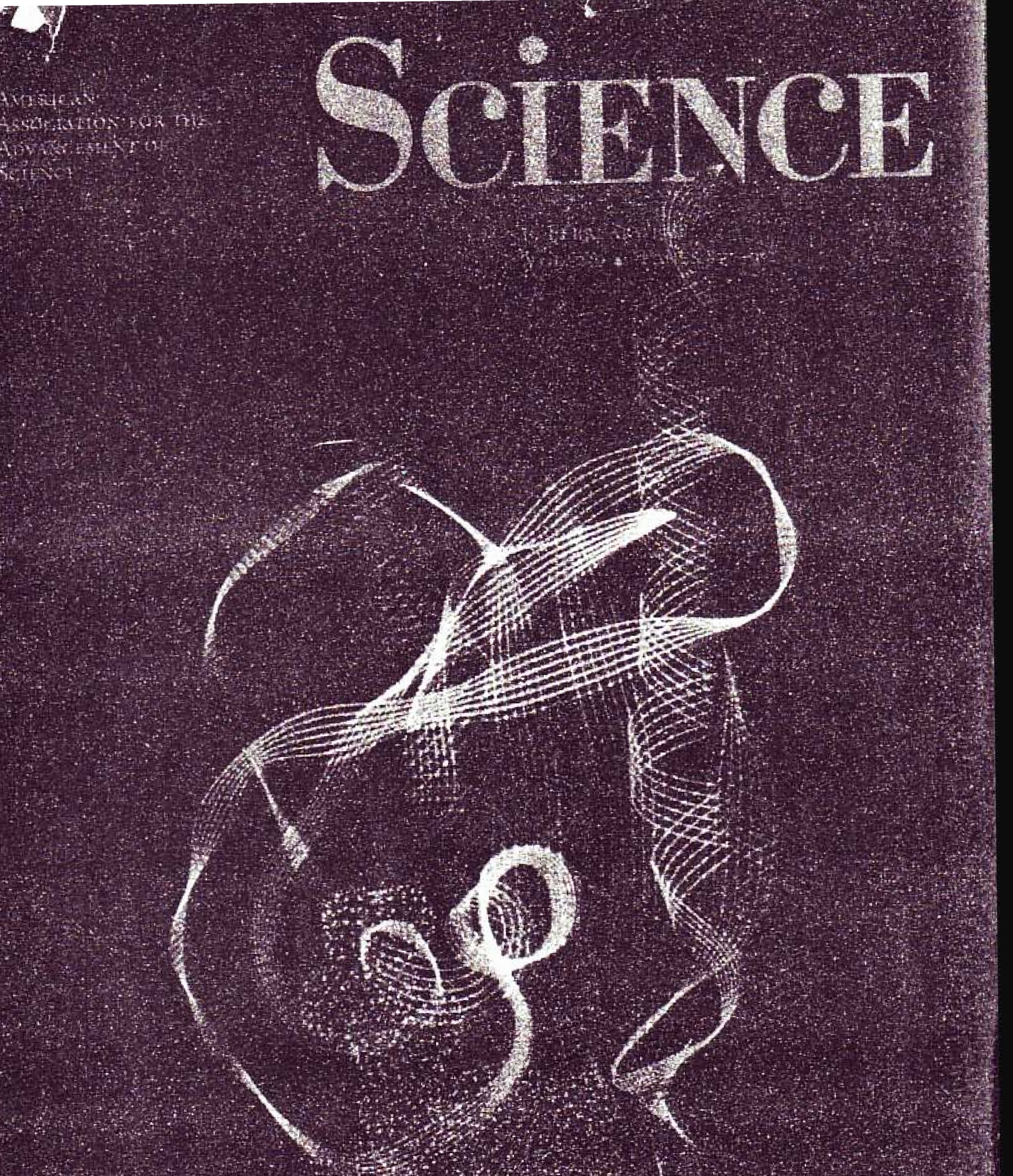


New Data Intensify the Agony Over Ecstasy

The controversy over ecstasy—an abused designer drug that may sometimes be a useful aid in psychotherapy—is far from settled, leaving its legal status uncertain

ECSTASY, a potentially dangerous designer drug, appears to be growing in popularity among some college students. At the same time, researchers studying the drug's effects in animals are coming up with disturbing data about its toxicity to brain cells.

Some psychiatrists advocate the use of ecstasy in psychotherapy, but none has ever done a controlled clinical trial with the drug, making its precise toxicity or efficacy in people impossible to determine. The result is a confusing and often contradictory picture of ecstasy's effects, and the turmoil has led to several changes in the drug's legal status (see box).

There appears to be no doubt, however, that in animals ecstasy—also known as XTC, Adam, MDMA, or MDM—produces neurological damage. In rodents and primates, the drug injures a specific population of nerve cells in the brain that use serotonin as a neurotransmitter. "We can give 10,000 times the human dose of LSD to a rat and it does not cause serotonin neurotoxicity. But two to three times the human dose of ecstasy will damage serotonin neurons in the monkey," says Stephen Peroutka of Stanford University School of Medicine. Whether this toxic effect is permanent and whether ecstasy similarly damages neurons in the human brain is still unknown.

To date, no one has done a formal epidemiological study on how widely used ecstasy is. But a recent informal survey at Stanford indicates that about one-third of its undergraduates have used ecstasy at least once. "The most important question now is whether this drug is a human neurotoxin," says Peroutka. "And there may be some anecdotal evidence to suggest that it is."

Ecstasy, or 3,4-methylenedioxymethamphetamine (MDMA), is a drug hybrid—a cross between the hallucinogen, mescaline, and the stimulant, amphetamine. Despite the lack of scientific data about the effects of MDMA in humans, anecdotal accounts of its effects are abundant. "This is a very seductive drug," says Peroutka, who presented information about the drug at the recent Winter Conference on Brain Research.* "Ninety percent of the students who tried the drug said they felt euphoric, more verbal, and had a sense of closeness with other individuals." But during this acute phase of the drug's effects, most users also experience jaw clenching, teeth grinding, and an increased alertness that is not conducive to studying.

The drug causes a distinct hangover and by the second day its negative side effects are pronounced. More than 30% of 369 students in the informal survey reported drowsiness and muscle aches, including sore jaw muscles. About 20% reported depression and difficulty concentrating. Although students often use the drug at parties, they avoid school nights because the effects the second day can be so bad, says Peroutka. And, with subsequent use of MDMA, the "good" effects often decrease and the "bad" ones can magnify.

These effects, both acute and delayed, are somewhat similar to those described by Richard Ingrasci of Watertown, Massachusetts, a psychiatrist in private practice. Ingrasci strongly advocates the use of MDMA in psychotherapy and has testified at the Drug Enforcement Administration (DEA) hearings that one or two doses of the drug can be remarkably effective in helping patients gain needed insight that they may not otherwise achieve.

"Over a 5-year period, I administered MDMA to individuals and couples—about 250 people in total," says Ingrasci. "The drug eliminates anxiety and defenses. People were able to achieve insight into their emotional makeup."

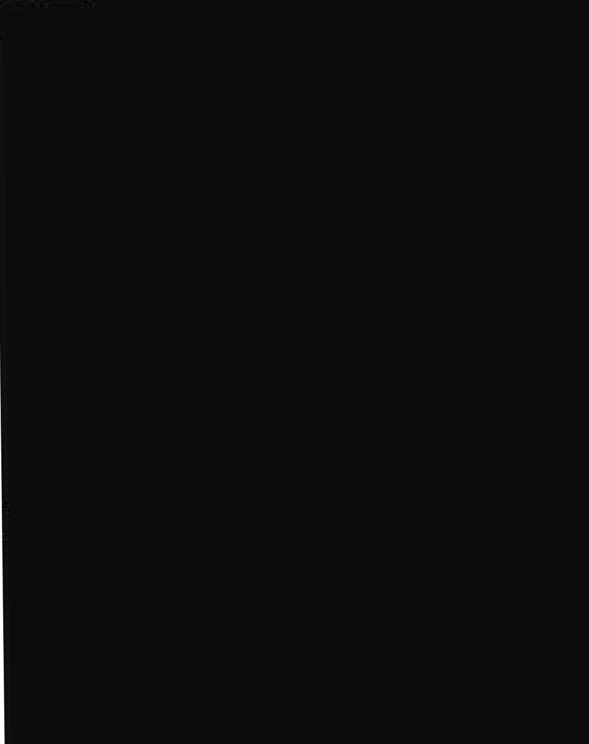
According to a spokesman for the American Psychiatric Association, which has more than 34,000 members, very few psychiatrists have ever administered MDMA to patients as an adjunct to psychotherapy.

Other anecdotal information indicates that MDMA and a closely related drug were associated with five deaths in humans. But neither MDMA nor MDEA (3,4-methylenedioxyethamphetamine) could be pinpointed as the direct cause of any of the deaths. Reporting in the 27 March 1987 issue of the *Journal of the American Medical Association*, Graeme Dowling of the universities of Calgary and Alberta in Canada and his colleagues wrote, "Death as a consequence of the use of these drugs appears to be rare, but it does occur; this outcome may be more common in individuals with underlying cardiac disease."

The most concrete information about the biological action of MDMA comes from animal studies. George Ricaurte of the Institute for Medical Research in San Jose, California, and his colleagues find that in rats and monkeys, repeated injections of MDMA selectively destroy the endings of nerve cells in the brain that release serotonin, also called 5-hydroxytryptamine, as a neurotransmitter. But research also shows that different animal species vary in their response to the drug.

"The monkey is much more sensitive to MDMA, with respect to serotonin depletion, than the rat," says Ricaurte, who also

*The Winter Conference on Brain Research was held from 23 to 30 January at Steamboat Springs, Colorado.



Damaged neurons. *Bright areas in sections through rat brain stem show (A) normal staining for serotonin uptake sites and (B) decreased staining in MDMA-treated rat. The bright areas in the midlines of both brains indicate that, in the rat, cell bodies of serotonin neurons are relatively unaffected by MDMA.* [*Photo courtesy of E. De Souza and G. Battaglia*]

spoke at the meeting. "We see a dose-response effect with the drug. The highest dose in monkeys [which is about two to three times the human dose] produces a 90% depletion of serotonin nerve terminals. And in the cell bodies of neurons in the dorsal raphe nucleus, a group of nerve cells located at the base of the brainstem, we see abnormal inclusion bodies. So in the monkey, MDMA has effects on nerve cell bodies, not just on the terminals."

In their most recent experiments, Ricaurte, Lou DeLanney, Ian Irwin, and William Langston, also of the Institute for Medical Research, find that a single oral dose of MDMA does produce toxicity on serotonin neurons in the monkey. This dose is two to three times higher than a typical single dose taken by a person. "The oral route is at least one-half as effective as the injected route for the drug," says Ricaurte. "The single dose is less toxic but it still produces a 30% depletion of serotonin neurons, so the effect is smaller and it is not as widespread." Ricaurte and his colleagues measured these effects 2 weeks after giving the monkeys a single oral dose, a time at which he believes any neurotoxic effects should be evident and any pharmacological effects of the drug should have worn off. What Ricaurte does not know, however, is how long the effects on serotonergic cells last. "At the present time we have no idea how permanent these damaging effects are," he says.

Errol De Souza of the National Institute on Drug Abuse and the Johns Hopkins University in Baltimore and Thomas Insel of the National Institute of Mental Health have monitored the behavioral effects of repeated doses of MDMA in monkeys. "For the first couple of days, there is no obvious change in behavior," says De Souza. "But on the third and fourth days, the monkeys just don't sleep. This is very characteristic of depletion of serotonin." In addition, De Souza notes that after injection of a single low dose of MDMA comparable to the amount a person takes, the monkeys become extremely passive. "They stop exploring their environment and we see changes in self-grooming behavior," he says.

According to Ricaurte, the behavioral effects of ecstasy are likely to be subtle because it interacts with serotonergic neurons. "One of the unique features of the serotonin system in the brain is that it sends out widely diffuse fibers that touch nearly every part of the neocortex," says Ricaurte. "Because of this widespread innervation, serotonin appears to regulate mood and play a role in cognition, sleep, food intake, aggressive behavior, sexual activity, and perception of pain. And with every one of these behaviors,

Legal Limbo for Ecstasy

The legal status of ecstasy has just changed for the third time in less than 3 years. At issue is whether the drug should be classified as a Schedule I controlled substance, which would ban all medical use without explicit permission from the Food and Drug Administration (FDA).

No pharmaceutical company makes ecstasy and the FDA has never approved it. Only one research protocol has been submitted to test ecstasy but it was dropped after the Drug Enforcement Administration (DEA) classified the drug as a Schedule I compound in 1985. Now, in the light of new data about the drug's neurotoxicity, chances of human studies on ecstasy's medical potential seem unlikely. The drug is currently in a state of legal limbo because a recent court ruling forced the DEA to remove ecstasy from its list of Schedule I substances.

Ecstasy, or MDMA (3,4-methylenedioxymethamphetamine), was first developed in 1914 by E. Merck in Darmstadt, Germany, as an appetite suppressant but was never marketed. Until about 4 years ago, the drug was not a controlled substance. Psychiatrists who gave it to their patients made it or had it made in private laboratories. But in July 1984, the DEA proposed that the drug be added to its list of Schedule I substances. The DEA classifies a substance as Schedule I if it has no accepted medical use, it is believed to have a high potential for abuse, and it has not been shown to be safe even if given under medical supervision. (Heroin and LSD are identified as Schedule I substances.)

The DEA's scheduling announcement for MDMA prompted a small group of psychiatrists who advocate its use in psychotherapy to request hearings on the drug. These began in January 1985, but in their midst, DEA classified MDMA in Schedule I on an emergency basis. This occurred, says Frank Sapienza of DEA, because of increasing reports that MDMA was being abused, and because researchers were reporting that MDA (3,4-methylenedioxyamphetamine), the compound from which MDMA is derived, is toxic to a population of brain neurons in rodents.

Meanwhile, the DEA hearings on MDMA's permanent classification continued. "MDMA is extremely gentle and remarkably effective for helping people to gain insight about themselves," says Richard Ingrasci, a psychiatrist in private practice in Watertown, Massachusetts. "Reports that people have panic attacks or other problems after taking the drug are probably true, but are very rare. This is a compound that needs to be researched."

The DEA asked Joel Kleinman, a psychiatrist and neuropharmacologist at the National Institute of Mental Health, to review the testimony of the psychiatrists who advocated the use of MDMA and give his opinion. "Although these reports make interesting reading, their lack of scientific design, methodology, and controls makes them scientifically unsound," Kleinman wrote in his testimony. He emphasized that the psychiatrists who testified had only anecdotal data to show that MDMA had a medical benefit.

The administrative law judge at the DEA hearings recommended that MDMA should be classified, not as Schedule I, but as a Schedule III compound. This was the classification sought by the psychiatrists who were advocates of MDMA because it meant that the drug had an accepted medical use. But in November 1986, the DEA administrator permanently classified MDMA as a Schedule I substance.

That was still not the final word, however. Lester Grinspoon of Harvard Medical School then contested the Schedule I status of MDMA in the Federal Court of Appeals in Boston. He appealed on the basis of his own experience with MDMA, and his long-standing conviction that psychiatrists should be free to explore the use of mind-altering drugs in psychotherapy. Last fall, the Boston court ruled in favor of Grinspoon and in January of this year, the DEA removed MDMA from its list of Schedule I substances.

"The point that came out of the court's ruling is not that MDMA should be removed from Schedule I, but that the DEA used an inappropriately narrow standard to determine what acceptable medical use of a compound is," says Sapienza. MDMA is now back in the DEA administrative office awaiting further review. A decision on its permanent classification is expected within the next month. ■ DMB

serotonin is thought to play an inhibitory role." Ricuarte reasons that if MDMA depletes the serotonin system in the human brain as it does in the monkey and rat brain, the removal of serotonin's influence might account for its disinhibiting effects in people.

Perhaps the most pressing scientific issues about MDMA concern its mechanisms of action. For example, why do people quickly develop a tolerance to the desirable effects of MDMA but not to the undesirable effects? Is there a relationship between the first- and second-day effects of MDMA in people and the toxicity evident 2 weeks after drug administration to animals? Is the toxicity permanent or can neurons recover? Is MDMA or a metabolite responsible for the observed effects in animals and people? And do the (+) and (−) isomers of MDMA, both of which are present in most preparations of the drug, differ in their biological effects?

As yet, researchers can only speculate about most of the answers. "The initial 'high' with MDMA is probably due to serotonin release," says Peroutka. He proposes that MDMA stimulates the release of serotonin from neurons, particularly those in the dorsal raphe. (A neighboring group of nerve cells in the median raphe nucleus also produces serotonin but is curiously unaffected by MDMA toxicity.) Under normal conditions, this initial depletion of serotonin from dorsal raphe neurons would be accompanied by reuptake of the transmitter into the terminal endings of the nerve cells that released it. Perhaps MDMA somehow alters the uptake process and the nerve cells remain depleted of serotonin.

As a result of Stanford's experience with MDMA use among its undergraduates, the university is planning an information program for its students. Because MDMA causes such specific neurological damage, researchers may use the drug as a tool with which to probe the function of serotonin in the brain, which is still not well understood. At this point, however, it does not seem likely that any clinical testing of the drug will be pursued. ■ DEBORAH M. BARNES

ADDITIONAL READING

A. T. Shulgin, "The background and chemistry of MDMA," *J. Psychoact. Drugs* 18, 291 (1986).
G. Ricaurte, G. Bryan, L. Strauss, L. Seiden, C. Schuster, "Hallucinogenic amphetamine selectively destroys serotonin nerve terminals," *Science* 229, 986 (1985).
S. J. Peroutka, "Incidence of recreational use of 3,4-methylenedimethoxymethamphetamine (MDMA, 'Ecstasy') on an undergraduate campus," *N. Engl. J. Med.* 317, 1542 (1987).
C. J. Schmidt, "Neurotoxicity of the psychedelic amphetamine, methylenedioxymethamphetamine," *J. Pharmacol. Exp. Therap.* 240, 1 (1987).
G. Ricaurte, L. DeLanney, I. Irwin, W. Langston, "Toxic effects of MDMA on central serotonergic neurons in the primate: Importance of route and frequency of drug administration," *Brain Res.*, in press.

Dear Editor, March 1 1988

It was agonizing to read your report concerning MDMA research (Feb.19, p 864-6). The Multidisciplinary Association for Psychedelic Studies, Inc. (MAPS), a non-profit scientific research and educational corporation that I direct has a Drug Master File for MDMA at the FDA, and I serve to coordinate the efforts of researchers who wish to actually use MDMA in their studies. Also, Dr. Ricaurte's primate studies that you mention have been partially funded by MAPS, as well as a study he is currently conducting wherein 29 MDMA users have volunteered to have spinal taps, in order to have their cerebrospinal fluid analyzed for neurotransmitter metabolite levels, and then compared to levels of a control group.

The statement in the sidebar, "Legal Limbo for Ecstasy," that only one research protocol has been submitted to the FDA seeking permission to conduct MDMA research is inaccurate and extremely ironic. Researchers from Harvard Medical School, University of California San Francisco Medical School, and University of New Mexico Medical School have all submitted IND applications to the FDA, and have all been denied permission to procede. These protocols have never been dropped due to DEA scheduling, and new data concerning neurotoxicity will soon be submitted to the FDA in support of these IND applications.

Two additional treatment protocols have been submitted to the FDA, and have been dropped. One of these was for the treatment of pain in a cancer patient who had previously been successfully treated with MDMA prior to its scheduling, and the other was for the treatment of unipolar depression in a patient for whom all alternative treatments had failed. Both of these protocols were dropped because the patients died after the FDA refused to permit MDMA to be used in either of these cases, citing the danger of possible neurotoxicity.

As for MDMA neurotoxicity, an extremely important fact was totally overlooked in the article. Millions of doses of MDMA have been consumed over the last fifteen years in the United States alone, and there is not one single documented case of anyone suffering any neurological complications as a result of their MDMA use. This does not mean that MDMA, when taken orally in therapeutic doses, doesn't possibly reduce serotonin. This simply means that if it does, there is no evidence of any functional or behavioral correlates of such changes. Even if researchers eventually find that certain doses of MDMA can reduce serotonin, calling that reduction of serotonin "damage", in the absence of evidence of harm, is extremely premature and prejudicial. Additionally, although the article quoted Errol De Souza concerning his observations of the behavioral effects of acute administration of injected MDMA in primates, his study in rats which demonstrated recovery of nerve cell functioning after MDMA neurotoxicity was not mentioned. (Battaglia, G.; De Souza,E.B. New Perspectives on MDMA (3,4, methylenedioxymethamphetamine). Substance Abuse, in press.)

What struck me as most ironic of all was the juxtaposition of two ideas in the story. We are told that it does not seem likely that clinical testing of MDMA will be pursued, and yet we are also told that unless controlled clinical trials are conducted it will be impossible to precisely determine human toxicity or efficacy. MDMA deserves to be researched, and then we can simply let the facts speak for themselves.

Sincerely,

Rick Doblin

SCIENCE

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29 March 1988

Mr. Rick Doblin
Multidisciplinary Association for
Psychedelic Studies
2105 Robinson Avenue
Sarasota, FL 33582

Dear Mr. Doblin:

Thank you for your letter of 1 March. I regret to say that we have decided not to publish it, as it is not possible to document many of your statements. We do, however, appreciate your interest and will keep your comments in mind should additional articles be prepared on MDMA research.

Yours sincerely,

Christ Gilbert

Christine Gilbert
Letters Editor

CG:jp

Dear Christine Gilbert, March 31,1988

I greatly appreciate the time that you took to speak with me today about the letter that I wrote concerning the article on MDMA. You had some questions concerning the documentation of certain claims that I made. I am enclosing a copy of the correspondence between the FDA and myself in regards to four IND applications that were submitted to them, and denied permission to procede. Three of the applications themselves are included in the package, the fourth by Dr. Francesco Di Leo was on behalf of my grandmother and is quite lengthy and is enclosed seperately. I am also enclosing several letters from the FDA and from Dr. Windom, the Assistent Secretary for Health, concerning her IND application.

A fifth IND had been submitted to the FDA by Dr. George Greer on behalf of a cancer patient that had been successfully treated for pain with MDMA, when it was still legal. The IND was denied, and then later was withdrawn after Dr. Greer's patient died.

If you wish to shorten my letter, I have a few suggestions. The first paragraph identifying myself could be dropped, and the third paragraph could also be dropped with the addition of one sentence to the end of the second paragraph stating "Two additional treatment IND applications were also submitted, unsuccessfully, to the FDA. They were withdrawn only after both patients died". The final paragraph commenting on the irony of the juxtaposition of several comments in the article could also be dropped, although I think that short paragraph pretty much sums up the current situation concerning MDMA research.

Thank you for seriously considering this controversial subject. If there are any further statements I made that you would like documented, or if you have any questions at all, please feel free to call me at (813) 921-1624 at any time.

Sincerely,

Rick Doblin