of neonaticide. They ascribe these reports to malingering. The authors suggest that the amnesic symptoms reported in my case series were also due to malingering and assert that the Dissociative Experiences Scale provided a psychiatric checklist as an alibi for the defendants (2).

The Dissociative Experiences Scale is a screening tool for general dissociative psychopathology as it appears in daily life circumstances, not merely at the time of pregnancy or childbirth. Amnesia is one factor among several in the Dissociative Experiences Scale. Spontaneous reports of amnesia in my study group focused on the time of delivery and viewing of the infant. The Dissociative Experiences Scale cannot preclude the possibility of malingering when secondary gain plays a pivotal role. Even so, I reported that two abnormally high scores in my study group suggested malingering. Nevertheless, Mendlowicz and colleagues raise the important issue of methodology.

A preponderance of the literature on neonaticide is derived from judicial statistics or retrospective chart reviews that have used varied and outdated diagnostic criteria (3). Contemporary reports of case interviews describe psychopathology similar to that reported in my study group (4, 5). One cannot infer cause and effect from a temporal relationship nor compare archival data derived from varied sources to contemporary interviewer data.

I addressed the lack of a malingering tool when I discussed the limits of my data. This accepted method of reporting suggests that the reader arrive at his or her own professional opinion given those limitations.

In appreciation of the authors’ concerns, I restate the purpose of my preliminary work. The vital need for further study of neonaticide should encourage inquiry and prompt phenomenological studies using structured interviews and contemporary diagnostic criteria. Once psychopathology is identified, strategies for treatment and prevention can be devised.

## References

1. Mendlowicz MV, Rapaport MH, Mecler K, Golshan S, Moraes TM: A case-control study on the socio-demographic characteristics of 53 neonaticidal mothers. *Int J Law Psychiatry* 1998; 21: 209–219
2. Steinberg M, Rounsaville B, Cicchetti D: Detection of dissociative disorders in psychiatric patients by a screening instrument and a structured diagnostic interview. *Am J Psychiatry* 1991; 148:1050–1054
3. Resnick PJ: Murder of the newborn: a psychiatric review of neonaticide. *Am J Psychiatry* 1970; 126:1414–1420
4. Bonnet C: Adoption at birth: prevention against abandonment or neonaticide. *Child Abuse Negl* 1993; 17:501–513
5. Green CM, Manohar SV: Neonaticide and hysterical denial of pregnancy. *Br J Psychiatry* 1990; 156:121–123

MARGARET G. SPINELLI, M.D.  
New York, N.Y.

## Seasonal Fluctuation in Schizophrenia

TO THE EDITOR: Jaana M. Suvisaari, M.D., Ph.D., and her colleagues suggested in their intriguing article (1) that procreation in the summertime represents a constant hazard, in addition to an irregular environmental risk factor, for schizophrenia. Are these two components independent variables or just two facets of a common pathogenic mechanism that might ultimately be preventable?

Using a novel climatic data set (2, 3), we compared their data with mean temperature and precipitation rates over the same time. The dramatic multiyear fluctuations, particularly the odds amplitude for patients born in 1955–1959, cannot be explained by the subtle climatic variations, neither in the more densely populated southern part nor in the rest of Finland. The fluctuations in schizophrenia births, which have also been reported from Denmark and Scotland (4), might rather be related to an additional stochastic factor prevalent in the north.

In comparison to the first account by Tramer (5), the reported data, showing the lower schizophrenic birth rates in July through August (1955–1959), reveal another potential clue to the environmental determinant of schizophrenia. In Switzerland, we have, in addition to the widely replicated excess of schizophrenia births in the winter and spring months, a second minor peak in July (5). This bimodal distribution mirrors the seasonal concentration of ticks (*Ixodes ricinus*) 9 months earlier, with a major peak in spring and a minor peak in autumn separated by a decrease in humidity in the summer (6). Ticks containing *Borrelia burgdorferi* are prevalent in the urban recreational areas of Helsinki. However, as in the Alps, the minimal mean temperature of 7°C required for tick activity (6) allows only one peak from May to September in Finland, during which time the annual precipitation is also highest. Tick activity coinciding with procreational preference in the summertime might thus represent the stable component. While a few autumn-feeding *I. ricinus* ticks are still active up to November in central Europe (6), the temperature falls below 0°C in Finland. Adverse weather conditions, known to underlie the stochastic year-to-year oscillations of tick populations (7, 8), might thus reflect the irregular component of schizophrenia births in the north.

Contrary to the current belief shared by Dr. Suvisaari et al. and others, neither the excess of schizophrenia winter births nor the excess of schizophrenia itself occurs at a constant rate worldwide. South of the Wallace line (9, 10), which limits the southward spread of species, including *B. burgdorferi*-transmitting ticks (6), seasonal schizophrenia trends appear to be insignificant or nonexistent, and in certain remote areas schizophrenia is even absent (11). We found only one psychotic patient in a neuropsychiatric survey comprising over 10,000 Papuans in the interior of New Guinea—fewer than expected (12). In Australia, where *Borrelia garini* is only sporadically introduced by migratory seabirds, *B. burgdorferi* could not be detected and cannot be transmitted by the local tick, *I. holocyclus*. It is not surprising after all that the higher rates of schizophrenia have been reported from the northeastern, northwestern, and Great Lakes states, which score the highest numbers of *Ixoid* tick populations and infections by *B. burgdorferi* (13).



An early prenatal event interfering with neuronal migration has been suggested to underlie the consistent pattern of cellular disarray observed in schizophrenia brains. This hypothesis, however, contrasts with the reported pregnancy and birth complications during the second and third trimesters related to hypoxic damage or viral infections, as suggested by Dr. Suvisaari et al. and others. However, since *B. burgdorferi* has direct access to host genes, which the intracellular pathogen exploits like a virus for its own replication, a novel mutation might thus affect a gene prone to be hit by *B. burgdorferi*, the cannabinoid receptor gene (14), which is known to induce both hypoxic resistance and neuronal migration.

#### References

1. Suvisaari JM, Kaukka JK, Lönnqvist JK: Season of birth among patients with schizophrenia and their siblings: evidence for the procreational habits hypothesis. *Am J Psychiatry* 2001; 158: 754–757
2. New M, Hulme M, Jones P: Representing twentieth-century space time climate variability, part I: development of a 1961–90 mean monthly terrestrial climatology. *J Climate* 1999; 12: 829–856
3. New M, Hulme M, Jones P: Representing twentieth-century space time climate variability, part II: development of 1901–96 monthly grids of terrestrial surface climate. *J Climate* 2000; 13: 2217–2238
4. Adams W, Kendell RE: Annual variation in birth rate of people who subsequently develop schizophrenia. *Br J Psychiatry* 1999; 175:522–527
5. Tramer M: Ueber die biologische Bedeutung des Geburtsmonates, insbesondere für die Psychoseerkrankungen. *Schwiz Arch Neurol Psychiatr* 1929; 24:17–24
6. Sonenshine DE: *Biology of Ticks*. New York, Oxford University Press, 1989
7. Korotkov IuS: [Cyclic processes in the dynamics of the population count of the taiga tick and their relation to weather and climatic conditions.] *Parazitologija* 1998; 32:21–31(Russian)
8. Talleklint L, Jaenson TG: Seasonal variations in density of questing *Ixodes ricinus* (Acari: Ixodidae) nymphs and prevalence of infection with *B. burgdorferi* s.l. in south central Sweden. *J Med Entomol* 1996; 33:592–597
9. McGrath JJ, Welham JL: Season of birth and schizophrenia: a systematic review and meta-analysis of data from the Southern Hemisphere. *Schizophr Res* 1999; 35:237–242
10. Torrey EF, Miller J, Rawlings R, Yolken RH: Seasonality of births in schizophrenia and bipolar disorder: a review of the literature. *Schizophr Res* 1997; 28:1–38
11. Dohan FC, Harper EH, Clark MH, Rodrigue RB, Zigas V: Is schizophrenia rare if grain is rare? *Biol Psychiatry* 1984; 19:385–399
12. Fritzsche M, Gottstein B, Wigglesworth MC, Eckert J: Serological survey of human cysticercosis in Irianese refugee camps in Papua New Guinea. *Acta Trop* 1990; 47:69–77
13. Brown JS Jr: Geographic correlation of schizophrenia to ticks and tick-borne encephalitis. *Schizophr Bull* 1994; 20:755–775
14. Fritzsche M: Are cannabinoid receptor knockout mice animal models for schizophrenia? *Med Hypotheses* 2001; 56:638–643

MARKUS FRITZSCHE, M.D.  
Adliswil, Switzerland  
JÜRIG SCHMIDL, PH.D.  
Zurich, Switzerland

#### Dr. Suvisaari and Colleagues Reply

TO THE EDITOR: Drs. Fritzsche and Schmidli misunderstand our article in that we did not suggest that procreation in the summertime represents a constant hazard for schizophrenia. We observed that both patients with schizophrenia and their unaffected siblings are more often born during the winter and spring months, suggesting that among parents of patients with schizophrenia, there is a tendency to have children more often during the winter and spring. This tendency may not be related to the offspring's risk of developing schizophrenia at all. It is also difficult to believe that there would be a link between a tendency of parents to have children during winter and spring and tick-borne infections.

However, we also observed that between 1955 and 1959 there was a pronounced seasonal variation in births of schizophrenia patients but not their normal siblings. On the basis of these findings, we suggested that the seasonal variation in schizophrenia births may consist of two components: a constant component caused by parental procreational habits and an irregular component caused by environmental risk factors that, when they occur, considerably increase the magnitude of the seasonal variation in births among patients but not their siblings and are genuine risk factors for schizophrenia. Infections caused by *B. burgdorferi* are one possible explanation for this irregular component. However, in Finland, Lyme borreliosis is endemic in southwestern coastal areas, in which the incidence of schizophrenia is lowest. In many northeastern areas, in which the incidence of schizophrenia is exceptionally high, ticks no longer survive (1–3).

Finally, we wish to point out that we do not share the belief that the incidence of schizophrenia is constant worldwide. In our other studies, we have shown that there is considerable temporal (4) and regional (3) variation in the incidence of schizophrenia in Finland, and we have also investigated time trends in the seasonal variation in births of individuals with schizophrenia (5). We have no reason to believe that this temporal and regional variation in the incidence of schizophrenia would be limited to Finland.

#### References

1. Wahlberg P, Granlund H, Nyman D, Panelius J, Seppälä I: Late Lyme borreliosis: epidemiology, diagnosis and clinical features. *Ann Med* 1993; 25:349–352
2. Wahlberg P: [Lyme borreliosis yesterday, today and tomorrow.] *Duodecim* 1995; 111:1298–1303(Finnish)
3. Haukka J, Suvisaari J, Varilo T, Lönnqvist J: Regional variation in the incidence of schizophrenia in Finland: a study of birth cohorts born from 1950 to 1969. *Psychol Med* 2001; 31:1045–1053
4. Suvisaari JM, Haukka JK, Tanskanen AJ, Lönnqvist JK: Decline in the incidence of schizophrenia in Finnish cohorts born from 1954 to 1965. *Arch Gen Psychiatry* 1999; 56:733–740
5. Suvisaari JM, Haukka JK, Tanskanen AJ, Lönnqvist JK: Decreasing seasonal variation of births in schizophrenia. *Psychol Med* 2000; 30:315–324

JAANA M. SUVISAARI, M.D., PH.D.  
JARI K. HAUKKA, PH.D.  
JOUKO K. LÖNNQVIST, M.D., PH.D.  
Helsinki, Finland

Reprints are not available; however, Letters to the Editor can be downloaded at <http://ajp.psychiatryonline.org>.