Letters to the Editor

Isoniazid-Induced Pellagra and the *N*-Acetyltransferase Gene Genotype

TO THE EDITOR: Pellagra is a disorder stemming from nicotinic acid deficiency and is still prevalent in certain parts of the world. It is characterized by mucous and cutaneous lesions as well as gastrointestinal symptoms. Significant neuropsychiatric conditions have been described in many patients with pellagra. The anti-tuberculosis agent isoniazid can induce pellagra. Isoniazid is metabolized by arylamine *N*-acetyltransferase, and individuals with a less active form of this enzyme do not break down isoniazid efficiently and are more susceptible to pellagra (1). We report a case of isoniazid-induced pellagra in an individual with the less active form of this enzyme.

Mr. A was a 63-year-old man who suffered from chronic glomerulonephritis with chronic renal failure for which he had been receiving conservative steroid therapy (a 30-mg dose of prednisolone daily) for 2 years. He was transferred to our psychiatric unit because of manic symptoms, including elevated and irritable mood and talkative and aggressive attitude. He had photosensitive dermatitis, with erosion in both hands and in the perioral region since 6 weeks before admission. He had been receiving a 400-mg dose of isoniazid daily for 2 years as a prophylaxis against pulmonary tuberculosis, which he had suffered 30 years earlier. His serum nicotinic acid concentration was 4.5 μg/ml. The isoniazid dose was discontinued, and daily administration of a 200-mg dose of nicotinic acid was begun. His skin lesions gradually improved and disappeared after 8 weeks. The manic symptoms subsided slowly after 3 months, and a slight psychomotor retardation developed and persisted for 2 months. After a second manic episode lasting 4 weeks, he fully recovered and was discharged.

To determine the *N*-acetyltransferase genotype, genomic DNA was extracted from whole blood. A polymerase chain reaction was performed to amplify the entire coding region of the gene, according to Cascorbi et al. (2). The polymerase chain reaction product was extracted and used as a template for sequencing by using a dye-terminator cycle-sequencing method.

Mr. A was homozygous for the allele having the 282C-to-T and 590G-to-A transitions. The *N*-acetyltransferase gene genotype is *6A/*6A, and the acetylation capacity should be slow (2).

In the present case, the *N*-acetyltransferase genotype might be a major risk factor for isoniazid-induced pellagra, considering that the frequency of the slow acetylating type is 8% in the Japanese population (3). The *N*-acetyltransferase genotyping test is simpler and easier to perform than the conventional phenotyping test. Therefore, in patients receiving isoniazid, the genotyping test may be helpful in preventing isoniazid-induced pellagra.

REFERENCES

1. Cohen LK, George W, Smith R: Isoniazid-induced acne and pellagra: occurrence in slow inactivators of isoniazid. Arch Dermatol 1974; 109:377–381
2. Cascorbi I, Drakoulis N, Brockmöller J, Maurer A, Sperling K, Roots I: Arylamine N-acetyltransferase (NAT2) mutations and their allelic linkage in unrelated Caucasian individuals: correlation with phenotypic activity. Am J Hum Genet 1995; 57: 581–592
3. Mashimo M, Suzuki T, Abe M, Deguchi T: Molecular genotyping of N-acetylation polymorphism to predict phenotype. Hum Genet 1992; 90:139–143

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Rapid Remission of OCD With Tramadol Hydrochloride

TO THE EDITOR: Obsessive-compulsive disorder (OCD) affects 1.9% to 3.3% of the general population in the United States (1). Specific selective serotonin reuptake inhibitors (SSRIs) are often effective in the treatment of OCD (1). However, these medications are slow to act, and many patients have an inadequate response. Opiates have been noted to be efficacious in treatment-refractory OCD (2–4). We describe using the analgesic tramadol in an attempt to provide rapid symptom remission in a previously untreated patient with OCD. Tramadol is an analgesic that binds to opioid receptors and inhibits the reuptake of norepinephrine and serotonin (5).

Ms. A was a 27-year-old white woman with a 10-year history of OCD. She presented approximately 5 weeks after giving birth to a healthy child. There was no history of tic disorder or OCD in her family. Because of the pain from a fourth-degree perineal tear requiring surgical repair, Ms. A was given a dose of the opiate oxycodone. She observed that her obsessions ceased entirely for several hours immediately following administration of the oxycodone. Following the birth of her child, Ms. A's symptoms worsened. For example, she developed time-consuming rituals around the preparation of her child's formula and spent hours smoothing out wrinkles in crib sheets to prevent her baby from succumbing to sudden infant death syndrome. She required constant reassurance from her spouse and other family members.

At the time of presentation, Ms. A had a Yale-Brown Obsessive Compulsive Scale (6) score of 26. Because of her previous response to opiates, a regimen of tramadol was initiated. Within 24 hours, she reported by telephone that her obsessions and compulsions had diminished significantly with the tramadol, 50 mg b.i.d. A week later, her Yale-Brown Obsessive Compulsive Scale score had dropped to 19. A dose of fluoxetine, 20 mg daily, was then added (after a discussion of possible serotonergic syndrome). Three weeks later, the fluoxetine dose was increased to 40 mg daily. During the first month of treat-

ment, Ms. A required up to 350 mg p.r.n. daily of tramadol in divided doses (50 mg–100 mg q.i.d.) to diminish her OCD symptoms; her doses of tramadol were increased by approximately 50 mg–100 mg increments weekly over the first 3 weeks because of her tolerance to the anti-obsessive effects. Side effects of tramadol consisted only of initial nausea and mild sedation. Six weeks after the initiation of the two medications, Ms. A found that she no longer required the as-needed doses of tramadol, and her Yale-Brown Obsessive Compulsive Scale score had dropped to 10.

The efficacy of SSRIs in the treatment of OCD has been well established. Tramadol may represent a useful initial treatment for patients with OCD because it has low abuse potential, low physical dependency, and mild tolerance (5), and it may provide rapid symptom reduction during SSRI titration. Controlled studies are required to demonstrate tramadol's effectiveness in the treatment of OCD.

REFERENCES

1. McElroy SL, Phillips KA, Keck PE Jr: Obsessive compulsive spectrum disorder. J Clin Psychiatry 1994; 55(Oct suppl):33–51
2. Warneke L: A possible new treatment approach to OCD. Can J Psychiatry 1997; 42:667–668
3. Shapira NA, McConville BJ, Pagnucco ML, Norman AB, Keck PE Jr: Novel use of tramadol hydrochloride in the treatment of Tourette's syndrome (letter). J Clin Psychiatry 1997; 58:174–175
4. Shapira NA, Keck PE Jr, Goldsmith TD, McConville BJ, Eis M, McElroy SL: An open-label pilot study of tramadol hydrochloride in treatment-refractory obsessive-compulsive disorder. Depress Anxiety 1997; 6:170–173
5. Lee CR, McTavish D, Sorkin EM: Tramadol. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. Drugs 1993; 46:331–340
6. Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, Heninger GR, Charney DS: The Yale-Brown Obsessive Compulsive Scale, I: development, use, and reliability. Arch Gen Psychiatry 1989; 46:1006–1011

TOBY D. GOLDSMITH, M.D.
NATHAN A. SHAPIRA, M.D., PH.D.
PAUL E. KECK, JR., M.D.
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Use of High-Dose Olanzapine in Refractory Psychosis

TO THE EDITOR: The recent introduction of olanzapine as an antipsychotic has enlarged the pharmacological armamentarium of clinicians. The literature on olanzapine concerns doses of 10 mg to 20 mg, and I am not aware of any literature on its efficacy above 30 mg. This letter reports two cases of refractory psychosis that responded to high levels of olanzapine.

Mr. A was a patient diagnosed with schizoaffective disorder starting in his teens. He had a mild stroke at age 37 and had some left-side residual weakness. He initially was on a regimen of fluphenazine hydrochloride, 15 mg b.i.d. orally, benztropine, 2 mg b.i.d. orally, and paroxetine hydrochloride, 50 mg in the morning. Because he had developed tardive dyskinesia, he was tapered off of the fluphenazine hydrochloride, taken off of the benztropine, and started on a regimen of propranolol hydrochloride, 10 mg b.i.d. orally, for tremors. A dose of risperidone was only partially effective up to 6 mg. Above that dose, the patient developed dystonias. A regimen of olanzapine was tried (gradually replacing risperidone), starting at 10 mg a week and increased gradually over several months to a dose of 50 mg. At this dose, his hallucinations and delusions disappeared. They reappeared when the dose was reduced to 40 mg. He had some dystonias at this dose but felt them preferable to hallucinations.

Mr. B was a patient in a locked psychiatric facility with a history of violence and psychosis. His diagnosis was schizoaffective disorder. Initially, he was on a regimen of fluphenazine hydrochloride, 20 mg q.i.d. orally, trihexyphenidyl, 5 mg q.i.d., and divalproex sodium, 250 b.i.d. orally. Mr. B had tardive dyskinesia and was floridly psychotic and aggressive. He had previously failed a trial of clozapine. His dose of divalproex sodium was increased to a therapeutic level (500 mg b.i.d. orally); the trihexyphenidyl and fluphenazine hydrochloride were phased out as a trial of risperidone (ultimately unsuccessful) was made. Doses of propranolol hydrochloride were added to try to reduce aggressive behavior, eventually reaching 20 mg in the morning, 10 mg in the evening, and 10 mg h.s. Risperidone was tapered off and olanzapine was gradually introduced and eventually increased to a dose of 50 mg. At this point, his violent behavior disappeared, and his hallucinations were reduced. (He said he could no longer hear Santa Claus but still had regular communication with God and the disciples.) More important, Mr. B began to have better concentration and could carry on appropriate conversations lasting 2 to 3 minutes. He did not have any side effects at this dose.

Laboratory monitoring of both patients did not indicate abnormal liver or kidney function. CBCs remained within normal levels. It is possible that in certain refractory psychotic patients olanzapine, at doses up to 50 mg, may have a positive therapeutic effect.

JAMES REICH, M.D., M.P.H.
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Fluoxetine for Clomipramine Withdrawal Symptoms

TO THE EDITOR: Selective serotonin reuptake inhibitor (SSRI) and clomipramine discontinuation may cause dizziness, paresthesia, lethargy, nausea, vivid dreams, insomnia, headache, movement-related symptoms, crying spells, anxiety, agitation, and irritability (1). Venlafaxine discontinuation can cause a similar syndrome (2). The case of a patient showing discontinuation symptoms after withdrawal of clomipramine, ameliorated by fluoxetine, is presented. A MEDLINE search did not locate similar reports.

Mr. A, a 42-year-old man with major depressive and panic disorders, was in remission for 1 year with clomipramine, 150 mg/day, and clonazepam, 2 mg/day. He discontinued the dose of clonazepam over 3 months without problems. Then clomipramine was gradually discontinued over 3 weeks (112.5 mg/day for 7 days, 75 mg/day for 7 days, 37.5 mg/day for 7 days, then stopped). On the day after his last dose, he had dizziness, nausea, depressed mood, anxiety, sweating, and vivid dreams. Seven days later, with the symptoms persisting, the dose of clomipramine was restarted at 75 mg/day. His symptoms disappeared in 1 day. Two weeks later, clomipramine was discontinued again (37.5 mg/day for 5 days, then stopped), but it was replaced by fluoxetine, 20 mg/day, started 1

week before. After clomipramine discontinuation, Mr. A had no problems. One week later, fluoxetine was discontinued (10 mg/day for 5 days, then stopped). No discontinuation symptoms appeared during the following weeks.

A sudden drop of synaptic serotonin levels may cause the discontinuation syndrome (3). Clomipramine's short half-life may be a risk factor (3). Tricyclic antidepressant discontinuation syndrome (related to cholinergic rebound) does not usually include dizziness, which is more typical of SSRIs (4). Other symptoms (nausea, vivid dreams, anxiety) may be related to clomipramine's anticholinergic effects (3). Fluoxetine, by increasing synaptic serotonin levels, may have prevented the reappearance of the clomipramine withdrawal symptoms. This argues against a cholinergic mechanism of the withdrawal syndrome. Fluoxetine's long active metabolite half-life may have prevented a new withdrawal syndrome from developing after fluoxetine discontinuation (3). Fluoxetine might be used to treat clomipramine discontinuation syndrome. It has been used during venlafaxine discontinuation (5).

REFERENCES

1. Schatzberg AF, Haddad P, Kaplan EM, Lejoyeux M, Rosenbaum JF, Young AH, Zajecka J: Serotonin reuptake inhibitor discontinuation syndrome: a hypothetical definition. J Clin Psychiatry 1997; 58(July suppl):5–10
2. Benazzi F: Venlafaxine withdrawal symptoms (letter). Can J Psychiatry 1996; 41:487
3. Schatzberg AF, Haddad P, Kaplan EM, Lejoyeux M, Rosenbaum JF, Young AH, Zajecka J: Possible biological mechanisms of the serotonin reuptake inhibitor discontinuation syndrome. J Clin Psychiatry 1997; 58(July suppl):23–27
4. Haddad P: Newer antidepressants and the discontinuation syndrome. J Clin Psychiatry 1997; 58(July suppl):17–22
5. Giakas WJ, Davis JM: Intractable withdrawal from venlafaxine treated with fluoxetine. Psychiatr Ann 1997; 27:85–92

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Chronic Psychotic Illness From Methamphetamine

TO THE EDITOR: In the past decade, methamphetamine abuse has been on the rise throughout the United States (1, 2). Although methamphetamine is generally taken orally or intravenously, crystal methamphetamine or "ice" is smoked. This manner of admission is highly addictive. It is odorless, difficult to detect, and less expensive and longer lasting than crack. Vaporized crystal methamphetamine, when inhaled, is rapidly absorbed through lung capillaries and has pharmacokinetics similar to intravenous amphetamines. With continued abuse, crystal methamphetamine usually leads to paranoid, often violent, psychotic states accompanied by auditory and tactile hallucinations. Many, but not all, patients improve with abstinence and symptomatic treatment with low-dose neuroleptics. Brain damage to dopamine and 5-hydroxytryptamine receptors from the vasoconstriction and neurotoxicity of methamphetamine has been documented in animals (3). Our experience in Hawaii has provided some clinical evidence to support this.

While binding sites and cerebral perfusion deficits resulting from cocaine and crack abuse have been mapped out with single photon emission computed tomography (SPECT), identifying focal and long-term perfusion deficits in frontal and temporal lobes (4–6), no known study of cerebral perfusion in crystal methamphetamine abusers has been published to date. To assess brain perfusion deficits in crystal methamphetamine abusers, we used SPECT to scan 21 crystal methamphetamine abusers with psychotic symptoms. Scans were read by qualified neuroradiologists who were blind to the diagnoses. Length of crystal methamphetamine abuse ranged from 3 months to 10 years. No patients' charts showed a history of psychotic diagnosis or symptoms before the use of crystal methamphetamine. Sixteen of the 21 (76%) crystal methamphetamine abusers had focal perfusion deficits distributed in the frontal, parietal, and temporal lobes. A similar cerebral perfusion profile has been described for those who exhibit violent or aggressive behavior (7). Although our study group size was small, dose and length of exposure appear to be related to the extent of the perfusion deficits. In a few additional crystal methamphetamine abusers with psychotic symptoms, multiple SPECT scans have been done to document deficits over time—even years after crystal methamphetamine has left their bodies.

The "ice age" in Hawaii has shown methamphetamine abuse to be both debilitating and dangerous. Our preliminary findings suggest that crystal methamphetamine abuse leads to short-term and potentially long-term functional abnormalities linked to violence. Further research is needed. Clinical data and SPECT scans on crystal methamphetamine abusers are now being reviewed.

REFERENCES

1. Office of National Drug Control Policy. Methamphetamine: Facts and Figures. Rockville, Md, Office of National Drug Control Policy, 1997
2. Baberg HT, Nelesen RA, Dimsdale JE: Amphetamine use: return of an old scourge in a consultation psychiatry setting. Am J Psychiatry 1996; 153:789–793
3. Seiden LS: Neurotoxicity of methamphetamine: mechanisms of action and issues related to aging. National Institute on Drug Abuse Research Monograph Series 1991; 115:72–83
4. Holman BL, Carvalho PA, Mendelson J, Teoh SK, Nardin R, Hallgring E, Hebben N, Johnson KA: Brain perfusion is abnormal in cocaine-dependent polydrug users: a study using technetium-99m-HMPAO and SPECT. J Nucl Med 1991; 32:1206–1210
5. Weber DA, Fanceschi D, Ivanovic M, Atkins HL, Cabahug C, Wong CTC, Susskind H: SPECT and planar brain imaging in crack abuse: iodine-123-iodoamphetamine uptake and localization. J Nucl Med 1993; 34:899–907
6. Volkow HD, Hitzemann R, Wang GJ, Fowler JS: Long-term frontal brain metabolic changes in cocaine abusers. Synapse 1992; 11:184–190
7. Amen DG, Stubblefield M, Carmichael B, Thisted R: Brain SPECT findings and aggressiveness. Ann Clin Psychiatry 1996; 8:129–137

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Kandel's Challenge to Psychoanalysts

TO THE EDITOR: Eric R. Kandel, M.D. (1), has done the field of psychiatry, and psychoanalysis in particular, an interesting and valuable service. Acknowledging the place psychoanalysis had as a major mentalist perspective in psychiatry throughout the latter part of the century, Dr. Kandel has put us on notice: the future of psychiatry and psychoanalysis will be guided by efforts to integrate the biological and psychological sciences.

Dr. Kandel makes a most articulate statement of the broadly held view that the mind is dependent on the brain, that it is really a complex of functions of the brain. He adds to this one of the clearest statements to date of the importance of the two-way street between brain and mind. The idea of the feedback loop, from gene expression to phenotype to modifying gene expression, may be a paradigm for the interaction at many levels in the brain/mind system. This, in fact, would be a model for both the effects of pharmacology and psychotherapy, which enter into the complex system of feedback loops at different levels. The experience-dependent alteration of gene expression is profound in its implications because experience dependence implicates everyday experience, psychotherapeutic experience, and psychopharmacological experience.

If our e-mail is any guide, psychoanalysts were offended by Dr. Kandel's somewhat dismissive attitude toward psychoanalysis. Most were appalled by his description of his residency program, which seems to have been uniquely benighted, even for the 1960s. It is interesting that many a resident in current training programs could make the same kind of complaint, only now the longed-for presence would be a dynamically trained supervisor.

A growing number of psychoanalysts are writing about the important bridges to be built between disciplines. The rich fund of information derived from the phenomenology of clinical experience and some of the complex concepts derived therein—such as representation, motivation, internalization, intrapsychic conflict, transference, defense, and dissociation—could enrich cognitive neuroscience and could, in return, lead to enrichment of psychoanalytic theory by neuroscientific research. The caveat about Dr. Kandel's article is that he stresses the input from neurobiology and underemphasizes the potential information coming from the "high end," thereby encouraging the trend away from psychoanalytic input in psychiatric training programs. This is unfortunate. It is clear to us that the future complete psychiatrist or analyst should be sophisticated about brain function at many different levels, just as the well-educated cognitive scientist should understand the phenomena emerging from psychoanalysis. The model of the interaction of bottom-up and top-down processes could be the conceptual basis for future research. Dr. Kandel's article should be a wake-up call for neural scientists as well as psychoanalysts.

REFERENCE

1. Kandel ER: A new intellectual framework for psychiatry. Am J Psychiatry 1998; 155:457–469

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TO THE EDITOR: Eric R. Kandel, M.D., valiantly tries to show the molecular basis of psychopathology and psychotherapy, but I fear that the chasm between brain and mind remains unbridged. Suggesting a molecular basis for the way in which experience changes the brain provides a mechanism for the way in which experience and brain interact but leaves unanswered how one becomes the other and what part this plays in psychopathology and psychotherapy. We already know that brain and mind interact. And we know, for some disorders, that some of the variance of etiologies comes from biological factors and that drugs can effect marked changes in some symptoms. I do not see what Dr. Kandel's "new intellectual framework" adds.

He says that there are "critical biological underpinnings to all social actions"(p. 460). This may be important or trivial, depending on the circumstances. Understanding the biological details of how Rembrandt moved his muscles while painting hardly explains much about his artistic genius. Dr. Kandel does say that "for many aspects of group or individual behavior, a biological analysis might not prove to be the optimal level or even an informative level of analysis." That's just the point. Reducing something to biology may or may not be helpful.

Dr. Kandel criticizes social scientists who believe in a "radical mind-body dualism," but demonstrating that experience alters the brain does not resolve this dualism. Fuller knowledge about how genes function does not account for how a thought, feeling, or choice becomes a physical thing. We avoid this dualism only by closing our eyes.

We accept the interaction of brain and mind, but this is not materialistic monism. Psychiatry should not have to choose between allying itself with neurology, psychology, or sociology. It should seek knowledge anywhere, if pertinent to understanding and treating psychopathology.

It is strange that Dr. Kandel believes that further biological knowledge can help psychoanalysis. It would be helpful if he supplied an example of how any crucial psychoanalytic hypothesis can be proved or disproved by a biological or psychological experiment. He cites the example of patients with lesions of the medial temporal lobe losing the ability to acquire new explicit memory for people and things but who retain the ability to learn motor skills. He takes this as a challenge to psychoanalysts to find where their unconscious is, with its struggle for expression and modification of unacceptable thoughts and desires. What experiment would prove or disprove that?

If we found lesions that removed usual behavioral restrictions and others that increased them, would they provide a scientific basis for psychoanalysis? We scarcely need new studies to show that many mental functions occur outside of awareness. That hardly proves any psychoanalytic hypothesis.

ARTHUR RIFKIN, M.D.
Glen Oaks, N.Y.

TO THE EDITOR: In "A New Intellectual Framework for Psychiatry," Eric R. Kandel, M.D., proposes a framework "that derives from current biological thinking about the relationship of mind to brain." He notes that "academic psychiatry transiently abandoned its roots in biology and experimental medicine and evolved into a psychoanalytically based and socially oriented discipline that was surprisingly unconcerned with the brain as an organ of mental activity," and he urges "a renewed involvement of psychiatry with biology and with neurology."

He cautions, however, that "it would be unfortunate, even tragic, if the rich insights that have come from psychoanalysis were to be lost in the rapprochement between psychiatry and the biological sciences" and calls for psychoanalysis to be "embedded in the sciences of human cognition," where its ideas "can be tested."

There is doubt, however, as to whether the loss of psychoanalysis would be tragic for academic psychiatry. Kraepelin, arguably the founder of modern psychiatry, characterized the ideas of psychoanalysis as "castles in the air," far removed from the "sober method of clinical observation" (1). By contrast, his goal, whenever confronted with a disorder, was patient investigation aimed at discovering "the seat and extent of the morbid changes (in the brain) that have caused it" (2).

If academic psychiatry wishes to reestablish its roots with biology, it could do no better than look to the scientific foun-

dations laid by Kraepelin. Psychoanalysis, for all its richness, rather than being protectively held on to, should be kept at a skeptical arm's length unless and until its ideas have passed the test of sober scientific inquiry.

REFERENCES

1. Kraepelin E: Dementia Praecox and Paraphrenia. Huntington, NY, Robert E Krieger Publishing, 1971
2. Kraepelin E: One Hundred Years of Psychiatry. New York, Philosophical Library, 1962

DAVID P. MOORE, M.D.
Louisville, Ky.

TO THE EDITOR: In his excellent article, "A New Intellectual Framework for Psychiatry," Eric R. Kandel, M.D., raises disquieting issues for today's practicing psychiatrist. He calls attention to the need for imparting knowledge about the newest advances in the biological aspects of mental illness. Fortunately, he also recognizes the necessity of the psychosocial skills as well. He did not fall into the trap of advocating for the brain at the expense of the mind.

However, he did not present a solution for the problems he raised. Where is the practicing psychiatrist to get the training and education that is so necessary? We have to think not only of the young medical students or psychiatrists in training. But what of those out in the field? Books, articles, and lectures cannot fulfill the need for advanced training in neuroanatomy, molecular biology, genetics, and psychopharmacology. It seems to me that only medical schools can undertake the task of postgraduate education, and sadly, this does not seem to be perceived either as a primary task or as a secondary one.

I hope that Dr. Kandel's article can stimulate efforts to deal with the problem.

LEO H. BERMAN, M.D.
Bridgeport, Conn.

TO THE EDITOR: I am responding to a challenge issued to psychoanalysts by Eric R. Kandel, M.D., to provide experimental evidence for an unconscious related to instinctual strivings and sexual conflict now that a cognitive unconscious has been identified for memory. I believe my research group has met that challenge in a series of studies published in refereed experimental journals.

In one study (1), we showed that unconscious conflicts over sexual and aggressive impulses are associated with distinctive time-frequency features of event-related potentials that result in correct classification of stimuli related to these conflicts only when the stimuli are presented subliminally. When the stimuli are presented in full consciousness, the brain responses no longer correctly classify these stimuli, strongly suggesting that repression is at work. We also published a book in which our research is described in detail and is related to psychoanalytic, cognitive, and neurophysiological frames of reference (2).

In other studies (3, 4), we published evidence that raises serious questions about the relationship to the unconscious holding for explicit and implicit memories, cited by Dr. Kandel. Our evidence supports the claims that explicit memories can form unconsciously and that consciously formed explicit memories can prime—that is—have implicit effects in consciousness. Taken together, these findings imply that explicit memories need not form (or at least consolidate) in consciousness and, once out of consciousness, can act like implicit memories, thus blurring the line drawn between explicit and implicit memories. Our findings, however, agree with psychoanalytic theory's bearing on the importance of screen memories and transferences that are not (or at least need not be) enactments of procedural or implicit memories but of repressed explicit memories that nevertheless remain unconsciously active and influence consciousness in the absence of any awareness of their unconscious source.

On the whole, I enjoyed Dr. Kandel's article and look forward, as he does, to the inclusion of psychoanalytic insights into the exciting interdisciplinary efforts under way in psychiatry, molecular biology, cognitive psychology, and neuroscience. I believe that research such as ours can make a contribution to that integration.

REFERENCES

1. Shevrin H, Williams WJ, Marshall RE, Hertel RK, Bond JA, Brakel LA: Event-related indicators of the dynamic unconscious. Consciousness and Cognition 1992; 1:340–366
2. Shevrin H, Bond JA, Brakel LAW, Hertel RK, Williams WJ: Conscious and Unconscious Processes: Psychodynamic, Cognitive, and Neurophysiological Convergences. New York, Guilford Press, 1996
3. Wong PS, Shevrin H, Williams WJ: Conscious and nonconscious processes: an ERPindex of an anticipatory response in a conditioning paradigm using visually masked stimuli. Psychophysiology 1994; 31:87–101
4. Wong PS, Bemat E, Bunce S, Shevrin H: Brain indices of nonconscious associative learning. Consciousness and Cognition 1997; 16:519–544

HOWARD SHEVRIN, PH.D.
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TO THE EDITOR: Eric R. Kandel, M.D., advocates adopting a new intellectual framework for the purpose of training future psychiatrists. Despite an admirable review of recent advances in neuroscience, Dr. Kandel's article leaves two disturbing questions unanswered. First, to what precisely is he objecting, and second, might there be overlooked, undesirable consequences in adopting his framework?

Dr. Kandel asserts that medical students are not attracted to psychiatry because they sense that psychiatric training "is often based primarily on doing psychotherapy." I would venture to say that most psychiatry training directors would disagree with this unsubstantiated assertion, claiming instead that their programs provide more than "just a nodding familiarity with the biology of the brain." Even if Dr. Kandel's assertion were true, it does not follow that psychiatric training is necessarily rooted in the particular brand of psychotherapy that he seemingly chiefly decries—psychoanalysis.

While Dr. Kandel is careful to make note of the importance of learning as well as social and developmental factors in accounting for the efficacy of psychotherapy and "the variance of a given major mental illness," respectively, his framework is clearly intended to place "greater emphasis on biology." I fear that the adoption of more overtly biological paradigms will result in psychiatry's losing its already somewhat tenuous clinical credibility. My credibility with the department of family practice in which I work and teach, for example, is not based on my superior knowledge of neuroscience, my "facility with validated and objective criteria," nor even my knowledge of psychopharmacology. Rather, it is primarily based on my ability to calm agitated patients, elicit the hopes and fears of those who are ill, and earn the trust of the mistrustful—skills that have been developed through painstaking training and practice. Dr. Kandel's framework does not

necessarily preclude the teaching and acquisition of these skills, but I fear that as psychiatry becomes more deeply embedded in overtly biological models, the result will be the further erosion of those assessment and therapy skills that are less than well understood from the biological perspective.

Some would argue that psychiatry's rush to gain credibility in medical circles has already had unfortunate unanticipated consequences. Gary Tucker (1), for example, has recently argued that the adoption of DSM paradigms has resulted in just such consequences, robbing the profession of its distinctive richness and clinical validity.

One of Dr. Kandel's chief aims is to transform psychiatry into a profession that "will take its commitment to the training of biological scientists more seriously." In changing the conceptual framework of psychiatry with this aim in mind, let us not forget the careful training needed to acquire those clinical skills essential to the establishment of personal, human connections with patients. If we lose those skills, we lose the patients and the opportunity to use our large and growing knowledge of neuroscience to help them.

REFERENCE

1. Tucker GJ: Putting DSM-IV in perspective (editorial). Am J Psychiatry 1998; 155:159–161

ROBERT HIERHOLZER, M.D.
Fresno, Calif.

TO THE EDITOR: Eric R. Kandel, M.D.'s, vision of twenty-first century psychiatry is the latest and probably the most sophisticated version of biological reductionism. Proclaiming that everything including learning, social experiences, and environmental factors is, or will be, ultimately represented by a genetic code creates a dangerous cleavage between basic and clinical research and implies that empathetic listening and insight leave "little room for intellectual contents." Thus, one gets the impression that only biologically minded psychiatrists are intellectual, that only those who do research are intellectual, and that orientations other than the biological one lack curiosity, originality, substance, and truth-seeking objectives.

Psychoanalysis's domination of American psychiatry certainly had a strong ideological bent (1), which made it dogmatic, rigid, and intolerant. Alas, the implication from Dr. Kandel's article is that everything in psychiatry should be subjected to the biological orientation and the research it fosters. Advocating the neurologization of psychiatry reflects perhaps little experience in the profound human encounter that psychotherapy as well as evaluation, diagnosis, and disposition planning—in short, clinical work—entails. Psychiatry has always resisted compartmentalization and has always pursued a comprehensive, integrative approach. Predicting its demise and its replacement by hybrids such as "psychoanalytically oriented neuroscience" or "biologically based psychoanalysis" is nothing new (2). Many medical students who choose psychiatry today do so because they still see it as a clinical endeavor and want to practice its humanistic message. Neuroscience may become the basic research field that Dr. Kandel advocates, whereas the clinical approach to the care of and research on suffering human beings will still be called psychiatry.

The remark that psychoanalysis lacks a scientific or "questioning" tradition ignores the attempts and contributions of many psychoanalysts (3). The different cultures of biology, psychoanalysis, and psychiatry as fields of inquiry should be recognized, and justice should be done to the richness of the interface, interactions, and linkages that confer equal relevance to the genetic basis of behavior and to its environmental or sociocultural components (4).

The dominance of biological psychiatry in academic departments and residency training programs in the 1990s is undeniable. That psychopharmacology, neuroendocrinology, or biochemistry are not, strictly speaking, the brand of biology (genetics, molecular biology) that Dr. Kandel advocates does not deny such a trend. We should be aware, however, of the dangers of science becoming an ideology, with all of its potentially dogmatic implications. By no means do I imply that such was Dr. Kandel's intention, but the risk is that his piece may nurture the narrow views of scientific absolutism.

REFERENCES

1. Sabshin M: Science, pragmatism and the progress of psychiatry, in Contemporary Themes in Psychiatry. A Tribute to Sir Martin Roth. Edited by Davison K, Kerr A. London, Gaskell, 1989, pp 3–11
2. Torrey EF: The Death of Psychiatry. New York, Wiley & Sons, 1974
3. Marmor J (ed): Modern Psychoanalysis. New Directions and Perspectives. New York, Basic Books, 1968
4. Eisenberg L: Seed or soil: how does our garden grow? (editorial). Am J Psychiatry 1996; 153:3–5

RENATO D. ALARCON, M.D., M.P.H.
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Dr. Kandel Replies

TO THE EDITOR: I am grateful to the *The American Journal of Psychiatry* for giving me the opportunity to answer the letters it received in response to my article "A New Intellectual Framework for Psychiatry." Because that article was written for the 100th anniversary of Columbia's Psychiatric Institute, I focused on issues that concern academic psychiatry. In contrast, many of the letters to the *Journal* in response to the "Framework" article came from the psychoanalytic community. These letters raise two issues that I would like to address here: 1) that the article is dismissive of psychoanalytic ideas and 2) that the article is incorrect in suggesting that biology can be helpful in testing the scientific worth of psychoanalysis.

David D. Olds, M.D., and Robert A. Glick, M.D. (and a number of other readers), grasped completely the arguments that I tried to present in the "Framework" article but are concerned that I give short shrift to psychoanalysis. This may seem to have been the case because the article was not focused on psychoanalysis. But this was not my overall intention. I have great respect for the insight into human mental processes that psychoanalysis has opened up for us, and I believe that psychoanalysis provides the most coherent and interesting view of the human mind that we have.

The "Framework" article represents the elaboration of a line of thought that I began to develop 20 years ago in the Elvin Semrad Memorial Lecture (1) and continued a few years later (2). In both of these articles, I outlined the debt biology owes to the psychoanalytic perspective. Indeed, even a casual perusal of *Principles of Neural Science*, the textbook that I wrote with James Schwartz and Thomas Jessell (3)—I might add, for a largely nonpsychiatric readership—makes it clear that our thinking has been influenced and enriched by psychoanalysis.

In those earlier writings, I emphasized that psychoanalysis and the biology of mental processes represent different perspectives on a common problem, much like classical genetics

and molecular biology in the 1950s approached common problems from different perspectives. Psychoanalysis is, in the best sense, a part of biology; it is part of the analysis of mental processes, and these functions must have their foundation in the physical brain. Conversely, those aspects of biology that aspire to contribute to the science of the human mind must take the insights of psychoanalysis into consideration. Isn't it inevitable that biology and psychoanalysis should collaborate in their common interest? Why should this suggestion be regarded as demeaning? Did the emergence of molecular genetics demean either molecular biology or classical genetics? Do we think less of Mendel or of his discovery of genes since Watson and Crick have shown us how the double helical structure of DNA could explain the template function of genes?

I would guess that Drs. Olds and Glick would agree with the view that neuroscience and psychoanalysis could both benefit from greater interaction. Except for details that are unimportant, I do not think Drs. Olds and Glick and I disagree.

Whereas Drs. Olds and Glick say that I dismiss psychoanalysis, Dr. Arthur Rifkin and others argue that it is biology that should be dismissed when it comes to understanding mental functions. Rifkin asks, how can biological knowledge possibly help psychoanalysis? It would be helpful, he argues, if I could give an example of how any crucial psychoanalytic hypothesis can be proved or disproved by a biological or psychological experiment.

The view expressed by Dr. Rifkin is a return to a dualist (I am tempted to say Cartesian) position, which, in my view, needs to be addressed head-on if psychoanalysis is to continue to grow intellectually.

In 1894, Freud correctly argued that biology was not advanced enough to be helpful to psychoanalysis. It was premature, he thought, to bring the two together. The view that Rifkin and a number of psychoanalysts have, one century later, is more radical than Freud's by far. Rifkin's argument is not that biology and psychoanalysis are not yet ready for marriage but that biology is ill suited as a partner to psychoanalysis.

The last two decades have made it clear that psychoanalysis needs to grow scientifically if it wants to continue to influence how we think about mental processes. It therefore seems natural to suggest that biology offers an opportunity for such growth. I have further argued that psychoanalysis and biology are both likely to benefit from such an interaction. If biology is to explore the mind, biologists will need all the guidance they can get from students of mental processes.

One has to acknowledge that we are still far from establishing a biological foundation of psychoanalysis. In fact, we do not as yet have a satisfactory biological understanding of any complex mental processes. Therefore, it is quite possible that a convergence of biology and psychiatry is still a bit premature. Yet even now, the two disciplines are beginning to influence one another, and it is inconceivable to me that biology will not eventually make deep contributions to the understanding of mental processes. There must be a biological basis for the dynamic unconscious, for psychic determinism, for the role of unconscious mental processes in psychopathology, for drives, for transference and other attachments, and for the therapeutic effectiveness of psychoanalysis, to list only some central issues.

Having said that, I do not mean that psychoanalysis will be reduced to neuroscience. Psychoanalysis is much broader in scope than neural science. It will take from neuroscience only those tools and concepts it finds useful. Rather, I see a merger occurring between psychoanalysis, cognitive psychology, and neural science in which each influences the thinking of the other two disciplines and together they develop a more effective science of human behavior—one that has substantially greater scientific worth in explaining mental processes than each of the disciplines alone.

The point of neural science is not to prove or disprove psychoanalytic hypotheses, although it will, in certain cases, do just that. For example, I think the biology of memory has taught that there are many other types of unconscious processes besides the dynamic unconscious. Similarly, I think the emerging biology of gender—genotypic gender, phenotypic gender, gender identification, and sexual orientation—are bound to teach us a great deal about sexual orientation specifically and about drives in general. Although we probably do not need biology to convince us that Freud's analysis of the Schreber patient's case was flawed, I feel fairly confident that in the next two decades biology will tell us quite directly whether the concept of latent homosexuality has any meaning whatsoever and what, if anything, it has to do with paranoia. It may tell us to what degree male homosexuality is due to genes or brain anatomy on one hand or a possessive mother, a weak or hostile father, or other social influences on the other.

The relationship of biology and psychoanalysis is an issue of major scientific importance, and our positions in this debate will directly influence how we educate young psychoanalysts. Because I cannot begin to discuss a problem of this magnitude in this brief response, I have addressed it in the Special Article that appears elsewhere in this issue.

REFERENCES

1. Kandel ER: Psychotherapy and the single synapse. The impact of psychiatric thought on neurobiological research. N Engl J Med 1979; 301:1028–1037
2. Kandel ER: From metapsychology to molecular biology: explorations into the nature of anxiety. Am J Psychiatry 1983; 140:1277–1293
3. Kandel ER, Schwartz JH, Jessell TM (eds): Principles of Neural Science. Norwalk, Conn, Appleton & Lange, 1991

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Tranquilizing Effects of Smoking Cessation

TO THE EDITOR: The simple, elegant study by Robert West, Ph.D., and Peter Hajek, Ph.D. (1), serves to question the widely accepted notion that cessation of smoking leads to anxiety; hence, the myth that smoking has a calming effect.

The authors postulate that previous reports of anxiety following smoking cessation are related to the fact that many quitters may not have abstained completely. The authors note that nicotine substitution is used in many smoking cessation programs, but they do not comment on the fact that continuing to introduce this anxiogenic agent into the body by means other than smoking may simply perpetuate the sympathomimetic properties of nicotine. Incidentally, it would have been interesting to have noted the pulse rates of the smokers in this study. Because the notion that smoking cessation leads to anxiety predates the use of nicotine substitutes, perhaps we are dealing with the effects of decades of advertising that emphasizes the soothing, calming, beneficial effects of smoking.

Although the authors stated that "sessions focused on group discussion of abstinence and had no relaxation or stress management components" (p. 1592), they somehow must have conveyed a supportive, positive approach to have 70 of 101 patients abstinent at 4 weeks.

The consensual validation of the anxiolytic effects of smoking cessation should be helpful to physicians who deal with tobacco addiction.

REFERENCE

1. West R, Hajek P: What happens to anxiety levels on giving up smoking? Am J Psychiatry 1997; 154:1589–1592

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Near-Drowning Experiences and Panic Disorder

TO THE EDITOR: I read with great interest the article by Colin Bouwer, M.B., and Dan J. Stein, M.B. (1), on past traumatic suffocation experiences as a risk factor for panic disorder. I have made similar observations, confirming their hypothesis.

After two panic disorder patients' spontaneous declarations of near-drowning experiences, I began to ask my panic patients about their past traumatic suffocation experiences—namely, near-drowning experiences in water. Twenty (33%) of 62 patients with DSM-III-R panic disorder that were seen in a 6-month period reported that they had experienced a life-threatening and frightening suffocation experience preceding the onset of their panic disorder. Their mean age at the time of the suffocation experience was 13.88 years (range=5–55, SD=10.75), and their mean age at the onset of panic disorder was 29.69 years (range=15–57, SD=10.04). Sixteen (47.1%) of 34 patients with prominent respiratory symptoms and four (14.3%) of 28 patients with nonprominent respiratory symptoms reported a near-drowning experience. The difference between subtypes (2) was significant (χ^2=7.54, df=1, p=0.006). Three patients noted that they had experienced multiple instances of near drowning, and another patient had a near-drowning experience with a foreign object stuck in the throat. Among the patients with near-drowning histories (N=20), three patients were moderately phobic and four patients were severely phobic to bodies of water (N=7, 35%), although they knew how to swim.

Furthermore, five (14.7%) other patients with prominent respiratory symptoms described histories of an object stuck in the throat, which caused fear of choking to death. Although the data were statistically nonsignificant, Verburg et al. (3) first reported that a history of objects stuck in the throat is higher in panic patients (13.4%) than in other anxiety-disorder patients (5.9%). Likewise, some patients in our group described other possible forms of trauma. One patient described falling from a 10-meter height onto his chest, causing a dyspnea severe enough to create an intense fear of death at the age of 9 years. Two additional patients reported witnessing scenes in which drownings occurred. One had witnessed her daughter's rescue from a near drowning and a close friend's drowning in a pool.

In conclusion, traumatic suffocation histories may, indeed, play an etiological role, at least in some panic patients. However, traumas other than those mentioned in the Bouwer and Stein article (1) must also be considered. A broad spectrum of trauma (e.g., foreign objects in the throat or chest trauma) and witnessing the real and serious danger of the suffocation of others may also predispose individuals to panic disorder.

REFERENCES

1. Bouwer C, Stein DJ: Association of panic disorder with a history of traumatic suffocation. Am J Psychiatry 1997; 154: 1566–1570
2. Briggs AC, Stretch DD, Brandon S: Subtyping of panic disorder by symptom profile. Br J Psychiatry 1993; 163:201–209
3. Verburg K, Greiz E, Meijer J, Pols H: Respiratory disorders as a possible predisposing factor for panic disorder. J Affect Disord 1995; 33:129–134

TUNÇ ALKIN, M.D.
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Drs. Bouwer and Stein Reply

TO THE EDITOR: We were pleased to learn that Tunç Alkin, M.D., has collected data documenting that panic disorder is associated with a history of near drowning and that this association is particularly strong when panic attacks are characterized by prominent respiratory symptoms. Although his study lacked a control group, his findings are certainly consistent with our own and appear to lend further support to the suffocation hypothesis of panic disorder (1).

We also appreciate Dr. Alkin's drawing attention to different forms of suffocation possibly associated with panic disorder. In their article on the association of respiratory disorders and panic disorder, Verberg et al. (2) included a question on a history of "objects stuck in the throat," and indeed, this seems to be a useful question in this context. It is interesting that in his article McNally (3) concludes that choking episodes may be followed by choking phobias that respond to anti-panic treatment.

Whether the association between panic disorder and a history of traumatic suffocation is a causal one is, of course, paramount. A skeptical reader might wonder whether panic disorder patients are simply more likely to remember past episodes of suffocation or choking than others. Ultimately, more objective methodologies will be needed if this association is to be explored in depth.

REFERENCES

1. Klein DF: False suffocation alarms, spontaneous panics, and related conditions: an integrative hypothesis. Arch Gen Psychiatry 1993; 50:306–317
2. Verburg K, Greiz E, Meijer J, Pols H: Respiratory disorders as a possible predisposing factor for panic disorder. J Affect Disord 1995; 33:129–134
3. McNally RJ: Choking phobia: a review of the literature. Compr Psychiatry 1994; 35:83–89

COLIN BOUWER, M.B.
DAN J. STEIN, M.B.
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Alveolar Ventilation During Hyperventilation by Panic Disorder Patients

TO THE EDITOR: We are concerned about the study on the hyperventilation test of panic disorder patients by Laszlo A. Papp, M.D., and colleagues (1). Their article is one of the most comprehensive studies on the psychophysiological parameters of panic patients; however, the study might have some additional value that escaped the authors' attention during the discussion of their data.

We noticed that during cognitive behavioral psychotherapy for panic disorder, some patients, following our request to hyperventilate, started to breathe with sounds reminiscent of a dog panting in hot weather. According to physiological data, panting (high-frequency breathing with low tidal volume) by dogs increases minute ventilation, air change, and

evaporation of the mucosa but avoids real hyperventilation. Because the effective part of a breath is the tidal volume minus the respiratory dead space, the result multiplied by the respiratory rate is the alveolar (minute) ventilation. In spite of the increase in minute ventilation, the alveolar ventilation during panting may be unchanged because of the decrease of tidal volume.

We hypothesize that our panic disorder patients tried to avoid real hyperventilation by using a similar, ineffective, formal hyperventilation with low tidal volume that can help them in natural panicogenic situations as well. This formal hyperventilation is the opposite of the (deep and not-so-fast) respiratory pattern of trained athletes.

According to the authors' data, during the hyperventilation test, the "nonpanicker" panic disorder patients breathed with the lowest tidal volume. (The highest tidal volume belonged to the "panickers"; comparison subjects had medium values.) The difference between the data increases markedly if we consider the problem of respiratory dead space and alveolar ventilation. Estimating the alveolar ventilation of the subjects by using an average value of respiratory dead space (140 ml–150 ml), we found that while the alveolar ventilation of nonpanicker patients increased slightly (it almost remained stable), in the two other groups, the increase in alveolar ventilation was remarkable, especially among panickers. The patients can also be divided into two sets concerning alveolar ventilation: those who change their alveolar ventilation less, or more, than the comparison subjects. The group of nonpanicker patients contained not only those who did not really hyperventilate but also those whose panic attacks did not have any connection with the hyperventilation syndrome. We can assume that the difference between the "panters" and the patients who really hyperventilated would be more obvious if the subjects had not been encouraged to maintain a respiratory rate of 30 breaths per minute. Most likely, the "panters" would have increased their respiratory rate to over 30 breaths per minute so as to be more similar to the panting we observed in a large group of panic disorder patients.

REFERENCE

1. Papp LA, Martinez JM, Klein DF, Coplan JD, Norman RG, Cole R, de Jesus MJ, Ross D, Goetz R, Gorman JM: Respiratory psychophysiology of panic disorder: three respiratory challenges in 98 subjects. Am J Psychiatry 1997; 154:1557–1565

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Dr. Papp and Colleagues Reply

TO THE EDITOR: We appreciate the comments by Imre Janszky, M.D., and Maria Kopp, M.D., Ph.D., and welcome the opportunity to clarify our data. Indeed, the role of anatomical (and functional) dead space may be of particular relevance in the respiratory physiology of panic disorder patients. For instance, as we have shown elsewhere (1) that the diminished ability of panic patients to expel CO_2 following tryptophan depletion may be related to anomalies in dead space. It is true that, because of dead space, increasing respiratory rate with unchanged or decreased tidal volume "panting," as a general rule of physiology, will diminish the acid-base effects of hyperventilation in subjects without significant pulmonary pathology. While panting clearly works for dogs in hot weather, the hypothesis that low-tidal-volume hyperventilation using dead space is a successful coping mechanism for panic disorder patients in response to anxiogenic situations is not supported by our data. First, the difference in tidal volumes between panicking and nonpanicking patients during the hyperventilation period was not significant. Second, if the patients are divided into panickers (N= 16) and nonpanickers (N=38) according to self-rating during the hyperventilation period (in table 2, p. 1560, panic rating is based on self-rating during 5% CO_2 inhalation), the difference in tidal volumes is reversed (panickers: 359 ml; nonpanickers: 388 ml; n.s.). The suggestion that without the instruction to maintain a respiratory rate of 30 breaths per minute nonpanicking "panters" would increase their respiratory rate the most is again unlikely in view of our data. While it is possible that CO_2- and hyperventilation-induced panics involve different mechanisms, we found that it was the panicking group that increased respiratory rate the most during CO_2 challenges. It is not surprising that successful breathing retraining is based on instructing panic disorder patients to slow their respiratory rate and learn to adjust tidal volume to meet their metabolic needs.

REFERENCE

1. Kent JM, Coplan JD, Martinez J, Karmally W, Papp LA, Gorman JM: Ventilatory effects of tryptophan depletion in panic disorder: a preliminary study. Psychiatry Res 1996; 64:83–90

LASZLO A. PAPP, M.D.
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Estrogen for Elderly Men With Dementia

TO THE EDITOR: In her special article, Mary V. Seeman, M.D. (1), does not comment on the possible relationship between female hormones and reduced aggressive behavior. Estrogen has been used to decrease aggressive physical behavior in elderly men with dementia (2). In another study, women with dementia who had never received estrogen scored higher on a rating scale for aggressive behavior than women with dementia who currently or formerly received estrogen (3).

Ironically, an article in the same issue of the *Journal* as Dr. Seeman's (4) referred to the possible contribution of seasonal variations in testosterone levels to the occurrence of homicide. Perhaps aggressive behavior should be included as another example of a disturbance with hormone-mediated risks and buffers.

REFERENCES

1. Seeman MV: Psychopathology in women and men: focus on female hormones. Am J Psychiatry 1997; 154:1641–1647
2. Kyomen HH, Nobel KW, Wei JY: The use of estrogen to decrease aggressive physical behavior in elderly men with dementia. J Am Geriatr Soc 1991; 39:1110–1112
3. Wiseman EJ, Souder E, Liem PH: Estrogen use and psychiatric symptoms in women with dementia. Clin Gerontologist 1997; 18:81–82
4. Tiihonen J, Räsänen P, Hakko H: Seasonal variation in the occurrence of homicide in Finland. Am J Psychiatry 1997; 154: 1711–1714

EVE J. WISEMAN, M.D.
Little Rock, Ark.

Mood Improvement From Transcranial Magnetic Stimulation

TO THE EDITOR: I am writing regarding the study by Mark S. George, M.D., and colleagues (1) that reported mood improvement from transcranial magnetic stimulation. I believe that the statistical analyses performed were incorrect and that the proper analyses would show nonsignificant effects.

The data presented by the authors show that patients who received active treatment began with a Hamilton Depression Rating Scale score of 30; this fell to 23 after 2 weeks of active medication and increased to 26 after a subsequent 2 weeks with a placebo (sham treatment). The other patients (who were given the sham treatment first) began with a baseline Hamilton rating scale score of 26; this increased to 30 after 2 weeks on the sham treatment and fell to 27 after the subsequent 2 weeks on active treatment. Note that the group that received the sham treatment first was actually doing somewhat worse after active treatment than it had been at the beginning of the study.

The main problem with the analysis is that the authors used "change in Hamilton score" (treatment minus baseline) as their major outcome variable, but there was no washout period, so the value they used as the baseline for the second period of treatment was the rating at the end of the first phase of treatment. This, in a sense, doubles the importance of the rating at the end of the first period and, according to some authors (2), is clearly improper; Hills and Armitage (2) state that "there can be no second baseline without a washout period" (p. 16).

Also, the standard approach in analyzing a crossover study is to look first at period (not order) effects and period-by-treatment interactions. If there is a period effect or a period-by-treatment interaction, the second phase of the crossover study should not be analyzed. Dr. George and colleagues did not perform these initial analyses, and it seems quite possible that there was a significant period-by-treatment interaction because almost all of the evidence that magnetic stimulation was helpful occurred in the first period of treatment.

There may be other reasons for further evaluating transcranial magnetic stimulation. However, I believe that a more traditional analysis of this data would not yield a statistically significant evidence of benefit, so this should not be considered a positive study.

REFERENCES

1. George MS, Wassermann EM, Kimbrell TA, Little JT, Williams WE, Danielson AL, Greenberg BD, Hallett M, Post RM: Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. Am J Psychiatry 1997; 154: 1752–1756
2. Hills M, Armitage P: The two-period cross-over clinical trial. Br J Clin Pharmacol 1979; 8:7–20

JEFFREY A. MATTES, M.D.
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TO THE EDITOR: In an interesting contribution, Mark S. George, M.D., and colleagues concluded that daily left prefrontal repetitive transcranial magnetic stimulation improved mood in patients with depression, although only one of 12 patients improved more than 50% on the Hamilton Depression Rating Scale. In December 1997, we conducted an open pilot study of repetitive transcranial magnetic stimulation in a group of seven outpatients who had been free of antidepressant medication for at least 2 weeks. All patients were female and ranged in age from 41 to 66 years. Their initial scores on the 17-item Hamilton rating scale ranged from 20 to 29 points. We used a Cadwell rapid-rate stimulator and a Cadwell water-cooled figure-8 coil. Motor threshold was determined, as usual, by use of an electromyogram. We stimulated patients 10 times within a 2-week period, Monday to Friday, at 90% of the motor threshold for 5 seconds at 10 hz for 20 trains, with 1 minute between trains, over the left prefrontal cortex. If after four treatments there was no effect, intensity was raised to 100% of motor threshold. Results were assessed on the Hamilton rating scale on Mondays after the first and second weeks. Of the seven patients, one started antidepressants after 1 week, and two started antidepressants the day after the last treatment. Although we have no Hamilton rating scale scores for these patients after 2 weeks, we conclude that repetitive transcranial magnetic stimulation was unsuccessful in these patients. The average improvement on the Hamilton rating scale for the four patients who completed the study was 5 points, similar to the result of Dr. George and colleagues. Only one patient (F) improved more than 50% on the Hamilton rating scale, with a reduction from 22 to 10 points. One other patient (B) improved more than 25% (from 29 to 21 points). A third patient (D) showed minimal improvement (from 23 to 19 points) but also a remarkable decline in the (ab)use of pain medication, from 16 to three pills (nonsteroidal anti-inflammatory drugs and acetaminophen) daily. She also cut back on smoking, from the first day of repetitive transcranial magnetic stimulation onward. Maybe repetitive transcranial magnetic stimulation has an effect on addictive behaviors. All patients who showed at least minimal response used either no benzodiazepines (D and F) or relatively few (B; alprazolam, 0.125 mg/day). All other patients used higher doses of benzodiazepines. It is possible that benzodiazepines block or obscure the effect of repetitive transcranial magnetic stimulation in depression. A formal study of this aspect seems warranted. Our preliminary conclusion is that a clinically relevant effect of repetitive transcranial magnetic stimulation over the left prefrontal area on depression remains questionable.

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WILLEM A. NOLEN, M.D., PH.D.
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Dr. George and Colleagues Reply

TO THE EDITOR: With the ability to noninvasively interrupt or augment cortical activity, repetitive transcranial magnetic stimulation is a powerful new tool using an innovative paradigm (altering regional brain activity or circuits); and we welcome rigorous critical discussion.

Jeffrey A. Mattes, M.D., argues that our statistical analysis was incorrect. We have analyzed these data in multiple ways for several different reviewers and have found positive effects. Obviously, a crossover design study for depression has many limitations, but this study was a step in a natural progression from open studies of transcranial magnetic stimulation in depression to this quick crossover study and now to more rigorous double-blind, parallel designs. Among the 15 ongoing double-blind transcranial magnetic stimulation studies in depression, one report has even directly compared

transcranial magnetic stimulation with ECT, finding equal efficacy (1). A large U.S. multisite transcranial magnetic stimulation trial for depression in medication-free unipolar patients is now under way, and the combined results from this work will have the statistical power to completely settle the issue of transcranial magnetic stimulation's putative antidepressant effect within the next 2 years.

Eugene A.M. Schouten, M.D., and colleagues report on an open study of seven patients in which some had modest declines in Hamilton Depression Rating Scale scores while several nonresponders were taking benzodiazapines. They question whether benzodiazapines block the putative transcranial magnetic stimulation antidepressant effect. Their comments highlight the major issue in this emerging field, which is why are there such widely different ranges in antidepressant effects (11 of 17 psychotically depressed patients had a greater than 50% drop in Hamilton rating scale scores with 1 week [2]; 21 of 50 (42%) had a greater than 50% drop in a 1-week open trial [3]). The likely reason for these varying effect sizes is that we do not yet understand transcranial magnetic stimulation's effects on neurons nor its antidepressant actions. Numerous variables, including concomitant medication use, have varied across the studies to date (e.g., population, transcranial magnetic stimulation coil, intensity, frequency, dose). The transcranial magnetic stimulation field, now organized as the International Society of Transcranial Stimulation, is maintaining an active clinical trials database (http://www.ists.unibe.ch/ists/TMSAvery.htm). Sorting through all of these parameters in clinical trials will be slow and expensive. We place great hope in recent efforts by our group at the Medical University of South Carolina and others in combining transcranial magnetic stimulation and functional neuroimaging, particularly echoplanar blood-oxygen-level-dependent functional magnetic resonance imaging (4). By examining regional brain changes during transcranial magnetic stimulation in health and disease, carefully varying the parameters (e.g., intensity, location, frequency), and observing real-time changes in local and remote brain activity, it is hoped that one can identify combinations of parameters that are more likely to have the most potent antidepressant effects. The combination of rigorous double-blind clinical trials with neuroimaging will likely help transcranial magnetic stimulation assume its position within psychiatry, either as an interesting investigative tool (at the least) or as a powerful new form of therapy for depression and other disorders—or both.

REFERENCES

1. Grunhaus L, Dannon P, Schrieber S: Effects of transcranial magnetic stimulation on severe depression: similarities with ECT (abstract no. 254). Biol Psychiatry 1998; 43(Aug suppl):76s
2. Pascual-Leone A, Rubio B, Pallardo F, Catala MD: Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet 1996; 348:233–237
3. Figiel GS, Epstein C, McDonald WM, Amazon-Leece J, Figiel L, Saldivia A, Glover S: The use of rapid rate transcranial magnetic stimulation (rTMS) in refractory depressed patients. J Neuropsychiatry Clin Neurosci 1998; 10:20–25
4. Bohning DE, Shastri A, Nahas Z, Lorberbaum JP, Anderson SW, Dannels WR, Haxthausen EU, Vincent DJ, George MS: Echoplanar BOLD fMRI of brain activation induced by concurrent transcranial magnetic stimulation. Invest Radiol 1998; 33: 336–340

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Reprints of letters to the Editor are not available.

Correction

The data for table 2 in the article "Association Between Eye Tracking Disorder in Schizophrenia and Poor Sensory Integration" by David E. Ross, M.D., et al. (October 1998, pp. 1352–1357) have been reanalyzed. The corrected table is presented below. In addition, the MANOVA in the first paragraph in the Results section should read Wilks's lambda=0.64, F=39.98, df=2, 141, p<0.0001.

TABLE 2. Scores on Subscales of the Neurological Evaluation Scale for Normal Comparison Subjects and Schizophrenic Patients With and Without Eye Tracking Disorder

	Square Root of Score[a]					
	Normal Comparison Subjects (N=90)		Schizophrenic Patients Without Eye Tracking Disorder (N=36)		Schizophrenic Patients With Eye Tracking Disorder (N=18)	
Subscale	Mean	SD	Mean	SD	Mean	SD
Sensory integration	1.3	0.7	1.8	0.9	2.3	0.6
Motor coordination	0.5	0.6	1.1	0.8	1.4	0.9
Sequencing of complex motor acts	0.6	0.7	1.3	1.1	1.7	1.1
Other neurological signs	2.0	0.8	2.9	0.8	3.0	0.9

[a] Subtotals of the number of signs present were used for each subscale. The data then were transformed by taking the square root, in order to allow for use of parametric statistical techniques.