sensitive than are humans, and therefore may not be a useful model for humans.[4]

Leonard A. Sagan, MD
Electric Power Research Institute
Palo Alto, Calif

1. Wever R. Circadian rhythmicity of man under the influence of weak electromagnetic fields. In: Moore-Ede MC, Campbell SS, Reiter RJ, eds. *Electromagnetic Fields and Circadian Rhythmicity.* Boston, Mass: Birkhauser Boston Inc; 1992:121-140.
2. Lintzen T, Boese G, Muller M, Falk H, Eichmeier J, Ruhrenstroth-Bauer G. The stability of the circadian rhythm of the green finch (*Carduelis chloris*) either in a weak 10-Hz electric field or a negatively ionized atmosphere. In: Moore-Ede MC, Campbell SS, Reiter RJ, eds. *Electromagnetic Fields and Circadian Rhythmicity.* Boston, Mass: Birkhauser Boston Inc; 1992:141-150.
3. Groh KH, Ready MA, Ehret CF. Chronobiological effects of electric fields. In: Wilson BW, Stevens RG, Anderson LE, eds. *Extremely Low Frequency Electromagnetic Fields: The Question of Cancer.* Columbus, Ohio: Battelle Press; 1990.
4. Reiter RJ. Effects of light and stress on pineal function. In: Wilson BW, Stevens RG, Anderson LE, eds. *Extremely Low Frequency Electromagnetic Fields: The Question of Cancer.* Columbus, Ohio: Battelle Press; 1990.

Ecstasy, the Serotonin Syndrome, and Neuroleptic Malignant Syndrome—A Possible Link?

To the Editor.—We read with interest the report on 3,4-methylenedioxymethamphetamine (ecstasy).[1] The toxic effects of this drug—hyperthermia, autonomic instability, increased motor restlessness, and death by renal failure—appear to be similar to certain features of both the "serotonin (5-HT) syndrome"[2] and neuroleptic malignant syndrome (NMS).

The serotonin syndrome has been reported in depressed patients who are taking a combination of medications that enhance central nervous system serotonin function such as tryptophan, monoamine oxidase inhibitors, and other antidepressant medications. The most frequently reported symptoms that comprise the syndrome are changes in mental status, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering, and tremor. The precise etiology of the syndrome is unclear, although some evidence supports the theory that it is caused by hyperstimulation of the 5-HT_{1A} receptor in the brainstem and spinal cord. This is based on animal research in which 5-HT_2 antagonism with specific 5-HT_2 antagonists, mianserin hydrochloride and pipamperone, could not reverse the serotonin syndrome in rats, but nonselective 5-HT antagonists, such as cyproheptadine hydrochloride, were able to reverse the syndrome, presumably through 5-HT_{1A} receptor blockade.

In humans, methysergide maleate, a nonspecific serotonin antagonist, has been used to successfully treat the serotonin syndrome,[3] as have β-blockers,[4] which also act as 5-HT_{1A} antagonists. Perhaps these therapies could be used in cases of ecstasy toxic effects.

Neuroleptic malignant syndrome occurs in psychiatric patients who are treated with dopamine-blocking agents, and its etiology is unclear. The most commonly agreed on features of NMS are hyperthermia, rigidity, fluctuating consciousness, and autonomic instability.[5,6] The acute depletion of dopamine is thought to account for the profound rigidity seen in these patients. The subsequent hyperthermia, tachycardia, elevated creatinine phosphokinase levels, and renal failure from rhabdomyolysis may result from this rigidity. Treatment of NMS usually involves neuroleptic discontinuation, use of adjunctive bromocriptine, and/or dantrolene sodium and supportive measures such as cooling blankets, hydration, and respiratory support. Again, these measures, with the exception of bromocriptine, may be useful in the treatment of ecstasy toxic effects.

Ecstasy is a "messy" drug. Its structural similarity to amphetamines suggests that it effects both dopamine- and serotonin-containing neurons. Hence, its toxic effects resemble both NMS and the serotonin syndrome. Because of the interplay between these two neurotransmitter systems in the brain (eg, 5-HT_2 antagonism increases firing of dopamine neurons in animals),[7] the serotonin syndrome and NMS may represent a spectrum of adverse effects that occur when there is perturbation in the balance of these two neurotransmitters. Ecstasy may exert its toxic effects by its combined effects on both these systems.

Donna Ames, MD
William C. Wirshing, MD
UCLA
Los Angeles, Calif

1. Randall T. Ecstasy-fueled 'rave' parties become dances of death for English youths. *JAMA.* 1992;268:1505-1506.
2. Sternbach H. The serotonin syndrome. *Am J Psychiatry.* 1991;148:705-713.
3. Sandyk R. L-dopa induced 'serotonin syndrome' in a parkinsonian patient on bromocriptine. *J Clin Psychopharmacol.* 1990;51:222-225.
4. Guze BH, Baxter LR Jr. The serotonin syndrome: a case report. *J Clin Psychopharmacol.* 1986;6:119-120.
5. Levenson JL. Neuroleptic malignant syndrome. *Am J Psychiatry.* 1985;142:1137-1145.
6. Guze BH, Baxter LR Jr. Neuroleptic malignant syndrome. *N Engl J Med.* 1985; 313:163-166.
7. Ugedo L, Grenhoff J, Svensson TH. Ritanserin, a 5HT_2 receptor antagonist, activates midbrain dopamine neurons by blocking serotonergic inhibition. *Psychopharmacology.* 1989;98:45-50.

In Reply.—The report of toxic reactions to the designer drug, ecstasy, in Ms Randall's[1] report bears a striking resemblance to the serotonin syndrome reported in psychiatric patients.[2] Like some patients with the serotonin syndrome, individuals who used ecstasy were noted to have hyperthermia, tachycardia, disseminated intravascular coagulation, rhabdomyolysis, and acute renal failure.

The serotonin syndrome is characterized by some or all of the following symptoms: hyperthermia, tachycardia, autonomic instability, agitation, diaphoresis, myoclonus, shivering, tremor, and mental status change (ie, confusion or delirium).[2] Clinical reports describe symptoms ranging from very mild to life-threatening. We previously reported a near-fatal case in which the patient developed hyperthermia, disseminated intravascular coagulation, rhabdomyolysis, and acute renal failure.[3]

The serotonin syndrome has been reported in patients who are treated with a combination of agents that markedly enhance brain serotonin activity. The most common serotonergic drug interactions associated with this syndrome include monoamine oxidase inhibitor (MAOI)-tryptophan, fluoxetine-MAOI (a contraindicated combination), fluoxetine-tryptophan, and MAOI-meperidine hydrochloride.[2] The serotonin syndrome has been produced in animals with a variety of serotonergic drugs and is characterized by rigidity, tremor, myoclonus, seizures, Straub tail, lateral head shaking, and autonomic instability. The fact that nonselective serotonin (5-HT) antagonists such as methysergide, cyproheptadine, and metergoline can block the serotonin syndrome in animals further indicates that 5-HT receptor activation mediates the serotonin syndrome.[4]

Since ecstasy (MDMA) augments central serotonin function by stimulating neuronal serotonin release, it is likely that some of the reported cases of ecstasy toxic effects represent the serotonin syndrome. Furthermore, it is possible that the amino acid drinks ("smart drinks") that individuals ingest in addition to ecstasy (during the all-night dance sessions or "raves") contain significant levels of tryptophan, which could markedly enhance the serotonergic effect of ecstasy.

Current treatment of the serotonin syndrome involves the immediate removal of suspected medication(s) and various supportive measures. In severe cases, these may involve active cooling or dantrolene sodium for hyperthermia, anticonvulsants for seizures, or monitoring in an intensive care

unit. Although prospective treatment data are lacking, one might consider the use of serotonin antagonists such as methysergide or cyproheptadine as adjunctive treatment for the serotonin syndrome.

Richard Friedman, MD
New York, NY

1. Randall T. Ecstasy-fueled 'rave' parties become dances of death for English youths. *JAMA.* 1992;268:1505-1506.
2. Sternbach H. The serotonin syndrome. *Am J Psychiatry.* 1991;148:705-713.
3. Miller F, Friedman RA, Tanenbaum J, Griffin A. Disseminated intravascular coagulation and acute myoglobinuric renal failure: a consequence of the serotonergic syndrome. *J Clin Psychopharmacol.* 1991;11:277-279.
4. Gerson SC, Baldessarini RJ. Motor effects of serotonin in the central nervous system. *Life Sci.* 1980;27:1435-1451.

Heterosexual Transmission of HIV

To the Editor.—We are pleased to see a feature in the medical literature addressing the fact that the right health education message may not be enough to protect women against human immunodeficiency virus (HIV) infection.[1] The issue of women's ability to perceive themselves at risk and to negotiate safer sex and the role of society's perceptions of masculinity have been discussed, particularly in the sociological and anthropological literature, for some time.[2]

We would, however, like to take issue with Dr Guinan's assertion that a comprehensive program to prevent HIV infection to women should emphasize "having one lifetime partner."[1]

Health education campaigns aimed at heterosexual transmission of HIV infection have often centered on recommending monogamy, particularly in Africa, or at least have presented casual sex as the main risk. We believe that this is not an accurate reflection of risk of HIV transmission to women and may cause a false sense of security in those following the advice. If most heterosexual intercourse involving infected individuals took place in stable relationships, long-term partners are most at risk from unprotected sex.[3] In Sweden, 53 heterosexual partners of people with HIV infection were infected: 32 by steady partners and 21 by casual partners. In the United States, having a partner who used drugs, but not the number of partners, carried a significant risk of HIV infection. Of 35 women who acquired HIV heterosexually in Copenhagen, 10 were infected by a cohabiting partner. In the United Kingdom, 80% of women with heterosexually contracted acquired immunodeficiency syndrome (AIDS) were infected by a long-term partner.[4] In Rwanda, the prevalence of HIV infection among women reporting a single lifetime sexual partner was 21%.[5]

The emphasis on promiscuity and prostitution in research on AIDS and women, especially in Africa, may reflect an interest in women as transmitters, rather than recipients, of infection. It has also been suggested that this results from a perception of women as either bad (promiscuous and at risk) or good (monogamous and not at risk).[6]

The emphasis on monogamy ignores the fact that an increasing number of men are infected, and mostly not through heterosexual contact. Even a recommendation of monogamy, except with partners in at-risk groups, presupposes that most women are aware of their partners' risk activities. In the study in Copenhagen, only one of the 25 women with partners in a high-risk group was aware of the partner's risk activities when the relationship started.

The emphasis on monogamy can give women a false sense of security: in the same study in Rwanda, 24% of the women who did not regard themselves as being at risk (most of whom were in monogamous relationships) were already infected.[5]

We believe the message should be that unless conception is desired, all sex should be safe sex, and conditions should be created to make this possible for all women.

Laura C. Rodrigues, PhD
Claudia Garcia Moreno, MD
University of London (England)

1. Guinan ME. HIV, heterosexual transmission, and women. *JAMA.* 1992;268:520-521.
2. Schoepf GB. Women, AIDS and economic crisis in Central Africa. *Can J African Studies.* 1988;22.
3. Rodrigues LC, Garcia Moreno C. HIV transmission to women in stable relationships. *N Engl J Med.* 1991;325:966.
4. Rodrigues LC, Evans B, Porter K. Heterosexual transmission of HIV. *BMJ.* 1992;305:364.
5. Lindan C, Allen S, Carael M, et al. Knowledge, attitudes, and perceived risk of AIDS among urban Rwandan women: relationship to HIV infection and behaviour change. *AIDS.* 1991;5:993.
6. Garcia Moreno C, Rodigues L. Safer sex and women in Africa. *Lancet.* 1992;340:57-58.

In Reply.—Drs Rodrigues and Garcia Moreno do not define safe sex, and therefore, their recommendations are unclear. The risk of acquisition of HIV increases with increasing number of sex partners. We should teach our children that having intercourse with multiple partners is unhealthy and also how to protect themselves if they choose to have sex. Both messages are also essential for adults. Which one is emphasized may depend on the particular clinical situation, but neither message should be excluded.

Mary E. Guinan, MD, PhD
Centers for Disease Control and Prevention
Atlanta, Ga

CORRECTIONS

Addition to Affiliation.—In the Original Contribution entitled "Survival Rates With Coronary Artery Disease for Black Women Compared With Black Men," published in the October 14, 1992, issue of THE JOURNAL (1992;268:1867-1871), the affiliation footnote at the bottom of the first column on page 1867 should include the following: "Drs Cooper and Ghali were affiliated with Cook County Hospital, Chicago, Ill, during the time of data collection for this study."

Incorrect Percentage.—In the Letter entitled "The AMA and the Physicians Committee for Responsible Medicine," published in the August 12, 1992, issue of THE JOURNAL (1992;268:788-789), an error occurred in the reply on page 789. The first sentence of the last paragraph of this reply should read as follows: "The PCRM has failed to gain widespread acceptance among the medical community and its membership represents less than 0.5% [not 0.005%] of the total US physician population."