Hall. MDMA RANDALL '92

Ecstasy-Fueled 'Rave' Parties Become Dances of Death For English Youths

THE ILLEGAL designer drug ecstasy—promoted by some as a safe, nontoxic means to "warm, loving relaxation"—has killed at least 15 young people in England in the last 2 years and caused severe toxicity in numerous patients, experts report from that country's National Poisons Unit. In almost every case, a recreational dose of the drug had been taken at a dance club or party where crowds danced vigorously in popular, all-night dance sessions called "raves."

In most of the serious cases reported, the users had collapsed unconscious or started to convulse while dancing. By the time they were noticed and taken to emergency departments, their body temperatures had soared as high as 110°F (43.3°C), their pulses were racing, and their blood pressures were plummeting. These patients with severe toxicity usually developed disseminated intravascular coagulation, rhabdomyolysis, and acute renal failure. Despite treatment, death sometimes ensued from 2 to 60 hours after admission, usually due to severe hyperthermia accompanied by disseminated intravascular coagulation.

Severe or fatal reactions of this type are virtually undocumented in the US drug abuse literature concerning ecstasy (also known as MDMA for its chemical name, 3,4-methylenedioxymethamphetamine). But this pattern of illness has recently become all too familiar in British medical journals (*J R Soc Med.* 1991; 84:371; *J R Soc Med.* 1992;85:61; *BMJ.* 1992;305:5,6,29; *BMJ.* 1992;305:309-310; and *Lancet.* 1992;339:677-678).

The most recent report, published 6 weeks ago, describes seven fatalities, all associated with rave dances (*Lancet.* 1992;340:384-387). The report also describes seven cases of unexplained hepatotoxicity (including one death) attributed to a history of ecstasy use.

According to the authors, the pattern of illness and the amounts of MDMA ingested rule out the possibility of an overdose. In most cases the user had taken only a few tablets or capsules. By comparison, one analytically documented MDMA overdose—allegedly 42 tablets taken at home—was accompanied by no symptoms other than a "hangover" with tachycardia and hypertension. The patient's plasma MDMA level was 7.72 mg/L, which is six to 70 times greater than the plasma levels measured in the fatal cases.

John Henry, MD, consulting physician for the National Poisons Unit at Guy's Hospital, London, England, and lead author of the most recent *Lancet* report, says that prolonged, vigorous dancing (which may itself be an effect of MDMA) may compound the pharmacologic effects of the drug. The amphetamine-derived MDMA has been shown to increase body temperature in rats, presumably by interfering with serotonin metabolism in the brain.

Higher ambient temperatures seem to intensify this effect, and the hot, poorly ventilated environments of some nightclubs, together with inadequate fluid replacement, may be sufficient to elevate body temperature to lethal levels in susceptible individuals, Henry suggests.

The finding has relevance for the international medical community because the rave culture is now being exported to the United States and other countries (see accompanying article). Henry urges physicians to be aware of the drug's pharmacologic effects when it is combined with this type of dancing. Cases of severe hyperthermia or unexplained jaundice or hepatomegaly should suggest possible MDMA toxicity, he says.

For the patient who is taken acutely ill, medical treatment is urgent and includes control of convulsions, measurement of core temperature, rapid rehydration, active cooling measures, and possibly use of the antispasmodic drug dantrolene (*Anaesthesia.* 1991;47:686-687).

A 'Cultural Reformulation'

Of great interest to Henry is how the drug has been adopted by, and has perhaps even catalyzed, the new rave culture in England—similar, he says, to the Acid Test parties of the 1960s and the use of LSD (lysergic acid diethylamide) and amphetamines. The drug's association with the rave scene has led to its enormous popularity in England. An estimated half-million people in that country have taken MDMA, he says, most of them young people.

MDMA use had been widespread in both the United States and England throughout the 1980s, but in a much different context, and with different outcomes. Users usually took it while they were alone or with a small group of people. Ninety percent of users in one US study said the drug made them feel euphoric, more verbal, and closer to other individuals. Some called it the "love drug."

In a study done at Stanford (Calif) University School of Medicine in 1987—at the peak of the drug's popularity in the United States—39% of the undergraduates reported they had used MDMA at least once (*N Engl J Med.* 1987;317:1542-1543).

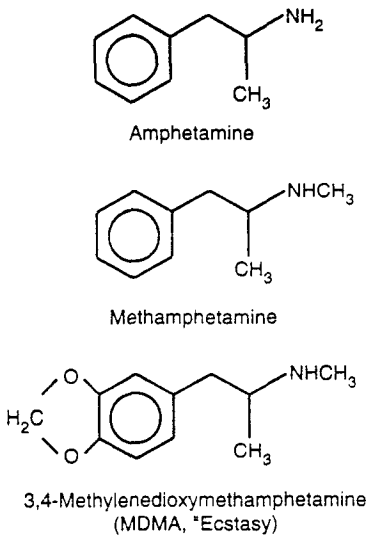
In the late 1980s, the drug was " 'reformulated,' " Henry says, "not in the pharmacologic sense, but in the cultural sense." The rave scene in England provided a "new 'formula,' a new package, a new culture." And it is this new cultural context that has, unfortunately, provided a real-life showcase for ecstasy's previously unknown lethal potential.

Before this "reformulation," the handful of reported fatalities were mostly cardiac arrhythmias in individuals with underlying natural disease (*JAMA.* 1987; 257:1615-1617).

Many users did experience adverse effects, however. In a 1986 study, 29 volunteers were given 75 mg to 150 mg (a "recreational dose") of pure MDMA by psychotherapists (*J Psychoactive Drugs.* 1986;18:319-327). All 29 experienced undesirable physical symptoms: 28 lost their appetite, 22 had trismus or bruxism, nine had nausea, eight had muscle aches or stiffness, and three had ataxia. Sweating was common, and tachycardia and hypertension were recorded. Afterward, 23 people noted fatigue for hours or days, and 11 had insomnia.

The mechanism by which MDMA elevates body temperature is still a matter of speculation, although experts suspect it involves the drug's interference with serotonin metabolism in the brain. In experimental animals, MDMA stimulates the release of this neurotransmitter from serotonergic neurons, particularly from those in the dorsal raphe. Under normal conditions, released serotonin is taken up into the terminal endings of the cells that released it. But in the presence of MDMA, this reuptake process is altered, leaving the nerve cells depleted of serotonin.

The waters are muddied, however,



Structural formulas of amphetamine, methamphetamine, and MDMA ("Ecstasy").

when one looks at clinical experience. Some experts have argued that there is no clinical evidence that people who use MDMA develop such typical symptoms of serotonin depletion as disorders of sleep, mood, and sexual function (*Arch Gen Psychiatry*. 1990;47:288-289).

Lewis Seiden, PhD, professor of pharmacology at the University of Chicago, Ill, conducted extensive research on the neurotoxicity of MDMA in the mid-1980s. When he heard of the recent reports of fatalities associated with the use of the drug in English nightclubs, he was reminded, he says, of a well-established phenomenon in amphetamine research called "aggregation toxicology": One solitary rat or mouse given an injection of amphetamine will survive. But several animals, confined in a small cage and given the identical dose of amphetamine, will die.

Over the years, one of several proposed explanations for this phenomenon has been amphetamine-induced hyperthermia, Seiden says.

On the other hand, one "can't make the assumption the MDMA is just a fancy form of amphetamine," points out Steven Karch, MD, research director of the Trauma Center at the University Medical Center of Southern Nevada, Las Vegas. "The molecules are very close structurally [figure]. But then again, all stimulants look roughly the same."

Seiden also speculates that because MDMA is such a potent serotonin-releasing agent in the brain, it might also effect serotonin-releasing cells elsewhere in the body. Ninety percent of the serotonin in the body is located outside the brain, much of it in the gut and mast cells, he says.

The Long Road to Rave

MDMA has a long, controversial history that spans nearly a century, says Karch, who is also editor of the *Forensic Drug Abuse Advisor*.

The patent for MDMA was initially granted in 1914 to E. Merck in Darmstadt, Germany, as an appetite suppressant. The compound's toxicology wasn't systematically studied until the early 1950s, under a US Army contract with a group at the University of Michigan, Ann Arbor. The results of these studies were eventually declassified and published in 1973, when it was revealed that MDMA is somewhat less toxic than MDA (another amphetamine derivative), but more toxic than the hallucinogen mescaline (*Toxicol Appl Pharmacol*. 1973;25:299-309).

No pharmaceutical company has ever made MDMA, nor has the Food and Drug Administration approved it. A small number of psychiatrists have advocated its use in therapy, based on the belief that it lowers patients' defenses and promotes trust and confidence.

In 1985, after several studies showed neurotoxicity in animals, the Drug Enforcement Agency classified MDMA as a Schedule I compound. Schedule I compounds, such as heroin and LSD, are believed by the agency to have a high potential for abuse and no currently accepted medical use.—by Teri Randall

'Rave' Scene, Ecstasy Use, Leap Atlantic

THE BRITISH rave counterculture, and its liberal use of ecstasy (MDMA), has become a hot export to the United States, wrapped in a high-tech music and video package and supported by low-tech laboratories that illicitly produce the drug stateside.

An August 19, 1992, article by United Press International says that a clampdown on rave parties by British authorities has inspired several English rave promoters to move their business to the United States. Staged in empty warehouses or open fields outside San Francisco or Los Angeles, their parties are drawing thousands of young Californians on designated weekend nights.

Partygoers—attired in *Cat in the Hat*–hats and psychedelic jumpsuits—pay $20 at the door to dance all night to heavily mixed, electronically generated sound, surrounded by computer-generated video and laser light shows. They pay another $3 to $5 for "smart drinks"—amino acid–laced beverages that reputedly enhance energy and alertness. And for another $20, those so inclined can purchase an ecstasy tablet (see accompanying article).

Many observers can't help but draw comparisons to the LSD-laced "human be-ins" of a quarter-century ago. The scene has come full circle, they add, noting that several Los Angeles raves have been hosted by Timothy Leary's son. The elder Leary, a former Harvard professor who advocated the use of LSD (lysergic acid diethylamide) three decades ago, has made several appearances at his son's raves, calling them "high-tech Acid Tests."

Large raves also have been staged in New York, NY, and other urban centers in the United States. Their popularity is increasing in parts of India, Indonesia, Belgium, and New Zealand, and a promoter is working to popularize the scene in Sweden, United Press International reports.

So far, there appear to be no published reports of death or severe toxicity caused by MDMA use.

Most of the MDMA available in England is supplied by clandestine laboratories in the Netherlands. In the United States, the drug is made predominantly on the West Coast by small-scale operators, says Joseph Bono, supervisory chemist, special testing, Drug Enforcement Agency.

The synthesis of MDMA requires minimal knowledge of chemistry. Illicit laboratories are often set up in kitchens, mobile trailers, or garages with little concern for cleanliness. Reactions may be set up in cookie jars. Solid products may be removed with coffee filters; and the coffee filter may be thrown back into the reaction vessel for a second synthesis step (*J Forensic Sci*. 1988;33:576-587). Bono detects a lot of contaminants and by-products in the samples that reach his laboratory for analysis.

"We're not dealing with Smith, Kline, and French here. We're dealing with people who are just interested in turning out a product," Bono says. "If it assays at 50% as opposed to 100% or 95%, they don't really care. And what is that other 50%? Who knows?"

—by Teri Randall