

Mania-Like Episodes Associated With Ranitidine

SIR: Ronald F. Billings, M.D., and Murray B. Stein, M.D., reported three cases of depression associated with ranitidine (1). We would like to point out the possibility of mania-like episodes following treatment with this H₂-receptor blocker, which until now have not been reported, to our knowledge.

Ms. A, a 60-year-old alcohol-addicted woman, was referred to our neurology department because of tonic-clonic generalized and right-side seizures, followed by right hemiparesis. She had no history of affective disorder. An EEG showed left anterior epileptiform activity; CAT scan showed only mild diffuse atrophy. Radionuclide scanning and CSF analysis produced normal findings.

With enteral alimentation and administration of clonazepam (3 mg/day i.v.), carbamazepine (1200 mg/day), thiamine (500 mg/day), pyridoxine (500 mg/day), and cyanocobalamin (1000 µg/day), Ms. A improved slowly. Three weeks after admission, her seizures had ceased and her consciousness was normal; only a slight left hemiparesis and intermittent myoclonus of the left arm remained. Laboratory tests showed normal serum transaminase and bilirubin levels, increased gamma glutamyltransferase (80 U/liter) and alkaline phosphatase (240 U/liter) levels, elevated beta (9 g/liter) and alpha (18 g/liter) globulin levels, and normal ESR, hemogram findings, and creatinine and electrolyte levels. The clonazepam and carbamazepine were withdrawn.

After hematemesis occurred, a duodenal ulcer was diagnosed by fibroscopy. Ranitidine (two 150-mg tablets per day) was then prescribed. Two days later, the patient suddenly presented a manic state. She became excessively talkative and euphoric, with flight of ideas and unmotivated bursts of laughter. She talked while singing, called out to strangers, made puns, spoke in a provocative manner, fantasized, and uttered delirious thoughts, sometimes aggressively.

Withdrawal of ranitidine, without any other therapeutic change, completely relieved the manic symptoms within a few hours. Three days later, ranitidine was again prescribed. After she had taken 150 mg/day for 4 days and then 300 mg/day for 9 days, Ms. A relapsed into the same manic state. All symptoms were relieved within a few hours after the ranitidine was again withdrawn.

There is some evidence for the responsibility of ranitidine for these two mania-like episodes: they occurred a few days after this drug was started, they disappeared after its withdrawal, there was no other therapeutic change, and the prompt disappearance of symptoms is not surprising in view of the pharmacokinetic characteristics of ranitidine (2). As far as we know, no mania-like symptoms have ever been reported to be associated with the use of the other drugs administered to our patient, and these drugs were withdrawn before the second episode.

There have been reports of other neuropsychiatric disorders—drowsiness, confusion, delirium, visual hallucinations (2–4), and depression—following treatment with H₂ receptor blockers (ranitidine or cimetidine), but we believe this to be the first report of acute mania.

The mechanism is unknown, but ranitidine crosses the blood-brain barrier (2), and there is experimental evidence in animals of cerebral H₁ and/or H₂ histaminic receptors that have the capacity to bind not only antihistamines but also some antidepressant drugs (5, 6). However, the therapeutic

effects of these may be related to other mechanisms. Alcohol-dependent liver and brain disturbances may have favored the occurrence of CNS side effects in our patient, as has already been reported in cases of confusion following cimetidine or ranitidine administration (3, 4).

REFERENCES

1. Billings RF, Stein MB: Depression associated with ranitidine. *Am J Psychiatry* 1986; 143:915–916
2. Price W, Coli L, Brandstetter RD, et al: Ranitidine-associated hallucinations. *Eur J Clin Pharmacol* 1985; 29:375–376
3. Mani RB, Spellun JS, Frank JH, et al: H₂ receptor blockers and mental confusion (letter). *Lancet* 1984; 2:98
4. Silverstone PH: Ranitidine and confusion (letter). *Lancet* 1984; 1:1071
5. Coupet J, Szuchs-Myers VA: Brain histamine H₁ and H₂ receptors and histamine sensitive adenylylate cyclase: effects of antipsychotics and antidepressants. *Eur J Pharmacol* 1981; 74: 149–155
6. Kanof PD, Greengard P: Brain histamine receptors as targets for antidepressant drugs. *Nature* 1978; 272:329–333

OLIVIER DELERUE, M.D.
JEAN-PHILIPPE MULLER, M.D.
ALAIN DESTEE, M.D.
PIERRE WAROT, M.D.
Lille, France

More on Haircutting and Psychosis

SIR: In response to a letter to the Editor by Kirk Strawn et al. (1) concerning haircutting propensities of psychotic patients, I can provide two additional cases.

Mr. A, a 28-year-old white man with the diagnosis of chronic undifferentiated schizophrenia and mild mental retardation, was hospitalized for the 12th time after his chronic auditory hallucinations became more accusatory and he felt strangers were laughing at him on the street. He denied having command hallucinations but said he had thought of overdosing on aspirin or a household cleanser. He had shaved his head and eyebrows several days before admission, attempting to conceal this with a fur hat he wore indoors. He had also shaved part of his head before being hospitalized two years earlier. He ultimately revealed that his reason for haircutting was to avoid being mistaken by passersby for a handsome movie star who he felt was homosexual.

Ms. B, a 41-year-old black woman with chronic paranoid schizophrenia, became preoccupied with religion and converted to a new faith. She stopped sleeping and caring for herself. Chanting "Little boys are good, little girls are bad and should be dead," she cut off her hair, then burned both the hair and her wigs. She felt that there was a special mark on her forehead.

Sweeney and Zamecnik (2) previously reported in the *Journal* on predictors of self-mutilation in patients with schizophrenia. Comparing nine schizophrenic patients who had disfigured themselves with matched schizophrenic control subjects, they found hair removal to be a statistically significant predictor of later more serious self-mutilation. "Of the nine self-mutilators, three men had shaved their heads and one woman had plucked out nearly all of her eyebrows and eyelashes just before the self-mutilative act" (2).

Haircutting dreams of neurotic analysands have been linked to the fairy tale of Rapunzel (3), and trichotillomania is a more obsessive psychopathological road to alopecia (4). I agree with Sweeney and Zamecnik that extreme haircutting may well signal self-destructive intent in psychotic individuals. Interestingly, however, neither of the two patients I have described went on to greater self-inflicted injury during several years of follow-up; nor, apparently, did any of the patients cited by Strawn et al.

REFERENCES

1. Strawn K, Ryken T, Black DW: Extreme haircutting and psychosis (letter). *Am J Psychiatry* 1987; 144:1102–1103
2. Sweeney S, Zamecnik K: Predictors of self-mutilation in patients with schizophrenia. *Am J Psychiatry* 1981; 138:1086–1089
3. Andresen JJ: Rapunzel: the symbolism of the cutting of hair. *J Am Psychoanal Assoc* 1980; 28:69–88
4. Greenberg H, Sarner C: Trichotillomania: symptom and syndrome. *Arch Gen Psychiatry* 1965; 12:482–489

JOHN MARKOWITZ, M.D.
New York, N.Y.

Suicide and Mortality From Diabetes

SIR: In the course of a major study of possible relationships between cancer and the environment, I have developed several large data banks (1). One of these covers the United States at the state level and includes mortality or incidence data for 74 diseases or groups of diseases. It also contains information on the spatial distribution of 221 climatic, geological, hydrologic, economic, and social variables. A second Canadian data bank is at the census division level, subdividing the country into 258 regions. It includes information on death from 33 causes during the period 1966–1976. In addition, this data bank contains chemical analyses of drinking water from 2,633 locations.

Given the growing literature discussing possible links between magnesium, serotonin, and 5-hydroxyindoleacetic acid (5-HIAA) and suicide (2, 3), I decided to search these banks for evidence of any possible spatial links between magnesium and suicide at the state and census division levels. In the United States the combined suicide rate for 1981 was used. In Canada, male and female mortality rates for the period 1966–1977 were used. The results were very unexpected and may be of interest to *Journal* readers. There appears to be a strong negative correlation ($r = -0.60314$, $p < 0.0001$) between suicide and diabetes in the United States. Although the negative Pearson correlation coefficients are weaker for the Canadian data, the same inverse relationships can be identified. For men, the correlation coefficient between suicide and diabetes was -0.20337 , while for women it was -0.20261 . In both instances, $p < 0.0001$.

This inverse relationship between mortality from diabetes and suicide appears, at least in part, to be linked to levels of environmental magnesium. In the United States, for example, diabetes had a strong negative correlation with magnesium-enriched soils ($r = -0.56342$, $p < 0.0001$). In contrast, both male and female suicide rates correlated positively with magnesium in Canadian drinking water: for men, $r = 0.21553$, $p < 0.0001$, and for women, $r = 0.08805$, $p < 0.0001$.

It is clear, therefore, that in both the United States and Canada the spatial patterns of suicide and diabetes appear to be negatively related. In part, this seems to be because suicide

levels rise with increases in environmental magnesium but diabetes mortality falls. I should like to stress that these results were very unanticipated.

REFERENCES

1. Foster HD: Reducing Cancer Mortality: A Geographical Perspective. Western Geographical Series, Number 23. Victoria, BC, Canada, University of Victoria, 1986
2. Banki CM: Biochemical markers for suicidal behavior (letter). *Am J Psychiatry* 1985; 142:147–148
3. Banki CM, Vojnik M, Papp Z, et al: Cerebrospinal-fluid magnesium and calcium related to amine metabolites, diagnosis, and suicide attempts. *Biol Psychiatry* 1985; 20:163–171

HAROLD D. FOSTER, PH.D.
Victoria, B.C., Canada

Neuroscience in the Future of Psychiatry

SIR: The article "The Future of Psychiatry" by Thomas Detre, M.D. (1), highlights many problems in contemporary psychiatry. The author's proposed solution, the "clinical neuroscientist," does indeed have merit. I cannot, however, agree with his complete dismissal of psychoanalysis and other psychologies. Attempting to explain all mental phenomena by neurochemistry is to make the same mistake that early psychoanalysts made by ascribing all mental phenomena to intrapsychic conflict. Music understood only as electromagnetic radiation would be very dull indeed!

I do not, therefore, agree with Dr. Detre's facile dismissal of the "Renaissance man." Granted, a clinician or researcher ought to focus on a given clinical problem area. It does not follow, however, that he or she should be restricted to the contributions of only certain basic sciences. The fine work, for example, of Daniel Stern (2) in infant development and Milton Viederman and Samuel Perry (3, 4) in consultation-liaison psychiatry clearly reflects the strength of broadly based data and skills.

Economic realities will change—possibly eliminate—the psychiatrist's role in the practice of psychotherapy. Dr. Detre cannot, however, deny the efficacy of psychotherapy in mental illness, even as he defines it (e.g., a recent National Institute of Mental Health multisite study established the efficacy of cognitive and interpersonal therapies in major depressive disorder). Psychiatrists must have some working knowledge of psychodynamic theory, learning theory, cognitive psychology, and family and other systems as well as individual, group, and family psychotherapy. Unless they do, they cannot 1) intelligently recommend such treatment to patients nor 2) work effectively with psychologists, social workers, and nurses in an interdisciplinary team. Perhaps psychiatrists should adopt a model comparable to the one used by physical medicine and rehabilitation. In that model, the psychiatrist leads a team of physical, occupational, and speech therapists and others.

I am willing to rise to the challenge that Dr. Detre has suggested by proposing the "clinical neuroscientist," but not if it requires tunnel vision.

REFERENCES

1. Detre T: The future of psychiatry. *Am J Psychiatry* 1987; 144: 621–625
2. Stern D: The Interpersonal World of the Infant. New York, Basic Books, 1985
3. Perry S, Viederman M: Management of emotional reactions to