Omega-3 Fatty Acids for Depression in Pregnancy

TO THE EDITOR: Recently, omega-3 polyunsaturated fatty acid augmentation of antidepressant medications was demonstrated as providing significant benefit in a 4-week, parallel-group, double-blind study (1) and our 8-week study (unpublished data of K.-P. Su et al.).

Depression during pregnancy affects both the mother and the child. Most drugs pass from mother to baby through the placenta in different degrees. Medicating depressed pregnant patients is a clinical dilemma. Omega-3 polyunsaturated fatty acids, with a possible antidepressant effect (1) and a lack of teratogenicity for the fetus (2), seem to be a favorable treatment alternative. We report here what is to our knowledge the first case of successful treatment with omega-3 polyunsaturated fatty acid monotherapy of a pregnant patient with major depressive disorder.

Ms. A was a 34-year-old married woman who came to our psychiatric service for a recurrent depressive episode at the 24th week of pregnancy. She had had a first major depressive episode 5 years earlier, when she was pregnant with her first baby. Ms. A did not receive any drugs, and the depressive episode remitted 9 months after childbirth. She had another two major depressive episodes between these two pregnancies, and she responded well to paroxetine, 20 mg/day.

When she came to our hospital, Ms. A refused antidepressant agents because of possible teratogenic effects and took only lorazepam, as needed, for insomnia. She did not have any history of substance abuse or any significant medical condition that might account for her depression. The results of laboratory tests (CBC and blood chemistry) were within normal limits.

Ms. A signed our informed consent form and began to take 4 g of ethyl eicosapentaenoic acid (EPA) and 2 g of docosahexanoic acid (DHA) per day, beginning in the 25th week of gestation. She was rated with the 21-item Hamilton Depression Rating Scale at every visit: weeks 0 (before EPA-DHA supplementation), 2, 4, 6, 10, and 18 (6 weeks after delivery).

Ms. A did not have any change in score between weeks 0 (Hamilton depression scale score=28) and 2 (score=29) but showed improvement in depressed mood, anhedonia, feelings of worthlessness, hopelessness, and guilt at week 4 (score=18) and experienced the disappearance of suicidal ideation at week 6 (score=10). After that, only initial insomnia and anxious feelings bothered Ms. A occasionally (week 10: score=6). She received paroxetine, 20 mg/day, after delivery, and her condition has remained stable (week 18: score=7). The baby was delivered and appeared normal in a general physical and neurobehavioral examination at birth.

We have previously reported on a pregnant woman with acute schizophrenia who showed improvement after omega-3 polyunsaturated fatty acid monotherapy (3). We believe that this case is the first report of a pregnant patient with major depressive disorder who was treated with omega-3 polyunsaturated fatty acid monotherapy. Since the patient received regular follow-up for 6 weeks before treatment with omega-3 polyunsaturated fatty acids, it is unlikely that the remarkable improvement was due to the clinical attention of regular visits. Because the patient had a depressive episode during her first pregnancy and after childbirth, we do not think that she had a spontaneous remission from this episode. Her improvement of depression was likely due to omega-3 polyunsaturated fatty acid treatment.

Reduced maternal DHA status after the second trimester (4) is associated with a high demand from the developing fetus for the rapid formation of its brain. Empirical studies of polyunsaturated fatty acids in the tissues (5), data from epidemiologic surveys (6), and results of therapeutic trials of polyunsaturated fatty acids (1) suggest that a deficit in omega-3 polyunsaturated fatty acids might cause major depressive disorder (7, 8). Supplementation with omega-3 polyunsaturated fatty acids is thought to have protective effects for pregnancy outcome in high-risk pregnancy (2). Because of its safety and psychotherapeutic effects, as well as its promotion of health for mothers and their infants, treatment with omega-3 polyunsaturated fatty acids is a promising approach for pregnant patients with major depressive disorder.

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Electrolyte-Balanced Sports Drink for Polydipsia-Hyponatremia in Schizophrenia

TO THE EDITOR: It is estimated that 10%–25% of patients with chronic schizophrenia develop polydipsia (1–4). One-third become hyponatremic. Seizures, coma, and death may occur when sodium levels fall below 120 mmol/liter (1). It is unclear why these patients develop polydipsia; one possibility is that enlargement of the ventricles impairs their baroreceptors.

Mr. A, a 56-year-old single white man with a 40-year history of chronic schizophrenia, was being treated with standard and atypical neuroleptics. He lived with his elderly mother. He had had two life-threatening episodes of hyponatremia-induced coma and was incapable of stopping his polydipsia. Mr. A was encouraged to drink only an electrolyte-balanced sports drink and also to take one salt pill with each meal.

Urinary frequency and enuresis were first noted. Later, seizures and a coma resulted in hospitalization, and a diagnosis of hyponatremia and rhabdomyolysis was made. His electrolyte level was stabilized, and he was then transferred to a psychiatric hospital. Other causes of hyponatremia, including the syndrome of inappropriate antidiuretic hormone secretion, renal disease, and Addison's disease, were ruled out. A computerized tomography scan suggested a stroke involving the caudate nucleus and generalized cerebral atrophy. Mr. A's sodium level fluctuated from 137 to 142 mmol/liter. He was discharged taking clozapine, olanzapine, and sertraline.

Recurrence of seizures resulted in rehospitalization. During Mr. A's second hospitalization, his serum sodium level fluctuated from 127 to 147 mmol/liter (four measurements were between 127 and 129 mmol/liter). Hospital treatment included behavior therapy, propranolol, fluoxetine, and olanzapine, but none of these benefited him (2).

One month after discharge, Mr. A's sodium levels were still below normal (127 mmol/liter) and appeared to be life threatening. He did not understand the importance of limiting fluid intake. His elderly mother was unable to monitor his drinking. Mr. A's fluid intake was limited to an electrolyte-balanced sports drink. He took one 19-mg salt pill with each meal. In the past year, his sodium levels have been normal, there have been no seizures, and his mental status has improved.

At the time this treatment was initiated, hyponatremia, coma, and death appeared possible. Use of previously recommended behavioral and pharmacological treatments were unsuccessful (1–4). While water restriction of a delusional polydipsic patient outside a hospital may not be feasible, an electrolyte-balanced solution may be lifesaving. This anecdotal observation requires replication. Of note is that this patient's mental status improved, as evidenced by enhanced orientation, with stabilized sodium levels.

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Biperiden for Excessive Sweating From Methadone

TO THE EDITOR: Methadone maintenance treatment is the most common pharmacological intervention for opioid dependence. In clinical trials (1, 2), about 45% of the patients in established methadone maintenance treatment suffered from excessive sweating.

Biperiden is an anticholinergic drug that is well known from clinical use in parkinsonism and schizophrenia. We present what we believe are the first reported cases of methadone-induced excessive sweating that were successfully treated with biperiden. During the observation period, all three patients had no additional medication, and none of them reported adverse effects such as sedation, dizziness, dryness of the mouth, or blurred vision.

Mr. A was a 30-year-old computer technician who had suffered from excessive sweating since adolescence. He tested different treatments, including Salvia tea, benzodiazepines, carvedilol, and atropine drops, but none of them worked. After entering methadone maintenance treatment (current dose: 50 mg/day), he suffered intolerable sweating, especially at business meetings. After he received biperiden during a psychiatric emergency to antagonize the extrapyramidal side effects of a typical antipsychotic, he noticed a cessation of sweating for several hours. With a dose of 2–4 mg/day of biperiden 3–4 days per week, we could reproduce and maintain this positive effect.

Mr. B was a 43-year-old electrician who had started methadone maintenance treatment 3 years earlier. He had never had a problem with sweating, but from the first day of taking methadone and independently of the dose (20–90 mg/day, currently 40 mg/day), he had to change his wet clothes numerous times a day and suffered from negative reactions at his workplace. Treatment with biperiden resulted in a prompt and stable cessation of the generalized sweating (current dose: 2 mg/day).

Mr. C was a 37-year-old man who had been taking methadone for 6 years (current dose: 18 mg/day). He had had a problem with sweating previously, but with methadone, it became much worse: "In the summer I felt like a hydrant. It was really crazy." Seeking help, he tried several remedies without any success. Finally, biperiden (a 4-mg controlled-release tablet every morning) resulted in an effective control of the symptom.

Little is known about the exact mechanisms by which methadone influences autonomic thermoregulatory control and produces increased sudomotor activity. However, the mainly centrally acting antimuscarinic agent biperiden appears to antagonize this overactivation very efficiently.

Recovery from opioid addiction can be a long-term process and requires prolonged periods of methadone maintenance treatment. Excessive sweating due to methadone may be so disturbing in the long run that the question arises if this is an important and yet underestimated reason for premature dropouts and treatment failures. Patients with a high level of psychosocial functioning seem to suffer from it especially. We think that the treatment of this important side effect needs more concern and that biperiden in a dose of 2–4 mg/day could be a significant contribution toward overcoming this treatment complication.

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Real-Life Research

TO THE EDITOR: We commend Ann A. Hohmann, Ph.D., M.P.H., and M. Katherine Shear, M.D. (1), on their attention to important issues in translating efficacy research to real-life research in the community. We are completing a trial of community-based support-education groups for single mothers (2), a population facing high poverty rates and an elevated risk of mental health problems, particularly depression. We considered similar issues before our trial. For example, we undertook feasibility work to determine appropriate identification and enlistment of study participants, adequate retention in groups, and acceptability and completion of evaluations. We contemplated the generalizability of the study setting, the similarity of the participants to those most in need, and the relevance of the outcome goals to the participants.

We wish to emphasize four specific issues arising from our trial. First, despite strong expressed community support for our trial, study recruitment is difficult. Readiness to change (3) and engage in treatment activities appears to be much lower in the community than in clinical settings, where mothers have been mobilized to ask for help with specific problems. Clinic participants anticipate assessment questionnaires, but community participants do not have the same expectations and may be less ready to complete questionnaires. It is not clear if we attract those *most* in need (most depressed? poorest?), but we attract mothers with expected sociodemographic and mental health characteristics who are ready to engage in the treatment process.

Second, we want to highlight the importance of the first contact with potential study participants. The person charged with engaging potential subjects must be able to describe the study in a clear, comprehensible manner and be inviting and encouraging. In our study, this person plays a critical role in reminding participants about group sessions and booking evaluations and has turned out to be a key person in both recruitment and maintenance.

Third, putting in place a standard outcome protocol is essential, but an openness to recognizing other relevant outcomes during the trial is important. We examine maternal well-being (mood, social support, self-esteem) and parenting—important outcomes to participants and those working with these mothers and their children. Preliminary qualitative results suggest that participating mothers may use the group as a stepping stone to other mainstream activities and services after participation. This was not identified as a relevant outcome at the outset but possibly constitutes one that is more important.

Fourth, the authors suggested that investigators undertaking community-based trials consider what is needed before continuing an intervention after the study if it is successful. This may be difficult to do in advance, since community research may provide model programs not easily replicated because of personnel or costs. Creating opportunities for academic-community partnerships may upgrade the relevance of academic studies and the scientific usefulness of community-based studies.

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Dr. Shear Replies

TO THE EDITOR: We thank Drs. Lipman and Boyle for their interesting comments on our article. This work does indeed sound like exactly the kind of study we were trying to outline. The observations about difficulties recruiting people and drawing attention to the importance of the first contact will be very useful for others embarking on community studies. The admonition that an intervention may have unpredicted effects is also very well taken. We disagree about the final point, however. We argue instead that one of the purposes of research in community settings is to calibrate the intervention to the realistic possibility of its poststudy implementation. To use an exaggerated metaphor, if a poor community is having transportation problems and a researcher wishing to solve the problem brings in a fleet of limousines to demonstrate that the problem can be solved, this is a study hardly worth doing. Limousines are not likely ever to be available in this community. Documentation that if they exist, people will ride in them is not helpful.

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Change in Brain Function With Placebo

TO THE EDITOR: I read the intriguing report by Andrew F. Leuchter et al., M.D. (1), of a comparison of brain quantitative electroencephalography (QEEG) in depressed subjects who received placebo and in those who received an antidepressant (fluoxetine or venlafaxine). For unknown reasons, the authors described the collection of QEEG measures at the end of the 1-week placebo lead-in period (1 week after baseline) but neglected to report these data.

According to the Hamilton Depression Rating Scale scores given in the article, much of the clinical improvement occurred early (by 1 week after baseline). If this is true, then QEEG data collected temporally closest to that transition could be the most informative. The most informative data from this study should not be left out of this article.

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Hagiographic Treatment of C.G. Jung

TO THE EDITOR: While it is understandable that space limitations prevented Sam C. Naifeh, M.D., from providing greater detail on C.G. Jung (1), the biographic information provided was so one-sided that it verged on the hagiographic. While Jung undoubtedly was a pioneer at a time when organic psychiatry was on hiatus, most of his ideas have not stood the test of time, and it is difficult to believe that psychiatry today owes any significant debt to his contribution.

All of his life Jung was obsessed with the idea of a collective unconscious, stemming from the notorious (and discredited) solar phallus dream (2). This spilled over into racial theories, and his more-than-tacit support for Nazi psychiatry was conveniently forgotten or blurred over after World War II (3). He wrote indiscriminately or wildly about a range of paranormal phenomena—such as astrology, alchemy, and telekinesis—without any attempt to challenge their irrational basis.

Furthermore, in his relationships with colleagues and patients, Jung's behavior was often unethical. After his split with Freud, his anti-Semitic utterances increased considerably. He had few qualms about sleeping with patients (to gauge the extent of Jung's malevolence, readers need only learn of his well-documented affair with the tragic Sabina Spielrein; see reference 4) and, furthermore, inflicted his lovers on his long-suffering wife and family.

All leaders or pioneers have their feet of clay, but the extent to which Jung's followers eulogize their hero is unacceptable. No less an authority than Henri Ellenberger used the fiction of a creative neurosis to explain away a psychotic illness (5).

Psychiatry needs more history, tinctured with respect for the difficulties of an earlier time when there were fewer certainties. However, ignoring Jung's appalling behavior, bizarre ideas, and extreme irrationalism does not provide a balanced picture or do the situation justice.

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Diabetes and Atypical Neuroleptics

TO THE EDITOR: In their survey of diabetes mellitus in patients receiving neuroleptics, Michael J. Sernyak, M.D., et al. (1) reported that the prevalence was 9% higher in those treated with atypical neuroleptics than in those treated with typical neuroleptics. Dr. Sernyak et al. acknowledged some of the limitations of their study, including the fact that it was retrospective, there was no attempt to determine diabetes status at baseline, and the screening period was only 4 months long. They acknowledged that this narrow time frame yielded a virtual cross-sectional group, precluding determination of the temporal relationship between neuroleptics and the development of diabetes mellitus—a basic requirement when assessing causality. Thus, they showed an association between atypical neuroleptic treatment and diabetes, but they did not establish causality.

Some other limitations are worth noting. No matched comparison subjects were used in this retrospective study. A history of alcoholism was significantly more common in the atypical neuroleptic group than in the typical neuroleptic group, and alcohol-induced pancreatitis may have accounted for at least part of the higher prevalence of diabetes in the former group.

Finally, the numbers of patients taking each agent varied widely, making statistical analyses difficult. For example, the percentage of patients taking quetiapine was so small that the odds ratio for diabetes in this group was higher than normal in the 40–49-year age range but lower than normal in the 60–69-year age range—a finding that is the opposite of what one would expect to see clinically (2).

The possibility that patients taking neuroleptics may develop diabetes is a valid question, but because of design limitations, the current study did not yield any answers regarding causality.

The authors are employees of AstraZeneca Pharmaceuticals.

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TO THE EDITOR: Dr. Sernyak et al. compared the presence of diabetes mellitus among schizophrenia patients within the Department of Veterans Affairs system who were treated with atypical neuroleptics (clozapine, risperidone, olanzapine, and quetiapine) and those who were treated with typical neuroleptics. Diagnostic data covered the period October 1998 through September 1999, and prescription data covered the 4-month period from June through September 1999. Associations between diabetes mellitus and neuroleptic treatment were made within this 4-month period, with index neuroleptics being essentially identified on the basis of the last neuroleptic prescription written during the period. While the study controlled for several confounding factors, limitations in design may have undermined the validity of its findings.

Patients were not screened for preexisting diabetes mellitus, although it appears that this could have been done with available data. Identification and exclusion of preexisting cases would have avoided the possibility of assigning to specific neuroleptics cases of diabetes mellitus due to previous

causes, including prior neuroleptic use. There is reason to believe that the likelihood of preexistence was not the same for all neuroleptics. For example, in a study on this subject by me and my colleagues (unpublished study by F.D. Gianfrancesco et al.), we found that 76% of the diabetes mellitus observed during treatment with quetiapine already existed within the 4 months before treatment, versus 70% for risperidone, 67% for olanzapine, and 71% for typical neuroleptics. Also, in 49% of the quetiapine-treated patients, treatment with quetiapine was immediately preceded by treatment with another neuroleptic, often olanzapine, whereas treatments with risperidone, olanzapine, and typical neuroleptics were immediately preceded by treatment with other neuroleptics in only 16%, 18%, and 13% of patients, respectively.

Exclusive use of ICD-9-CM codes to identify diabetes mellitus cases could have further affected results, especially given that preexisting diabetes mellitus cases were not removed from study. The presence of diabetes mellitus in a patient is more definitely determined if there is treatment, as evidenced by prescriptions for antidiabetics or insulin. An ICD-9-CM code for diabetes mellitus does not necessarily mean that a patient has tested positive or tested sufficiently positive to warrant more than monitoring. In some instances, ICD-9-CM codes for diabetes mellitus may have reflected follow-up examinations for patients whose diabetes mellitus had already disappeared because of a change in neuroleptics, for example.

Last, the study did not control for differences in treatment duration among the neuroleptic categories, which may have further biased its findings. It is reasonable to assume that the likelihood of acquiring diabetes mellitus from a neuroleptic treatment increases with exposure to that neuroleptic. Treatments with index neuroleptics could have started at any time before or during the 4-month study period. Neuroleptics with longer treatment durations may have been disadvantaged by the study design.

In summary, a more careful study would have controlled for preexisting diabetes mellitus and for differences in neuroleptic exposure and would have used more definite indicators of this condition, such as prescriptions for antidiabetic medications and insulin.

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Dr. Sernyak and Colleagues Reply

TO THE EDITOR: We welcome the opportunity to respond to the questions raised by Drs. Geller, MacFadden, and Gianfrancesco about our recent article reporting an association between prescription of atypical neuroleptics and diagnosis of diabetes mellitus in a group of nearly 40,000 patients. Although data on matched comparison subjects were not obtained, a multivariate adjustment procedure was employed. This statistical procedure is more appropriate in situations in which multiple agents are compared.

While the number of patients did vary from group to group, we do not think that this invalidates our analysis. To take the example offered by Drs. Geller and MacFadden, we suggest that, given the small numbers of patients receiving quetiapine (probably because of the short amount of time that quetiapine had been available at the time of the study), our findings of an association of the diagnosis of diabetes mellitus with quetiapine appear all the more striking. Indeed, the larger problem in studies of this kind is that a large number of patients increases the probability of finding statistically significant findings that are not clinically significant.

We agree with Drs. Geller and MacFadden that observational nonexperimental designs do not support causal conclusions, although their strength is that they allow evaluation of the outcomes of large numbers of patients treated under real-world conditions. However, we point out that a recent study designed to investigate just this causal connection between atypical neuroleptics and diabetes mellitus (1) produced findings consistent with many of ours.

Dr. Gianfrancesco reiterates several limitations that we stated in our article. Still, although we know very little about Dr. Gianfrancesco's data, they do appear to validate our supposition that some neuroleptics were much more likely to be switched to after the development of diabetes. However, the reliable determination of preexisting diabetes was beyond our capability at the time. Our group is working on another data set in an attempt to address this necessary compromise. The suggestion of controlling for treatment duration is also well taken. However, it seems that this would tend to bias the results in favor of the newest available antipsychotic—at the time, quetiapine—having the lowest odds ratio for the diagnosis of diabetes mellitus, which did not appear to occur.

While changing the case definition of diabetes would certainly change the number of patients so classified, how this would introduce biases against any particular antipsychotics is not clear, and, in fact, an analysis of prescriptions for hypoglycemic agents yielded substantially the same results as reported in the article.

The authors of both letters raise legitimate concerns about some of the limitations of our study that should, of course, be noted. However, we do not believe that these either represent a lack of care or substantively challenge the conclusions reached in our article.

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Brain Changes and Placebo

TO THE EDITOR: Helen S. Mayberg, M.D., et al. (1) observed that the patients in their study whose depression relented after treatment with either fluoxetine or placebo had nearly identical positron emission tomography (PET) brain scans. They concluded that the "facilitation of specific adaptive reciprocal limbic-cortical changes is necessary for depression remission, regardless of the mode of treatment" (p. 734).

Why "necessary"? This study shows only an association between the remission of depressive symptoms and regional changes in brain glucose metabolism, which represent changes in blood perfusion at these sites. No one knows why

brain tissue perfusion is different in depressed patients, if this difference causes depression, or if it is an epiphenomenon. There is an association here without a known meaning.

Dr. Mayberg et al. spoke as if they understand the connection between a depressed mind and a "depressed" brain. Implicitly, they claimed to have closed the infamous and confounding mind-brain gap. The fact is, we do not know how brain neural structure or function affects the workings of consciousness—in this case, mood. Our efforts to make this connection are still at the level of metaphor (written text) and virtual reality (colors on a monitor indicating signal intensity from a scanner). Nonetheless, Dr. Mayberg et al. posited the primacy of brain over mind.

It seems just as reasonable to propose that, as depressed individuals pathologically reconstruct key "self-structures" after experiencing a negative life event, this transformation drives a change in brain neural function that occurs at least partly through the well-studied hypothalamic-pituitary-adrenal axis.

The question then becomes, does a psychoneural synergy connect an individual's construction of his or her world with brain centers involved in mood modulation, and do these functional changes act as "ballast" to perpetuate depression? For severely depressed patients, perhaps changes in brain function do contribute to maintaining the depression; in mild to moderate depression, maybe not (which means the transformed "self-structure" here is the depression).

The "decade of the brain" crowned the belief that natural science offers the best approach to understanding human behavior. But how valid is the "hard" science that purports to close the mind-brain gap? In a recent issue of the *Journal*, Leuchter et al. (2), using quantitative electroencephalography (QEEG), found—contrary to the study by Dr. Mayberg et al.—that "placebo treatment induces changes in brain function that are distinct from those associated with antidepressant medication" (p. 122). As happens often in biological psychiatry, two studies purporting to measure the same phenomenon came to opposite conclusions. The authors of the QEEG article did, however, acknowledge that "these data do not prove a causal link between brain functional changes and the therapeutic effect of either medication or placebo" (p. 128).

Many of the natural science data on brain structure and function travel poorly across the mind-brain gap, as these data are used to explain the workings of consciousness.

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Dr. Mayberg and Colleagues Reply

TO THE EDITOR: We are pleased for this opportunity to respond to Dr. Muller. First, we want to clarify any perception that we identified causative relationships between brain changes and antidepressant response; we did not. We described an association between specific brain change patterns and a change in mood state in depressed patients that is common to treatment with either placebo or active medication. It is unfortunate that our concluding hypothesis, not only based on the findings of the study but considered in the context of other published studies examining pharmacological, cognitive, and somatic treatments, should lead to a critique that negates the value of imaging altogether in the study of major depression. Dr. Muller's comments suggest an underlying bias not consistent with the wealth of available scientific evidence.

While the cause of depression at the molecular and cellular levels remains unknown, we have learned much by studying brain changes induced by antidepressants. Monoamine reuptake inhibition, pre- and postsynaptic receptor regulation, transcription, and trophic changes are all described, and some of these can be assayed with functional neuroimaging (1). Similarly, net excitation and inhibition of specific neural pathways have been explored by using pharmacological probes and electrophysiological techniques, providing potential mechanisms for interpreting functional imaging findings identified by using PET as well as functional magnetic resonance imaging (2, 3). These basic scientific advances are of direct relevance to depression research and are likely to affect new treatment development.

Dr. Muller's characterization of functional brain imaging as "virtual reality," particularly his inaccurate description of the techniques used, reveals a lack of understanding of the physiological principles underlying this and other neuroimaging techniques. This explains his additional comments regarding QEEG and his incredulity that there might be differences between two distinct imaging studies of placebo response. That two different methods have identified measurable brain changes at all should be cause for celebration. To understand these differences requires direct comparison of the two methods in the same patients.

We are concerned with Dr. Muller's remark that we believe we have somehow closed the mind-brain gap. In regard to his statement that we somehow posit the primacy of the brain over the mind, we emphasize that our study was designed with the assumption that mind and brain are inseparable. While complicated, careful hypothesis-driven experiments can address aspects of complex behavior typified by a disorder like depression.

Finally, Dr. Muller's contention that much of natural science travels poorly along the mind-brain gap and his not-so-subtle message that it might be better not traveled at all is disturbing. To reduce the study of a clinical disorder to a philosophical construct broadly captured by the catch phrase "the mind-brain problem" or "consciousness" is not only to miss an important opportunity for potential scientific advance but also to reveal a bias that only undermines ongoing efforts to enhance communication between the neuroscience and psychotherapy communities that is necessary to ensure the best possible care of patients with depression and other psychiatric disorders. We look forward to future experiments in which areas of overlap between these complementary disciplines are explicitly examined (4).

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Misdiagnosis of Conversion Disorder

TO THE EDITOR: H. Brent Solvason, Ph.D., M.D., et al. (1) described a woman seen with leg weakness and back pain who was initially diagnosed as suffering from conversion disorder and subsequently turned out to have sporadic Creutzfeldt-Jakob disease. The authors usefully highlighted how organic disease may be important in generating symptoms that are medically unexplained, either directly by effects on brain function or because of more complex behavioral responses to illness. They also showed how our current somatoform classification leaves little room for a dual diagnosis of organic and functional disorder. This unsatisfactory either/or philosophy is perhaps one reason why doctors are reluctant to diagnose conversion disorder in the first place.

There is another important reason why doctors are reluctant to diagnose conversion disorder—the common belief that such patients have a high likelihood of developing neurological disease in the long term. This view has principally arisen from a widely cited but flawed 1965 article (2) that suggested that up to 61% of patients diagnosed with hysteria will eventually develop neurological disease. However, in the last decade, a number of studies have shown that for patients who have seen a neurologist, the rate of misdiagnosis at follow-up is actually between 5% and 10% (3–6). This is a level comparable with those for other neurological and psychiatric disorders.

An additional issue is whether Creutzfeldt-Jakob disease could have been diagnosed during the patient's lifetime in this case. Recent advances have aided the detection of sporadic Creutzfeldt-Jakob disease. CSF 14-3-3 protein has a sensitivity of 94% and specificity of 84% (better than a periodic EEG) (7), and T_2-weighted magnetic resonance imaging (MRI) shows a bilateral basal ganglia high signal in about two-thirds of patients but only 7% of appropriate comparison subjects (8). Such MRI abnormalities are usually not mentioned in radiology reports and need to be specifically excluded (8). Given the clinical suspicion of Creutzfeldt-Jakob disease in this patient, these tests may have helped to make a diagnosis during her lifetime.

Clinical vigilance for a missed diagnosis of neurological disease in cases of conversion disorder is essential. It would be a shame, however, if this case conference reinforced the erroneous idea that the development of neurological disease in such cases is the norm. Failure to make a positive diagnosis of conversion disorder can have serious adverse consequences. The patient may be denied appropriate treatment management that vitally depends on persuading him or her that the symptoms are reversible and not due to disease. We should not withhold the diagnosis simply because we occasionally get it wrong.

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Dr. Hayward and Colleagues Reply

TO THE EDITOR: Dr. Stone and colleagues make an excellent point: there can be a reluctance among psychiatrists to make the diagnosis of conversion disorder for fear the patient will develop a neurological disease that better explains the presentation of the illness. Dr. Stone and colleagues express concern that the case conference might reinforce an idea that development of a neurological disease in patients with a presentation most consistent with conversion initially is a common occurrence.

The case presentation was directed toward demonstrating how difficult it can be to establish a diagnosis of a neurological disease before there is a signature sign and how illness-related behavior, and interpretations of secondary gain, may sadly confound the clinician. It is helpful that a CSF assay for the 14-3-3 protein is now available, making a diagnosis of Creutzfeld-Jacob disease more straightforward in patients with otherwise ambiguous symptoms. In the case presented, there were no T_2-weighted hyperintensities in the basal ganglia or elsewhere on the MRI of the patient's head. Furthermore, at that time, diffusion-weighted scans were not available, although they appear to be a relatively sensitive marker for Creutzfeld-Jacob disease (1). Fortunately, other individuals with conversion disorder whom we have seen on our unit had an illness that was far clearer in presentation and responded to treatment.

It was not our intention to generalize the experience with this case conference in a way that would prevent a reasonable diagnosis of conversion in a patient with medically unexplained symptoms. However, a cautionary note is inherent in the history of the case we presented. It is expected that any diagnosis made on the basis of an apparent exclusion of other causes, as is the case with conversion disorder, be held with some degree of suspended disbelief. Clinical vigilance, as we noted, is essential.

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Symptom Factors and Clinical Subtypes in Mania

TO THE EDITOR: The report by Tetsuya Sato, M.D., Ph.D., and colleagues (1) is a welcome addition to our understanding of symptom factors and clinical subtypes in mania. As they noted, their findings have substantial overlap with our own (2).

The two analyses are consistent in key respects. Neither found a factor denoting general severity of illness. Both found a depression factor that was preeminent in the purely manic subjects as well as in those with diagnoses of mixed manic episodes. Both found that sleep disturbance did not load with any of the classical or nonclassical symptom factors in mania. It appears that insomnia in mania is not simply a correlate of psychomotor activation. Both found that the DSM-III-R/DSM-IV criteria substantially undercount the number of manic patients with depressive syndromes who were identified by the multivariate analyses, emphasizing the need for new, data-derived criteria for mixed bipolar episodes.

The individual factors are in broad agreement for depressed mood, psychosis, and irritable aggression. The studies diverge on whether the depressive symptom factor is bimodally distributed, which we found it to be. The factor termed "mania" in the study by Dr. Sato et al. was represented in our study as two factors—hedonic activation and psychomotor acceleration—reflecting our inclusion of additional hedonic symptoms such as sexuality and humor. Likewise, Dr. Sato et al. found a new symptom factor, depressive inhibition, based on symptoms that we did not evaluate.

In the cluster analysis by Dr. Sato et al. (1), the largest subgroup, pure mania, appeared as a residual group, with no positive loadings for any identified factor—not even factor 5, mania (Table 2). The factor scores have extremely large standard deviations, denoting a wide overlap of scores among the identified clusters and calling into question the interpretation of Dr. Sato et al. that "depressive mood, irritable aggression, and psychosis…are unlikely to coexist" (p. 972). Moreover, although they found that depressed mood and depressive inhibition are independent symptom factors, their cluster analysis did not distinguish patients with these two characteristics. Thus, their cluster analysis does not positively support Kraepelin's subclassification of mixed states.

In a report published after the article by Dr. Sato et al. was submitted, we described five subtypes of mania identified by grade-of-membership analysis (3). Type 1 is a nonpsychotic, relatively mild form of mania that corresponds to Kraepelin's "hypomania" and to subgroup 1 in the current report. Type 2 is a severe form of classical mania, with high levels of psychomotor activity, irritability, and psychosis, which corresponds to Kraepelin's "acute mania." Type 3 is a very delusional form of mania with relatively less severe classical manic symptoms that corresponds to Kraepelin's delusional mania and perhaps to subgroup 3 in the report by Dr. Sato et al. Type 4 is a severe form of mania with high levels of dysphoric symptoms and the complete absence of grandiosity or euphoria that corresponds to Kraepelin's anxious or depressive mania. Type 5 is an overall less severe form of dysphoric mania than type 4, with moderate degrees of depressive mood symptoms alternating or coexisting with grandiosity, humor, sexuality, and psychomotor acceleration. In the study by Dr. Sato et al., subgroup 4 seems to comprise patients similar to types 4 and 5 in our grade-of-membership analysis. Again, the similarities between the analysis by Dr. Sato et al. and our analysis are more impressive than any differences. Both groups agree that clinical care and research studies of manic patients may benefit from serious attention to the "rediscovered" heterogeneity of clinical subtypes.

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Dr. Sato and Colleagues Reply

TO THE EDITOR: After we submitted our article, two other research groups, using multivariate analyses, reported on manic subtypes (1, 2; Cassidy et al., 2001). Surprisingly, all reports, including ours, proposed almost the same subtypings. Similarities and minor differences between the Duke study (Cassidy et al., 2001) and ours are summarized by Drs. Cassidy and Carroll. Their letter calls into question our conclusion that atypical manic features, such as aggression, psychosis, and depression, are likely to separately characterize several manic subtypes since "the factor scores have extremely large standard deviations, denoting a wide overlap of scores among the identified clusters." It should be noted, however, that standardized factor scores were used in our study. The mean factor score and its standard deviation were set at 0.0 and 1.0, respectively. As shown in Table 2 of our article, it is not true that the factor scores reported "have extremely large standard deviations." Our factors, called depressive mood and psycho-

motor/thought inhibition, have relatively large standard deviations in our mixed subtype. This reflects a large variance of these syndromes within this subgroup, suggesting the possibility that this subtype consists of several lower-order subgroups. It would be interesting to determine whether these lower-order subtypes are similar to the two mixed subtypes proposed by Dr. Cassidy et al. and whether the depressive inhibition factor identified in our study plays a role in describing these lower-order subtypes. Until these issues are clarified, it is too early to state that our "cluster analysis does not positively support Kraepelin's subclassification of mixed states."

Swann and colleagues (1, 2) proposed four manic subtypes that more strikingly resemble our subtypes. Their depressive, delusional, classical, and irritable subtypes appear exactly to correspond to our mixed, psychotic, pure, and aggressive subtypes, respectively. While the aggressive factor characterized several manic subtypes in the study by Dr. Cassidy et al., that factor was reported in the study by Swann et al. as only prominent in one subtype (irritable mania), as was found in our study. Furthermore, the report on their multicenter placebo-controlled trial implied that their four groups had differential treatment responses to placebo, divalproex, and lithium (2). This suggests that both their and our manic subtypes may be validated in terms of acute treatment response.

An agreement of results derived from cross-sectional phenomenological data is only the first step in identifying clinically meaningful manic subtypes, although this agreement was reached by three independent studies. Further studies are required to determine the differential long-term natural history of the proposed manic subtypes. Differential responses to available maintenance treatments should also be investigated.

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Physical Anomalies and Schizophrenia Spectrum Disorders

TO THE EDITOR: Jason Schiffman, M.A., et al. (1) concluded that "minor physical anomalies may provide important clues to understanding schizophrenia spectrum disorders from a neurodevelopmental perspective" (p. 238). Minor physical anomalies certainly help clarify neurodevelopmental influences in the etiology of schizophrenia, but they may well raise more questions than they answer about the schizophrenia spectrum.

It is known that the prevalence of minor physical anomalies is higher than average in schizophrenia itself (2), and Dr. Schiffman et al. have now demonstrated higher scores for minor physical anomalies in subjects with paranoid and schizotypal personality disorders (1). There is also evidence that minor physical anomalies are greater in people without frank psychotic illness but who experience quasi-psychotic phenomena, such as quasi-delusional beliefs and psychosis proneness (3). Of interest, however, psychosis proneness is associated with smaller skull bases and longer, lower facial heights—features opposite those found in schizophrenia (3).

Furthermore, while high-risk genetic inheritance may (4) or may not (5) correlate with higher levels of minor physical anomalies in high-risk persons who develop schizophrenia, there is no correlation between high-risk genetic inheritance and minor physical anomalies in high-risk persons overall (6, 7). Even when unaffected siblings of persons with schizophrenia are found to have significant minor physical anomalies, these anomalies are quite different from those found in subjects with schizophrenia (8).

Combining these findings, we can conclude that minor physical anomalies in people with schizophrenia 1) are more numerous than those of comparison subjects, 2) are more numerous than, and are different from, those in unaffected people with high-risk genetic inheritance (e.g., offspring, siblings), and 3) are different from those in people with certain quasi-psychotic phenomena.

Thus, while a variety of psychotic and quasi-psychotic conditions may indeed belong on a clinical schizophrenia spectrum, they may well have arrived there by significantly different routes.

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Dr. Schiffman and Colleagues Reply

TO THE EDITOR: Dr. Kelly's letter makes an interesting point that we did not address in our article. There is a gradient of disorders related to schizophrenia (e.g., schizotypal personality disorder, quasi-psychotic conditions); each of these related disorders may, in part, have its origins in errors of fetal development. Each error of fetal development may be signaled by a specific set of minor physical anomalies. To a significant degree, the nature of the specific minor physical anomaly observed may be determined by the timing of disturbances during the process of gestation. This same timing of developmental disturbance may also help determine the nature of the neural developmental deficit and the associated behavioral disorder. Note that these conditions tend to result in the set of findings summarized by Dr. Kelly.

We have presented evidence (1) that a maternal influenza infection in the second trimester of gestation increases the risk of adult schizophrenia in affected offspring. More recently, we examined this same relationship in a large cohort of military recruits in Finland (2). The large size of the cohort enabled us to study exposure during a narrow window of gestation. We reported that maternal influenza in the 23rd week of gestation increased the risk for schizotypal personality disorder (assessed by the Minnesota Multiphasic Personality Inventory). In an article in preparation for publication, we report a higher risk for schizotypal personality disorder among young adults in Tangshan, China, who had been exposed to a severe earthquake (7.8 on the Richter scale) during their 23rd week of gestation (unpublished study by Machon et al.).

Perhaps the specific narrow window of development that is disturbed helps to determine the nature of the neural deficit and the consequent behavioral pathology, as well as the superficial minor physical anomaly indicants we observe.

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Affective Instability in Personality Disorders

TO THE EDITOR: In a recent issue, Harold W. Koenigsberg, M.D., et al. (1) presented a study focused on understanding the nature of affective instability in patients with personality disorders. They hypothesized that patients with borderline personality disorder have greater mood instability than patients with other personality disorders. Further hypotheses were made regarding specific mood states. Mood variability was assessed with the Affective Lability Scale, a self-report instrument intended to measure mood swings from baseline to elevations in specific mood states. Patients with borderline personality disorder demonstrated significantly greater lability than the comparison group in terms of anger, anxiety, and oscillations between anxiety and depression after control for a group of covariates, including gender, age, past and current major depression, bipolar II disorder, and cyclothymia.

These positive findings notwithstanding, the Affective Lability Scale has not been well validated in psychiatric populations as a measure of affective variability. Dr. Koenigsberg et al. acknowledged the need to relate the Affective Lability Scale to contemporaneous ratings of affect. We recently examined the association between subscale scores on the Affective Lability Scale and the daily mood ratings of 21 psychiatric outpatients (eight men and 13 women; age: mean=37 years, SD=11) enrolled in a psychosocial/psychoeducational group intervention for individuals with recurrent suicidal behavior. Written informed consent was obtained from the participants. The participants completed the Affective Lability Scale upon entry into the study and then completed daily global mood ratings on a single-item visual analogue mood scale (2) once in the morning and once in the evening over a 2-week period.

Two measures were derived from the ratings on the visual analogue scale: an affective lability score derived by computing the successive-difference mean square, which measured the average change in consecutive ratings over the period of study, and an affective intensity score derived by computing mean ratings over the period of study, measured in a positive direction. The results indicated that all Affective Lability Scale subscale scores were not significantly associated with the derived measure of affective lability (with Pearson's correlations ranging from –0.16 to 0.07). However, the Affective Lability Scale subscale scores for depression ($r=-0.56$, $p<0.05$), elation ($r=-0.62$, $p<0.01$), anxiety/depression ($r=-0.68$, $p<0.01$), and depression/elation ($r=-0.71$, $p<0.001$) were all significantly associated with the derived measure of affective intensity. Moreover, the associations of Affective Lability Scale subscales with affective intensity were significantly stronger than the correlations with our measure of affective lability for elation ($z=-2.78$, $p<0.01$), anxiety/depression ($z=-3.15$, $p<0.01$), and depression/elation ($z=-3.62$, $p<0.001$), with nonsignificant findings for the Affective Lability Scale subscale scores for depression ($z=-1.82$, $p<0.10$) and anxiety ($z=-1.77$, $p<0.10$). These findings raise questions about the validity of considering scores on the Affective Lability Scale to be measures of affective variability, and the results demonstrate a possible conflation of Affective Lability Scale scores with affective intensity. We agree with Dr. Koenigsberg et al. that measures of affective instability with established psychometric properties need to be developed and given research priority if this psychopathologic feature is to be better understood.

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Dr. Koenigsberg and Colleagues Reply

TO THE EDITOR: Dr. Links and colleagues report on a study of the correlation of the Affective Lability Scale with a single-item visual analogue scale of affective experience. They note that in their group of 21 outpatients, scores on this single item did not correlate with scores on the scale in a manner that they consider consistent with the validity of the Affective Lability Scale. We appreciate their interest in our scale and share their interest in validation of the Affective Lability Scale in a range of suitable populations. Unfortunately, their study is methodologically weak in at least three areas and yields results that are not germane to our study. There are several major limitations to the study, as well as a number of more minor ones.

First, the Affective Lability Scale was designed to study populations with unstable affect. There are no data presented regarding the diagnoses of the small group of subjects reported on and no indication that they come from populations theoretically manifesting affective lability. Our study had 152 patients who were carefully diagnosed with a procedure that included two separate structured diagnostic interviews (the Structured Interview for the Diagnosis of Personality Disorders and the Schedule for Affective Disorders and Schizophrenia) of high reliability. Thus, we compared groups of patients with clear DSM-IV diagnoses of conditions with putative unstable affect (borderline personality disorder) to patients with other personality disorder diagnoses in which stable affect is expected. Thus, the patients of Dr. Link and colleagues are not demonstrated to be in any way similar to ours, and the lack of detail regarding their diagnoses, regardless of reliability, renders their comparison with our study group problematic.

Second, the authors used a single item to measure affective experience. They present no data to suggest that this item has suitable test-retest reliability in their group. Both the Affective Lability Scale and the Affect Intensity Measure, the two scales used in our study, have well-documented test-retest reliability (0.84 for the global Affective Lability Scale and 0.81 for the Affect Intensity Measure). With no evidence of test-retest reliability, the most parsimonious explanation of variance over time in scores in patients with stable symptoms is error variance. Error variance due to test-retest unreliability, by definition, cannot correlate with systematic variance associated with reliable scores. Thus, the lack of correlation between an index of error variance (affective lability) and reliable scores on the Affective Lability Scale is completely expected and cannot address the issue of the scale's validity.

Third, there are multiple dimensions of affect, including intensity, instability, and polarity. Our study examined correlations between intensity and instability across polarity of affective experience. Dr. Links and colleagues ignore this well-replicated factor structure and present a single index of affective experience collapsing across three known orthogonal dimensions. They provide no data regarding the convergent and discriminant validity of their index, giving no idea as to what the other correlates of this single-item scale would be. Thus, we have no idea what their scale is measuring.

In conclusion, Dr. Links and colleagues, who suggest that their data call into question the validity of the Affective Lability Scale, overinterpret their data. We stand by our results and welcome more methodologically relevant tests of the Affective Lability Scale and other measures of affective instability.

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