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DECONSTRUCTING ECSTASY: THE POLITICS OF MDMA RESEARCH

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What is *Ecstasy*? Defined by the New Webster's Dictionary as a state of intense overpowering emotion, a condition of exultation or mental rapture induced by beauty, music, artistic creation or the contemplation of the divine, ecstasy derives etymologically from the ancient Greek *ekstasis*, which means flight of the soul from the body. The anthropologist, Mircea Eliade, who explored the roots of religious experience in his book *Shamanism: Archaic Techniques of Ecstasy*, has described the function of this intense state of mind among aboriginal peoples. Select individuals are called to become shamans, a role specializing in inducing ecstatic states of trance where the soul is believed to leave the body and ascend to the sky or descend to the underworld. The shaman is thus considered a "technician of the sacred", having been initiated through a process of isolation, ritual solitude, suffering and the imminence of death. Such initiation into the function of ecstatic states of consciousness, always accompanied by comprehensive tutelage from tribal elders, allows the shaman to assume for his tribal group the vital role of intermediary, or conduit, between the profane world of everyday existence and the sacred domains of alternative reality (Eliade, 1951; Schultes and Hofmann, 1992).

Modern conceptualizations of ecstasy, however, have expanded far beyond the realm of scholarly inquiry on archaic religions to the reach of contemporary cultural politics and scientific inquiry. As a cultural

commodity, ecstasy has become emblematic of a social movement attracting increasing numbers of disaffected youth in Europe and North America. Meeting together in the hundreds and the thousands, large groups of young people have congregated to engage in collective *trance dances*, or *raves*, often fueled by the ingestion of a synthetic psychoactive substance, known as *Ecstasy*. Arousing apprehension among parents and civic authorities, perplexed by this changing pattern of behavior among youth, the phenomenon of *ecstasy* culture has riveted societal concern on the potential dangers of its increasingly notorious chemical sacrament. In spite of substantial media coverage, along with millions of federal dollars for basic science research on neural mechanisms for possible brain injury caused by *Ecstasy*, however, full understanding of both its medical consequences and cultural impact have remained elusive.

Even within the current social context of harsh Drug War era legal penalties, *Ecstasy* use has climbed sharply among young people. A vast and unanticipated social experiment has occurred, with millions of adolescents and young adults worldwide consuming a drug which has eluded definitive understanding and over which societal and medical controversies persist. Given the magnitude of public health and cultural implications, an open and comprehensive review of the existing state of knowledge, from diverse perspectives, needs to be pursued. The outcome of such an inquiry into this modern rendering of the archaic technique of ecstasy should facilitate a more effective and salutary understanding and response to the condition Euro-American medicine and culture currently confront.

SOCIAL HISTORY

Since the early 1980s, the drug *Ecstasy* has commonly been considered to be 3,4-methylenedioxymethamphetamine (MDMA), though this identification has become increasingly problematic over the last decade. Classified as a phenethylamine, MDMA chemically has been noted to have structural similarities to both amphetamine and the hallucinogen, mescaline, as well as the essential oil safrole, found in sassafras and nutmeg. Though patented by Merck Pharmaceuticals in Germany prior to the First World War, MDMA was not explored

in animal models until the 1950s, when the U.S. Army Intelligence undertook the serial investigation of a variety of psychoactive compounds with potential "brain washing" application. MDMA itself was never administered to humans during this Cold War inspired phase of investigation, and remained unexplored until the 1970s. Its more hallucinogenic and longer acting analogue, 3,4-methylenedioxyamphetamine (MDA), however, was the object of official investigation as part of the infamous MK-ULTRA program of the fifties and sixties and had been administered to Army "volunteers", including one who was inadvertently overdosed and killed. Initial scientific investigations of MDMA itself occurred during the 1970s following the termination of military involvement, and were conducted by university and industry based medicinal chemists. Researchers, extending their inquiries to the effects on humans, were enthusiastic over the drug's unique psychoactive profile. The development of a new class of centrally active compounds was proposed, one with suggested therapeutic capacities, which would be named Entactogens. after a salient psychological feature of the drug, its capacity "to touch within". (Shulgin, 1986; Shulgin, 1990; Shulgin and Nichols, 1978; Shulgin and Shulgin, 1991).

Early scientific investigators, though without formal psychological schooling, were struck by MDMA's capacity to help people open up and talk honestly about themselves and their relationships, without defensive conditioning intervening. For several hours anxiety and fear appeared to melt away, even in subjects who were chronically constricted and apprehensive. By the late 1970s, a small number of mental health professionals had been introduced to the drug's range of psychoactive effects. Particularly impressed by MDMA's capacity to induce profound states of empathy, one of the strongest predictors of positive psychotherapeutic outcome, these first psychologists and psychiatrists who encountered the drug believed they had come across a valuable new treatment. First called *Adam*, to signify "the condition of primal innocence and unity with all life", MDMA augmented therapy functioned by reducing defensive barriers, while enhancing communication and intimacy. Hailed as a "penicillin for the soul", MDMA was said to be useful in treating a wide range of conditions, including post-traumatic stress, phobias, psychosomatic disorders, depression, suicidality, drug addiction, relationship difficulties and the psychological distress of terminal illness (Adamson, 1985; Adamson

and Metzner, 1988; Grinspoon and Bakalar, 1986; Greer and Tolbert, 1986; Downing, 1986; Riedlinger and Riedlinger, 1994).

Conscious of the lessons of history from the 1950s to the early 1970s, when researchers had been prevented from continuing their promising investigations of hallucinogen treatment models because of the cultural reaction to their spread among young people, efforts were initially undertaken to restrict the flow of information on MDMA. Hoping to avoid the fate of LSD and maintain MDMA's still legal status, its use for several years remained limited to a relatively small group of pharmacologists and health professionals. MDMA's advantages over the better-known hallucinogens as a putative psychotherapeutic adjunct were also noted. Compared to LSD, the prototype hallucinogen of the twentieth century, MDMA was a relatively mild, short-acting drug capable of facilitating heightened states of introspection and intimacy along with temporary freedom from anxiety and depression, yet without distracting alterations in perception, body image and sense of self. MDMA had neither the pharmacological profile nor the provocative reputation of LSD and, so they hoped, would not suffer the fate of political reaction and legal censure as the hallucinogens had in the late 1960s (Grof, 1990; Bakalar and Grinspoon, 1990; Grob, 1998).

It proved difficult, however, to keep MDMA a secret. Catalyzed by the call for hearings challenging the proposed scheduling of MDMA by the DEA, sensationalized media reports about a new psychotherapeutic "miracle medicine" began to attract the interest of drug dealers suddenly aware of the large potential profits to be made selling MDMA to young people. Soon, MDMA began to emerge as an alternative recreational drug on some college campuses, particularly in California and Texas, where for a period of time MDMA replaced cocaine as a new drug of choice. Although still popular as *Adam* among psychotherapists, MDMA now acquired a new name among youth, *Ecstasy*. In point of fact, the transformation of *Adam* into *Ecstasy* appears to have been a marketing decision reached by an enterprising distributor searching for an alternative code name, who concluded that it would not be profitable to take advantage of the drug's most salient features. "*Ecstasy* was chosen for obvious reasons," this individual later reported, "because it would sell better than calling it *Empathy*. *Empathy* would be more appropriate, but how many

people know what it means?" (Eisner, 1989; Beck and Rosenbaum, 1994).

The days of MDMA being the singular tool among an underground of informed psychotherapists were over. Now popularly known as *Ecstasy*, MDMA had been appropriated by the youth culture for use as a recreational drug. Spurred by media accounts reporting on both its suggested role in treatment and its new reputation as a "fun drug" among the young, use of MDMA spread. By the mid-1980s the inevitable political response began to take form. With the clear intention of tightening the federal regulatory controls of what was still a legal drug, the U.S. Drug Enforcement Administration (DEA) invoked the Emergency Scheduling Act and convened formal hearings in 1985 to determine the fate of MDMA. These highly publicized hearings, however, achieved the unintended effect of further raising public awareness of the new *Ecstasy* phenomenon, and led to marked increases in manufacturing and marketing of the drug. Media accounts polarized opinion, pitting enthusiastic claims of MDMA by proponents on the one hand, versus dire warnings of unknown dangers to the nation's youth on the other. Coverage of the MDMA scheduling controversy included a national daytime television talk show (the Phil Donahue program) highlighting the surprise disclosure by a prominent University of Chicago neuroscientist that recent (but as yet unpublished) research had detected "brain damage" in rats injected with large quantities of MDA (3,4-Methylenedioxyamphetamine), an analogue and metabolite of MDMA. Public debate was further confounded by the frequent confusion of MDMA with MPTP (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a dopaminergic neurotoxin that had recently been shown to have induced severe Parkinson's-like disorders in opiate addicts using a new synthetic heroin substitute. With growing concerns over the dangers of new "designer drugs," public discussion took an increasingly discordant tone (Beck and Morgan, 1986).

In the spring of 1985, a series of scheduling hearings on MDMA were conducted by the DEA in several U.S. cites where a collective of physicians, psychologists, researchers and lawyers gave testimony that MDMA's healing potential should not be lost to the therapeutic community. After hearing the dueling sentiments expressed by federal regulators and by those opposed to controls, the DEA administrative

law judge presiding over the hearings determined on the weight of the evidence presented that there was in fact sufficient indication for the safe utilization of MDMA under medical supervision and recommended Schedule III status. Not obliged to follow the recommendations of his administrative law judge, however, and expressing grave concerns that MDMA's growing abuse liability posed a serious threat to public health and safety, the DEA director overruled the advisement and ordered that MDMA be placed in the most restrictive category, Schedule I. Since then, with the exception of a three month period in late 1987 and early 1988 when it was briefly unscheduled due to a court challenge, MDMA has remained classified as a Schedule I substance (Young, 1986; Lawn, 1986).

In the decade following the MDMA scheduling controversy, patterns of use experienced a marked shift. With the failure to establish official sanction for MDMA treatment, most psychotherapists who had used the drug adjunctively in their work ceased to do so, unwilling to violate the law and jeopardize their livelihood through the use of a now illegal drug. In the wake of the highly publicized scheduling hearings, however, use among young people escalated. By the late 1980s interest in *Ecstasy* had spread from the United States across the Atlantic to Europe, where it became the drug of choice at marathon dance parties called *raves*. Beginning on the Spanish island of Ibiza, spreading across the Continent, and then back to the United States, *Ecstasy*-catalyzed *raves* drew increasingly large numbers of young people, often attracting more than 10,000 participants to a single event. Although use in the United States has tended to be cyclical, waxing and waning depending upon an often erratic supply, popularity in Europe remained high through the 1990s. With multiple illicit laboratories, including pharmaceutical manufacturers in former *Iron Curtain* countries, the European youth recreational drug market has been saturated with *Ecstasy* over the past decade (Saunders, 1993; Saunders, 1995; Capdevila, 1995).

By the late 1980s, the *Ecstasy* scene had attained particular prominence among young people in the United Kingdom. Between 1990 and 1995, British authorities estimated that the use of *Ecstasy* increased by over 4,000 percent. Starting in small London dance clubs, word rapidly spread of the euphoric, mood altering properties induced by *Ecstasy*, leading to larger and larger events throughout the British

Isles. Almost overnight an enormous black market for *Ecstasy* was created. Leisure patterns among the young began to change, with *Ecstasy* to an increasing degree replacing alcohol as a generational drug of choice. By the early 1990s, the economic and social certainties of the past in Great Britain had started to change. The free market boom pursued throughout the eighties by the Thatcher government had ended in recession, with increasing unemployment and constricting opportunities, particularly for young people. The freeing of inhibitions, the peer bonding and the sense of community engendered by *Ecstasy's* dance floor pharmacology provided a release from the oppressive social atmosphere and a sense that "all could be made right in the world". The *Ecstasy* scene had become, in the eyes of many observers, the largest youth cultural phenomenon that Great Britain had ever seen (Collin, 1998).

With the rapid expansion of *Ecstasy* culture in the United Kingdom, criminal gangs began to sense the opportunity for amassing large profits and moved in on the developing drug scene, rapidly taking control of the manufacturing and marketing of *Ecstasy*. Motivated solely by financial return and disinterested in the "purity" of the phenomenon, the quality of distributed *Ecstasy* began to erode. Other drugs began to replace MDMA as the sole component of *Ecstasy* pills, including diverse phenethylamine analogues (e.g. MDA, MDE), amphetamines, cocaine, opiates and even the dissociative anesthetic ketamine. The increasing use of amphetamine, sold both openly and as adulterated *Ecstasy*, began to change *rave* culture from a context of communal celebration to one of aggressive euphoria. Ignorance and lack of available information also pervaded the youth *Ecstasy* scene, as dangerous degrees of polydrug use increasingly became the norm. Intent to "prolong the buzz", users began to "stack" multiple doses of *Ecstasy*, along with alcohol and whatever other drugs were available. In just a few years, the *Ecstasy* scene had drifted far from what its earliest proponents had extolled as the gentle opening and spiritual nature of MDMA to the faster paced, increasingly dangerous, anything goes polydrug context of the evolving dance drug industry (Ziporyn, 1986; Buchanan and Brown, 1988; Wolff *et al.*, 1996; Winstock and King, 1996; Furnari *et al.*, 1998).

Although various estimates have been given on the extent of current *Ecstasy* use in the United States and Western Europe, the exact

incidence is not known. Saunders has stated that "millions" of young people in the United Kingdom have taken *Ecstasy*. A Harris Opinion Poll for the BBC in Great Britain presented data that 31% of people between the ages of 16 and 25 admitted to taking *Ecstasy*, most often at dance clubs, and that 67% reported that their friends had tried the drug. In a survey of school children across the whole of England, 4.25% of 14 year olds and, in another survey 6.0% of those aged 14 and 15 were reported to have taken *Ecstasy*. More recently, 13% of British university students questioned about their drug histories admitted to having tried *Ecstasy*. The popular British press has reported that an estimated 500,000–1,000,000 young people in Great Britain take *Ecstasy* every weekend (Harris, 1992; Beck, 1993; Sylvester, 1995; Sharkey, 1996; Saunders and Doblin, 1996; Parrott, 1998).

In the United States, according to a 1993 National Institute on Drug Abuse survey, 2% of all United States college students had admitted to taking *Ecstasy* in the previous 12 months. By the end of the decade, 8% of high school seniors reported having tried *Ecstasy*. A well publicized 1987 interview study of Stanford University undergraduate students reported that 39% had taken *Ecstasy* at least once in their lives. Later controversy revealed, however, that the research design was flawed by using data collected at the Stanford Student Union on Friday and Saturday nights where attractive young research assistants would solicit information from students. A methodologically stronger survey at Tulane University found that 24% of over 1,200 students questioned had experimented with *Ecstasy*. By the early 1990s, *Ecstasy* was described as having the greatest growth potential among all illicit drugs in the United States, with tens of thousands of new users allegedly introduced to the drug every month, particularly within the context of the *rave* scene. (Peroutka, 1987; NIDA, 1993; NIDA, 1999; Newmeyer, 1993; Cuomo *et al.*, 1994; D. J. McKenna, pers. com.).

As *Ecstasy* culture continued to grow in the nineties, youthful adherents were deprived of accurate information about the chemical catalysts they were ingesting. From inadequately informed media and chains of improbable rumor, a number of myths remained in general circulation among young ravers, ranging from beliefs that their coveted drug of choice was entirely safe to other convictions that *Ecstasy* could induce horrific nervous system damage, including the draining of spinal fluid. While media trumpeted sensationalist

accounts of *The Agony of Ecstasy*, a lack of clarity and understanding of the drug's true effects pervaded the youth scene. The knowledge accrued during the period of underground psychotherapy in the late 1970s and early 1980s that with repeated use MDMA's positive effects attenuated and negative side effects accentuated (thus making it the ideal therapeutic agent, to be used sparingly and with minimal abuse potential) had not filtered through to the young denizens of the burgeoning *Ecstasy* culture. Coupled with the omnipotence of youth, this ignorance of the drug's basic psychopharmacology led to wide scale over-use of the drug. As participants returned to weekend dance parties repeatedly from week to week, the prolonged use of *Ecstasy* began to take its toll. Over time and repeated use, the euphoria and the empathy would lessen, to be replaced by a jittery amphetamine-like experience. For days after their night of *Ecstasy* it was not uncommon for *ravers*, particularly those with some underlying vulnerability, to report dysphoric mood and cognitive dulling. Although *Ecstasy* was not physically addictive, certain individuals would demonstrate clear patterns of psychologically compulsive behavior. A *macho ingestion syndrome* typified some young men with a proclivity for ingesting five or more doses at a single setting. Safety limits that had been appreciated by older investigators from a long ago era hoping to develop new tools for healing no longer appeared to be operative in this new post-modern world of youth recreational drug culture.

The preferred mode of *Ecstasy* experience, the dance club setting, also appeared to heighten the risks for young *ravers*. Gathered closely together in crowded environments, often with poor ventilation and high ambient temperatures, large numbers of young people would dance exuberantly late into the night. By the early-1990s, reports of individuals dying of heat stroke during *raves* began to surface. Though relatively small in number compared to the enormous degree of use among youth in the United Kingdom, around 15 fatalities per year have been reported. In each of these cases, *Ecstasy* ingestion was associated with a catastrophic hyperthermic reaction leading to disseminated intravascular coagulation (DIC), rhabdomyolysis, and acute renal and hepatic failure, culminating in death. In contrast to the long forgotten therapeutic model of relaxing in a peaceful setting with easy access to sufficient fluid replacement, many of these tragic events occurred in dance clubs where management restricted supplies

of water in order to increase the sales of soft drinks. In one particularly unscrupulous establishment, the water taps were reportedly turned off in the bathrooms while tap water was sold over the counter at the bar for the price of a beer (Henry *et al.*, 1992; Matthews and Jones, 1992; Randall, 1992).

As awareness grew that *Ecstasy* could under certain circumstances cause injury to users, a movement arose within the *rave* community to ensure greater protection from dangerous influences. Efforts to promote harm reduction practices at *Ecstasy*-fueled dances, however, were solely supported by the community and their adherents. Virtually all government and enforcement agencies, by contrast, have appeared to interpret the harm reduction process entirely through the eyes of legal censure and prohibition. Privately sponsored safe dancing campaigns developed a code of conduct for *raves*, attempting to minimize the degree of risk encountered by young *ravers*. These harm reduction efforts would emphasize the monitoring of air quality and ambient temperature, provision of *chill out* rooms, easy access to cold water taps and the distribution of drug risk information.

Another ominous development of *Ecstasy* culture was the growing awareness that to an increasing degree not all *Ecstasy* was MDMA. Over a relatively short period of time, the shift to clandestine large-scale criminal manufacture and distribution networks had led to a breakdown of quality control. Adulterated black market *Ecstasy* flowed freely through the youth culture. *Ecstasy* could be MDMA (often of low quality), or it could be any one of a variety of other drugs. By the mid-nineties, only an estimated 40% of *Ecstasy* was actually MDMA. Some of this *ersatz Ecstasy* proved to be relatively innocuous, and included aspirin, caffeine and low dosages of ephedrine. Other batches proved to be far more hazardous, however, including the emergence at the end of the decade on both sides of the Atlantic of large quantities of dextromethorphan, a cough suppressant with powerful dissociative properties at higher dosages. Sold as *Ecstasy*, dextromethorphan could induce an overwhelming and prolonged experience. Particularly within the context of a *rave*, dextromethorphan was increasingly recognized as a highly dangerous substance, capable of causing serious medical harm both when taken alone and when taken in combination with MDMA. Besides competing with MDMA for cytochrome p450 2D6 hepatic enzymes, and thus imped-

ing MDMA's metabolism and elimination, dextromethorphan's anticholinergic effects also blocked perspiration, increasing the risk of dangerous overheating. To counter this insidious threat to the health and safety of young *dance* culture aficionados, harm reduction efforts have recently been directed towards providing on-site and affordable qualitative laboratory analyses of *Ecstasy* samples (Shewan *et al.*, 1996; Doblin, 1996; King, 1998; Schifano *et al.*, 1998; Sferios, 1999).

Loathe to be perceived as providing any tacit validation of the *Ecstasy* culture movement, government and health institutions have shunned the harm reduction approach, instead relying upon the message of primary prevention. Young people should simply avoid taking *Ecstasy*, they should *just say no!* To reinforce this zero tolerance strategy, considerable outlays of funding have been directed at establishing the precise mechanisms of destructive action of the drug. The study of MDMA neurotoxicity has received millions of dollars of government research funding over the last decade and a half to elaborate the magnitude of functional and structural injury to animal neurotransmitter systems. Experimentation using human subjects has in contrast received far less support, with none provided for efforts intended to explore the long-neglected MDMA treatment paradigms. While retrospective studies of human *Ecstasy* users have fit nicely into the prevailing belief system that MDMA may cause serious brain injury, it has proved virtually impossible to conduct any investigation of its putative healing capacity. Though never disproven, the MDMA treatment model has never been given the opportunity to test its safety and efficacy in alleviating suffering under ideal controlled circumstances. Efforts to initiate treatment studies on refractory patient populations in the United States have to date not been successful in obtaining final approval from federal regulatory agencies (although the FDA has recently expressed a willingness to approve well-designed treatment studies in refractory patient populations). Three basic Phase 1 prospective studies of normal human volunteers to study psychological effects, physiologic response, pharmacokinetics and neurotransmitter mechanisms have been allowed that administered pure MDMA in hospital research settings in the United States (at Harbor-UCLA Medical Center, the University of California San Francisco School of Medicine and the Wayne State University School of Medicine) (Grob *et al.*, 1996; Tancer and Schuster, 1997; Tancer and Johanson, 1999;

Harris *et al.*, 1999). By contrast, attempts extending from the mid-1980s to the present to use MDMA in controlled treatment protocols have not as yet received approval.

Only in Europe, in Switzerland from 1988 to 1993, were a group of clinical psychiatrists granted permission from their government to treat their patients with MDMA. Although authorities had failed to insist upon the implementation of prospective research designs, a retrospective analysis of treatment outcomes was eventually conducted (Gasser, 1995a; Gasser, 1995b). That study examined MDMA augmented psychotherapy of 121 patients, providing very encouraging results, indicating high degrees of treatment response along with acceptable safety parameters. In spite of those conclusions, subsequent and better designed investigations have not been conducted. Elsewhere throughout the world there have been only two other MDMA treatment protocols which have been submitted to their respective regulatory authorities. One is a study of rape victims with post-traumatic stress disorder at the Universitat Autonoma de Madrid in Spain. The other is a proposed investigation at the Harbor-UCLA Medical Center in the United States of patients with end-stage cancer whose depression, anxiety, alienation and pain have not responded to conventional therapies. A variety of plausible explanations for the failure to initiate formal programs of MDMA treatment research could be suggested, ranging from the need to maintain a political distance from illicit *Ecstasy* use to the long entrenched aversion to associating with the old hallucinogen treatment model. The central obstacle to formal regulatory approval, however, has remained the ongoing focus on the possibility that MDMA causes brain damage. Whether pure MDMA will ever be permitted in an optimally controlled treatment research context might ultimately hinge on the question of neurotoxicity.

NEUROTOXICITY

Pharmacologically, MDMA's site of action is largely within the serotonergic neurotransmitter system. Serotonin (5-hydroxytryptamine, 5-HT) is one of the monoamine neurotransmitters of the brain, and is synthesized from tryptophan through the intermediate compound

5-hydroxytryptophan. Serotonin is synthesized within 5-HT neurons, and is stored in synaptic vesicles. It is released by these vesicles into the synaptic cleft in response to the firing of 5-HT neurons, exerts an effect upon both pre- and post-synaptic receptor sites, and is then taken back up into the 5-HT neuron where it is again stored in synaptic vesicles. The serotonin neurotransmitter system is believed to play a critical role in the regulation of mood, anxiety, sleep, appetite, aggression, sexuality and temperature regulation.

The field of amphetamine analogue neurotoxicity began in the early 1960s, with the discovery that particular drugs were capable of causing severe changes within different neurotransmitter systems. Disruptions of the serotonergic (5-HT) system was first observed to occur in animal models injected with what would become known as the prototype serotonin neurotoxin, para-chloroamphetamine (PCA) (Pletscher *et al.*, 1963). PCA was observed to cause a prolonged decrease in brain concentrations of serotonin and 5-hydroxyindole acetic acid (5-HIAA), the primary metabolite of serotonin, without altering norepineprine or dopamine concentrations. Later studies found that tryptophan hydroxylase (TPH), the rate limiting enzyme in serotonin biosynthesis, was markedly decreased for up to several months following PCA administration (Sanders-Bush *et al.*, 1975).

Since the mid-1980s, evidence has accumulated that MDMA is capable of inflicting major changes on the brain serotonin system in laboratory animals (McKenna and Peroutka, 1990). Preclinical studies have consistently demonstrated that MDMA induces an acute, but reversible, depletion of serotonin. These findings have included time limited but sustained lower levels of serotonin, decreased metabolite (5-HIAA) levels, loss of synthetic enzyme activity (TPH), loss of serotonin uptake and loss of uptake sites for serotonin. Unlike the far more toxic PCA, however, which has been demonstrated in animals to damage serotonergic cell bodies (Harvey *et al.*, 1975), MDMA's effects are limited to axonal projections, with evident sparing of cell bodies. Over time following exposure to repeated, high dose MDMA administration, regeneration of serotonin axons does occur, with a gradual yet measurable increase in axon density (Molliver *et al.*, 1990). Rate of recovery varies depending upon species studied, with rats demonstrating greater degrees of reversible depletion than monkeys.

The impact on serotonin systems in laboratory animals subjected to administration of MDMA has been divided into short and long-term effects. Some of the acute effects of MDMA, including the rapid release of intracellular stores of serotonin, are believed to mediate the psychological and behavioral profile observed in humans in the first three to four hours after drug administration, whereas in animals the presumed neurotoxic effects begin to manifest about 12–24 hours later. Consequently, it is believed that neurotoxicity is not inextricably linked to the acute effects of the drug. Further demonstrating the separation between behavioral and laboratory neurotoxicity profiles has been the observation that administration to animals of fluoxetine (a serotonin re-uptake blocker) up to six hours after MDMA injection, blocks or attenuates the development of neurotoxicity (Hekmatpanah and Peroutka, 1990), whereas in human subjects the acute effects of MDMA (psychological, neuroendocrine and temperature) occur within minutes and peak in a few hours (Grob *et al.*, 1996).

Most animal investigations of MDMA have revolved around establishing the extent and mechanisms underlying neurotoxicity. Rats administered multiple high dosages of MDMA undergo what are described as serotonergic neurotoxic changes which persist for many months before full neurochemical recovery occurs. Significant variation can occur, however, with dosage, route of administration and species. An important area of neurotoxicity research has been the histopathological study of brain sections of animals given substantial dosages of MDMA. This model was elaborated in the early 1980s at the University of Chicago by senior neuroscientists C. R. Schuster and Lewis Seiden, and their student, George Ricaurte. Their first major contribution to the MDMA literature was a 1985 (Ricaurte *et al.*) study of what they described as classic signs of serotonin neurotoxicity in rats injected subcutaneously twice daily for four consecutive days with 20 mg/kg of the longer lasting MDMA analogue, MDA. Coincident in time with the legal MDMA hearings being conducted by the DEA, the release of the University of Chicago findings accentuated the growing fears stirred by the new and only recently publicized reports of *Ecstasy* use. The introduction of the concept of serotonin neurotoxicity into the debate over MDMA's legal status has had a lasting influence on public and scientific appraisal of the problem.

Utilizing the repeated high dose MDMA administration model in most animal experiments, investigators have found sustained effects on various aspects of serotonin neuronal architecture, specifically the axonal projections. In virtually all immunohistochemical studies, the changes induced by MDMA are limited to the axons, with evident sparing of the cell bodies. Effects also appear to be contained within the smaller distal axonal projections, and not the larger more proximal axons. Resprouting and regeneration of serotonin axon terminals does occur, although the time course for full recovery may be extensive and varies significantly between different species. The question of whether the axonal reconnections observed during recovery are "normal" or are damaged, however, has not as yet been definitively answered. In squirrel monkeys administered MDMA (5 mg/kg, subcutaneous) twice daily for four consecutive days, profound reductions of brain serotonin, 5-hydroxyindole acetic acid, and serotonin uptake sites persist even at 18 months (Ali *et al.*, 1993). Interestingly, the thalamus shows full recovery, while the hypothalamus shows an (apparent) overshoot in regeneration, suggesting that under some circumstances administration of MDMA can lead to a lasting reorganization of ascending serotonin projections. In a study with more relevance to the single time or occasional use, low dose therapeutic model, a "no-effect" level in monkeys of 2.5 mg/kg MDMA administered orally every two weeks for four months (totaling eight times) was established by Ricaurte (Karel, 1993). Either because of the highly politicized nature of the MDMA neurotoxicity debate, or for reasons that have as yet not been made entirely clear, this information has to date never been published in the mainstream scientific literature.

At the center of the controversy over the central nervous system effects of MDMA has been researcher George Ricaurte, who while still a student was the lead author of the 1985 paper on MDA neurotoxicity that played such a pivotal role in the DEA scheduling decision. For the following fifteen years, first at Stanford Medical School and then at Johns Hopkins-Bayview Medical Center, Ricaurte has built one of the most influential and well funded MDMA neurotoxicity research programs. Reluctant to support investigations designed to study MDMA's therapeutic efficacy and safety, Ricaurte has steadfastly contended that "even one dose of MDMA can lead to permanent brain damage" in humans. With each new study from his

laboratory being widely publicized in the media, Ricaurte has had an instrumental role in the evolution of scientific and cultural attitudes towards MDMA. A careful examination, however, of the neurotoxicity controversy, including some of Ricaurte's key research designs and patterns of data interpretation, may lead to a clearer and more objective understanding of MDMA's full range of effects and potential to cause harm.

Investigators tracking the histopathologic changes induced by MDMA have noted substantial variability between different species' susceptibility to the phenomenon. Larger species, particularly monkey models, appeared to have far more sensitivity to the drug's neurochemical effects, and even at relatively low doses sustain persistent measurable effects (Slikker *et al.*, 1988). Compared to smaller species, including the mouse, which appeared to be far more resistant to MDMA's effects (Battaglia *et al.*, 1988; Peroutka, 1988), prolonged changes in the density of distal axon projections as seen with immunohistochemical staining were consistently observed. Given such findings, Ricaurte has given prominence to the theory of interspecies scaling (Chappell and Mordenti, 1991), which proposes that different animal groups will respond to drug effects only according to their relative size. Depending upon weight (mg/kg) and surface area (mg/m^2), different species, depending upon how large they are, will have greater or lesser susceptibility to MDMA's presumed neurotoxic effects. This argument, heavily relied upon by Ricaurte, however, is flawed in its neglect of interspecies differences in pharmacokinetics and drug metabolism.

Although animal pharmacokinetics studies have not been avidly pursued, most likely a reflection of the pharmaceutical industries' lack of interest in MDMA, a related drug, fenfluramine, has had cross-species investigations of differences in drug metabolism (Caccia *et al.*, 1982). An appetite suppressant marketed widely for years, fenfluramine was recently the subject of controversy over suggested adverse cardiac valve effects that led to its removal from the market in 1997. Although the risk of cardiac valve injury now appears to be far less than feared when the original report was published (Burger *et al.*, 1999; Schiller, 1999), the ban on the drug is not likely to be lifted any time soon, given the long-term impact of the early media reports. Interestingly, fenfluramine has also been known for years to have virtually

identical long-term effects as MDMA on serotonin neurochemistry and neuronal architecture, and has similarly been the object of interest by the Ricaurte neurotoxicity team (McCann *et al.*, 1994; McCann and Ricaurte, 1995). Although the threat of fenfluramine neurotoxicity risk was used to combat industry efforts to have its isomer D-fenfluramine released on the market in the mid-1990s, the FDA approved the drug for clinical use. A critical reason behind the decision was the fact that fenfluramine had a long history of general use as an appetite suppressant, having been taken by over 25,000,000 people worldwide for more than three decades (Derome-Tremblay and Nathan, 1989), and yet no clinical syndrome of fenfluramine neurotoxicity had ever been described.

The relevance of the fenfluramine example also extends to the issue of drug metabolism. Basic pharmacokinetic studies have established that size may not necessarily be the critical determinant in species susceptibility to the immunohistochemical effect described as serotonin neurotoxicity. It is well known that there are large species differences in the pharmacokinetics and metabolism of fenfluramine (Marchant *et al.*, 1992). Interestingly, humans metabolize fenfluramine much differently than do squirrel monkeys, and are actually far closer in pharmacokinetic profile to smaller species like the rat. Humans also deaminate the drug more extensively than other species to polar inactive compounds that are excreted in the urine as conjugates. Thus, the norfenfluramine/fenfluramine metabolite ratio is much higher in most other species, particularly in the non-human primates where the level of the metabolite is 40 times greater than in humans (Johnson and Nichols, 1990; Caccia *et al.*, 1993). If fenfluramine's primary metabolite norfenfluramine has greater neurotoxicity than fenfluramine, paralleling the relationship between MDMA and its metabolite MDA, then perhaps humans have less reason to fear MDMA neurotoxicity than the Ricaurte monkey studies appear to suggest. To the degree that MDMA is as close to fenfluramine in its pharmacokinetics as it is in its serotonergic neurochemistry, then the relevance of neurotoxicity to the human example is diminished proportionally.

Nevertheless, a cavalier attitude towards MDMA's risks would be ill-advised. A variety of serious adverse events, entirely apart from the neurotoxicity hypothesis, may potentially occur. Pioneering human pharmacokinetics research with MDMA, which was recently

conducted by investigators at the Institut Municipal d'Investigacio Medica and Universitat Autonoma de Barcelona, Spain and also in the United States at the University of California San Francisco, sheds new light on the importance of safety parameters to understanding differential drug metabolism (Harris *et al.*, 1999; Mas *et al.*, 1999). In humans, various organs, particularly the cardiovascular system, experience a non-linear pharmacodynamic response to increased dosages of MDMA. With increasing dose, a disproportionate elevation of plasma levels occurs that is significantly greater than that which would have been expected from linear kinetics. From the public health and safety perspective, therefore, it would appear that a persistent fixation on the relative risks and implications of the serotonin neurotoxicity threat has hampered efforts to investigate more clinically relevant concerns, including risks of cardiac arhythmias, hypertension, cerebrovascular accidents and adverse drug–drug interactions at higher dosage levels of MDMA (Dowling *et al.*, 1987; Manchanda and Connolly, 1993; Harrington *et al.*, 1999).

Controversy has also existed over whether MDMA (and fenfluramine) fit the precise definition of neurotoxins. Concerned that the term "neurotoxicity" has been too broadly applied, James O'Callaghan, a neurotoxicologist for the U.S. Centers for Disease Control and Prevention, has questioned many of the assumptions upon which this area of research has rested, particularly whether MDMA causes degenerative conditions of the central nervous system. O'Callaghan has demonstrated that the standard techniques used to identify classic evidence of neuronal destruction, such as astrogliosis and silver degeneration staining, do not occur in rats treated with MDMA. Disputing the use of immunohistochemical evidence to interpret the significance of long-term reorganization of brain serotonergic neurotransmitter systems, O'Callaghan takes issue with the assertion that MDMA causes classic neurotoxicity. Evidence of lowered indices of serotonin, he states, should not necessarily be equated with the destruction of serotonin axons, as one would expect in bonafide serotonin neurotoxicity, because assessments of serotonin are only indicative of the presence of this transmitter in neurons, not the actual neuronal structures themselves. In other words, O'Callaghan contends that MDMA can decrease the level of serotonin without necessarily destroying serotonergic axons, much as water could be drained from a pipe

without there necessarily being structural damage to the pipe itself. Furthermore, the expected evidence of structural damage to serotonin neurons, glial proliferation, does not reliably occur. Known neurotoxins, including bilirubin, cadmium, tri-methyl tin, the dopamanergic neurotoxin MPTP and the classic serotonergic neurotoxins para-chloroamphetamine (PCA) and 5,7-dihydroxytryptamine (5,7-DHT) predictably induce a proliferation of enlarged astroglial cells. According to O'Callaghan, the failure to detect evidence of a reliable astrogliosis response caused by MDMA or fenfluramine through standard laboratory testing in rats, even in the presence of decreased neurochemical markers of serotonin, further detracts from the neurotoxicity argument and instead calls for the alternative model of "neuromodulation", where protein synthesis inhibition occurs as a natural extension of the pharmacological activity of the compounds (O'Callaghan, 1993; O'Callaghan, 1995; O'Callaghan and Miller, 1993; O'Callaghan and Miller, 1994). Of course, O'Callaghan's arguments are qualified by the relative persistence of the serotonergic deficits caused by MDMA. Simple adaptation or neuromodulation would not be expected to last for years or even months as a consequence of the application of a compound that did not in fact produce some degree of prolonged structural change. Nevertheless, the functional significance of such changes remains unclear.

Debate over the clinical relevance of the MDMA neurotoxicity data, along with the political pressures of the time, have restricted the development of alternative perspectives and interpretations of serotonergic system change. Examining the implications of extensive serotonin neurotoxicity induced by administration of the classic serotonin neurotoxin, 5,7-dihydroxytryptamine (5,7-DHT), neuroscientist Efrain Azmitia of the New York University School of Medicine has raised the question of brain plasticity. Using basic laboratory models, Azmitia has explored the possibility that serotonin may actually function as a neurodevelopmental signal. Through damage to specific populations of serotonergic neurons in the adult brain, latent mechanisms for new growth and axonal sprouting are reactivated and a compensatory growth response occurs from neighboring undamaged neurons. The implications of this *Awakening the Sleeping Giant*, as Azmitia titled his review of the subject (Azmitia and Whitaker-Azmitia, 1991), are considerable, given that serotonin has been implicated in

a variety of serious clinical conditions, including mood dysregulation, obsessive compulsive behaviors, eating disorders, sudden infant death syndrome, schizophrenia and Alzheimer's dementia. It might also be worth asking, whether the proposed concept of serotonin neuroplasticity could in fact be the basis for an entirely new approach to treating these often unresponsive and refractory conditions? That is, could the loss of certain aspects of serotonergic function actually be at the heart of the proposed therapeutic actions of MDMA? We know, for example, that serotonin neurons in the hippocampus exhibit a high degree of death and regrowth in response to corticosteroid levels. Furthermore, non-neurotoxic decreases in serotonin cause neuroplasticity in adult rats, decreasing the number of nonaminergic synapses in some brain areas (Azmitia, 1999). Within the field of MDMA neurotoxicity, however, Azmitia's theories appear not to have attracted much interest. Although this state of affairs might reflect the politically incorrect nature of even suggesting such a position, there are also issues of safety that cannot be neglected. Indeed, Azmitia's own studies that growth of cultured serotonin cells were stimulated by low concentrations of MDMA but injured at higher concentrations (Azmitia *et al.*, 1990), highlight the need to approach this issue with great caution. Nevertheless, recent awareness of the complexity of these serotonergic systems should spur further discussion of the implications and significance of the changes associated with the phenomenon of MDMA neurotoxicity.

From early on in the debate over MDMA neurotoxicity, the difficulty in demonstrating significant behavioral disturbances in laboratory animals administered large quantities of the drug has remained problematic. In many degenerative brain conditions it is known that 80–90% of the neuronal pathway must be lost for symptoms to appear, as is the case with dopaminergic deficits in Parkinsons Disease. There is no study, however, that has been able to provoke serotonergic losses of that magnitude in response to MDMA treatment, though of course it is not necessarily certain that 5-HT system loss to this degree is necessary for deterioration of clinical function to occur. Even so, there has been the expectation that states of serotonin dysregulation would manifest in disorders of mood, aggression, sexuality, eating, learning and memory. For many years, however, there were virtually no reports of abnormal animal behaviors induced by MDMA. Even

those subtle indices of behavioral change which have been identified, however, have not necessarily been evidence of injury. Investigators have reported findings ranging from enhanced conditioned and non-conditioned learning in some animals treated with MDMA (Romano and Harvey, 1993) to attenuation of alcohol consumption in others (Rezvani *et al.*, 1992). Although additional studies have found both slight impairment or no difference compared to control animal function (Slikker *et al.*, 1989; Robinson *et al.*, 1993), the lack of clear proof of injurious functional effect continues to confound the expectations of behavioral consequences in response to neuronal injury by MDMA.

A further cause for concern has been the lack of reports emerging of the long-term effects of high dose MDMA on non-human primate behavior. Recently, Ricaurte and his colleagues reported data describing the immunohistochemical effects in monkeys treated with MDMA seven years previous (Hatzidimitriou *et al.*, 1999). Although that report detailed persistent effects upon neurochemical markers of serotonin function, curiously there was no discussion of whether behavioral changes occurred. Given the extended period of time Ricuarte and his colleagues maintained the monkeys following their initial treatment with MDMA, seven years previously, one might expect the investigators would have had ample opportunity to observe these non-human primates prior to their eventual destruction, particularly if changes were seen. The field of evolutionary biology is rich with examples of how primate research models have furthered our understanding of the relationship between altered neurotransmitter function and animal behavior, including disorders of mood and aggression (Heinz *et al.*, 1998; Suomi, 1999). The lack of any information on the behavior of these monkeys housed by the investigators for seven years therefore remains puzzling.

Advances have occurred in the field of MDMA neurotoxicity research, leading to clearer understanding of the underlying mechanisms by which high, repeated dosages of MDMA induce serotonergic axonal loss. Several lines of evidence from these investigations suggest a critical role for oxidative stress and the generation of free-radicals that cause degeneration of serotonin axonal terminals (Sprague *et al.*, 1998). It has also been suggested by some investigators that metabolites of MDMA may be involved in the process. Furthermore, multiple neurotransmitter systems appear to exert an influence, as a variety of

substances have been demonstrated in laboratory models to be capable of blocking neurotoxicity, including the serotonin reuptake blockers fluoxetine and citalopram (Schmidt, 1987; Schmidt and Taylor, 1987), the serotonin antagonist ritanserin (Schmidt *et al.*, 1990), the dopamine antagonist haloperidol (Hewitt and Green, 1994), the N-methyl-D-aspartate antagonist dizocipline (Colado *et al.*, 1993) and the monoamine oxidase-B inhibitor L-deprenyl (Sprague and Nichols, 1995).

One of the most significant recent achievements investigators in the field have had, however, has been demonstrating the critical role thermoregulatory mechanisms exert on the development of MDMA neurotoxicity. Lewis Seiden, veteran neurotoxicity researcher at the University of Chicago School of Medicine, has reported that relatively small changes in ambient temperature provoke significant alterations in core temperature of MDMA treated rats but do not affect core temperature of control saline treated rats (Malberg and Seiden, 1998). As MDMA neurotoxicity is evidently dependent upon high core temperatures, preventing the development of hyperthermic states in experimental animals will reliably block the loss of serotoninergic terminals (Collado *et al.*, 1995; Broening *et al.*, 1995). The implications of this link between MDMA induced hyperthermia and potential serotonin neurotoxicity to human users are considerable, as temperature is a variable that can be easily regulated. The MDMA treatment paradigm, therefore, appears to be compatible with the imperative to avoid the generation of elevated body temperatures through the use of cool ambient environments, appropriate fluid replacement and the avoidance of physical exertion. On the other hand, the common recreational context of *Ecstasy* use at *raves*, where participants vigorously exercise (dance) for prolonged periods of time often in hot and poorly ventilated indoor environments, would appear to heighten risks for MDMA induced hyperthermia and magnification of any neurotoxic effect, as well as for malignant hyperthermia The critical point remains, however, that MDMA neurotoxicity may be entirely setting dependent and therefore completely preventable. When considering both the dangers of MDMA when used as a *rave* drug versus the importance of appropriate temperature control when establishing safety parameters for sanctioned investigations of treatment applications, the importance of these recent laboratory discoveries of the role

of thermoregulation are of great significance to future research developments.

The field of MDMA neurotoxicity research has also taken on the problem of trying to evaluate directly the effects of the drug on humans. Far more methodologically challenging than animal research, human studies have often failed to shed much light on the critical questions of MDMA's effects on health and safety. Indeed, to a regrettable degree, discrepancies between how studies were actually conducted and how they were reported in the literature have further clouded an already murky situation. Early work centered at the Stanford University School of Medicine, where Ricaurte in the late-1980s began to develop his program of human MDMA neurotoxicity studies. Attempting to investigate whether MDMA decreased levels of the primary metabolite of serotonin in cerebrospinal fluid (CSF), 5-hydroxyindole acetic acid (5-HIAA), Ricaurte compared a group of recruited *Ecstasy* users with a control group of chronic pain patients (Ricaurte *et al.*, 1990). Although understandable given human subjects committee restrictions on conducting lumbar puncture on normal volunteers in order to obtain CSF, an apparently unrecognized flaw in the design was that chronic pain is known to induce increased levels of serotonin function, including raised CSF 5-HIAA (Costa *et al.*, 1984; Ceccherelli *et al.*, 1989), thus placing the legitimacy of the findings of relatively low CSF 5-HIAA in *Ecstasy* users into doubt. Although a later report by Ricaurte's group has repeated the finding (McCann *et al.*, 1994), an earlier investigation from another group found no difference between a smaller sample of users and nonusers (Peroutka *et al.*, 1989).

A subsequent study, however, raised far more serious questions. Interested in examining MDMA's possible long-term effects on the L-tryptophan challenge model, an indirect measure of serotonin function, a collaborative study was developed by Ricaurte with investigators from Yale University. Publishing their study in the highly prestigious Archives of General Psychiatry, the collaborative team reported that MDMA exposure was associated with a trend towards reduced response to L-tryptophan, although the difference between the users and nonusers was not statistically significant (Price *et al.*, 1989). Subsequent scientific reports have sometimes referred to this report as if this difference was significant. What was neither reported

in the original article nor corrected by the investigators in the subsequent scientific literature, however, was the fact that the MDMA subjects used in this study were actually pre-selected from the larger group of original Stanford *Ecstasy* users on the basis of their having tested on the lower end of the CSF 5-HIAA spectrum. Utilizing a model of exploring whether markers of serotonin dysfunction are consistent across different tests may be an interesting question, yet given that this was not the purported intent of the study, serious questions about its significance remain (Grob *et al.*, 1990; Grob *et al.*, 1992; Grob and Poland, 1997). Since publication of the article in 1989, it has continued to be regularly cited as a critical piece of evidence for MDMA neurotoxicity in humans.

A logical area of investigation to extrapolate the findings of animal neurotoxicity research to the human model is the neuropsychological influence of presumed MDMA use. Dating back to the late-1980s investigators have conducted evaluations on the cognitive abilities of *Ecstasy* users. The first serious attempt to answer this question occurred in collaboration with the Yale L-tryptophan challenge study. Although concluding that *Ecstasy* users had signs of impaired cognition (Krystal *et al.*, 1992), as with the L-tryptophan study serious questions must be raised concerning basic research design. In addition to the unreported pre-selection subject bias of *Ecstasy* users in the earlier Stanford study who had tested on the low end of the CSF 5-HIAA spectrum, the Yale neuropsychological assessment methodology is also burdened by additional factors which might have predisposed *Ecstasy* subjects to performing less well than their non-Ecstasy using controls. For example, some of the *Ecstasy* subjects were tested the day after flying from the west coast to New York and several hours after having been administered intravenous L-tryptophan, the serotonin precursor amino acid known to produce sedation in some subjects. Non-*Ecstasy* using literature controls, on the other hand, tend to live locally and therefore are not subjected to cross-country air flight the day before testing. They are also not likely to receive earlier the day of their memory and concentration testing the sedating amino acid serotonin precursor L-tryptophan. In a pre-publication letter to a funder of the investigation, the study neuropsychologist acknowledged that "by and large, these results are striking for the fact that most subjects evaluated had IQ scores in the above average range or higher. Except

for the tests mentioned above (Memory and Tactual Performance Test) very few neuropsychological findings exist in this population. It should be noted that the memory findings for the paragraph are not uncommon in patients especially when anxiety, fatigue, or difficulties in attention or concentration exist in the individual. It is quite possible that the large number of impaired scores on the paragraph measures in this population are related to travel fatigue, being in a new environment, or being stressed in some way following the challenge testing that each subject performed" (R. Doblin, pers. com.). The actual published report, however, failed to adequately take into account these important extenuating circumstances. Even though the reported findings of memory impairment were slight and were not clinically significant, and in spite of the suspect methodology, the Yale study has become a cornerstone for the subsequent development of efforts designed to establish the neurotoxic impact of MDMA in humans. While subsequent studies have reported decreased performance in some memory tasks, these decreases are generally less than one standard deviation below the scores of the controls (a difference which is not considered even borderline impairment by clinical neuropsychologists).

Given the degree of risk young people expose themselves to while engaging in the exuberant activities of the *Ecstasy* culture, ranging from polydrug abuse to sleep and nutritional deprivation, there does exist a compelling need to construct and implement psychiatric investigations that will evaluate for signs of injury. Some researchers, particularly neuropsychologists in the United Kingdom, have contributed to our understanding of the short and long-term effects of marathon drug facilitated dancing on cognition and mood. Valerie Curran, a psychological investigator at the University of London, has described the persistent dysphoria and mild memory impairment experienced by *ravers* during the week following their weekend of drug fueled dancing (Curran and Travill, 1997). These "mid-week lows" were significantly more severe for *Ecstasy* users who were also regular users of cocaine and methamphetamamine. Curran's work, and those of her counterparts in the United Kingdom, have highlighted the degree to which the *Ecstasy* scene has been pervaded with polydrug abuse. In Curran's study, less than two percent of her *Ecstasy* subjects were not polydrug users. An added factor, has been the surge in

popularity of the dissociative anesthetic ketamine (Dalgarno and Shewan, 1996). Known to induce strong frontal lobe effects and cognitive dysfunction (Ellison, 1995), ketamine use has increased significantly among *Ecstasy* using *ravers*. British investigators, to a far greater extent than some of their American counterparts, have been revealing the actual context of *Ecstasy* use experienced by their research subjects. Excessive use of a variety of powerful psychoactive substances, taken at all night *raves* under conditions of nutritional and sleep deprivation, were all common histories for the *Ecstasy* users recruited into the British studies (Curran, 1998). Although clearly identifying dangers to vulnerable *Ecstasy* culture youth, the investigators acknowledge that these findings tell us far less about the true neuropsychological effects of MDMA.

In the United States, two major studies concluding that MDMA induced memory impairment were published by Ricaurte's group in the late-1990s (Bolla *et al.*, 1998; McCann *et al.*, 1999). Funded by federal grants, the findings of these investigations have received considerable publicity as part of the campaign informing the public that MDMA causes brain damage in humans. Unfortunately, fundamental flaws of research methodology, both reported and unreported, have again obstructed full understanding of what actually occurred. A recurrent problem in Ricaurte's program of retrospective human MDMA research has been his difficulty in providing adequately matched controls. Data published in one study clearly show the far greater exposure of *Ecstasy* subjects to a variety of different drugs when compared to non-*Ecstasy* using controls, including five times the exposure rates to cocaine and methamphetamine, four times the exposure to PCP and twice the exposure to inhalants. What the report does not provide, however, is the extent to which these different drugs were used by subjects and controls. Given the greater probability that the subjects who had considerable histories of *Ecstasy* ingestion were also far more likely to consume greater quantities of other drugs as well, this discrepancy between the two different groups may well be far more substantial than the published data would indicate. By contrast with the hard-living polydrug using *Ecstasy* subjects, many controls in these two studies were graduate student volunteers from the local Baltimore-Washington area, a group likely to have had far less exposure to drugs and the *rave* scene. Indeed, "*ecstasy* use" may be turning

into a catchword for a collection of variables that includes the infusion of many drugs into a stressful lifestyle, rather than a characteristic defined by *ecstasy* use per se.

Other puzzling statistical manipulations have been observed in the study by Bolla *et al.* (1998). Although the investigators report that there were no significant differences on memory testing between the 24 *Ecstasy* users and the 24 controls, they nevertheless concluded that "the extent of memory impairment correlates with degree of MDMA exposure". To reach such a conclusion, however, the investigators appear to have used a data chart that was surprisingly excluded from the published report (Nelson, 1999). This ancillary data revealed that in order to demonstrate memory impairment, the subjects had to be divided into a "Control Group", which included not only all 24 controls *but also the 13 subjects with less cumulative* ***Ecstasy*** *use histories*, versus a "High Dose Group", which comprised the remaining 11 subjects with the greater lifetime use of *Ecstasy*. What has been so troubling about this report, published in the peer reviewed journal *Neurology*, was that neither the number of *Ecstasy* subjects in the high and low dose groups, nor the inclusion of the 13 low dose *Ecstasy* subjects into a larger control group, were mentioned in the paper. Without these vital data, it is impossible to ascertain how the published findings could have been statistically determined. Even with this knowledge, however, and in spite of well-publicized assertions to the contrary, the evidence from these studies for MDMA induced memory impairment remains highly suspect.

In late 1998, another study was published purportedly attesting to MDMA's severe dangerousness to humans. Triggering media excitement and concern around the world, the Ricaurte group announced that by means of state of the art Positron Emission Tomography (PET) scans they had identified evidence of "neural injury" in the brains of *Ecstasy* users (McCann *et al.*, 1998). Uncritically accepting his conclusions as reported in the highly regarded British journal *Lancet*, the world press followed the lead of the *Times of London*, which announced on October 30, 1998 that Ricaurte had definitively demonstrated "Proof That *Ecstasy* Damages The Brain". Under close scrutiny, however, both the methodology and data interpretation employed by this particular study appear to suffer from some of the same limitations exposed in his earlier work. Although the rapidly

progressing field of modern brain imaging techniques offers great potential to aid our understanding of MDMA's effects on the brain, including the concern over possible neural damage, this most recent contribution from the Ricaurte team once again raises more questions than it answers.

Utilizing a recently developed technique to visualize components of the serotonin neurotransmitter system, Ricaurte attempted to demonstrate abnormal findings in a group of 14 *Ecstasy* using subjects compared with a second group of 15 normal controls who had never used *Ecstasy*. Essential data characterizing these two groups, however, is missing. Although the investigators say they administered a drug-history questionnaire to their subjects, these critical results are absent from the report. No information is therefore provided addressing the critical question of polydrug abuse among *Ecstasy* users. The degree to which these subjects may have had exposure to methamphetamine, cocaine, opiates, barbiturates, hallucinogens, ketamine, PCP, cannabis, inhalants, tobacco, alcohol or other substances in addition to *Ecstasy*, does not enter into the authors' interpretation of their reported data (Erowid, 1998a). Nor is there any discussion of the polymorphous nature of *Ecstasy* itself, that in addition to being MDMA it might also constitute other drugs, including MDA, MDE, MBDB, 2CB, methamphetamine, LSD, psilocybin, ketamine, PCP or dextromethorphan. Simply put by Ricaurte, the study succeeds in demonstrating the injurious effects of MDMA on the brain serotonin system. On closer inspection of the research design employed, however, it is apparent that by choosing subjects who reported taking *Ecstasy* on an average of 228 (70–400) separate occasions, 6 (1–16) times per month for 4.6 (1.5–10.0) years, the investigators were selecting a group of unarguably heavy users of *Ecstasy*. Indeed, the average dose of presumed MDMA reportedly taken by the subjects, 386 (150–1250) milligrams, is an exceptionally large amount, approximately three times the recommended therapeutic dose. It is difficult to believe that *Ecstasy* was the only drug used in high doses by these subjects. Given these inherent problems in methodological controls, attempts to extrapolate to the occasional (or one-time) low dose MDMA treatment model remain highly problematic.

For the PET technique used by the Ricaurte group, each subject was injected with a radioactive labeled marker that selectively binds to

serotonin (5-HT) transporters (the serotonin re-uptake sites) on the axons of serotonin neurons. These transporters consist of protein structures that are embedded in the membranes of nerve endings and are part of the interneuron communication system. The key finding, reported in the study, was that MDMA users showed decreased global and regional brain serotonin transporter binding compared with controls. Reporting that decreases in serotonin transporter binding positively correlated with the extent of previous *Ecstasy* use, the authors conclude by stating that they had demonstrated "direct evidence of a decrease in a structural component of brain 5-HT neurons in human MDMA users". Closer examination of the research design and method of data interpretation employed, however, reveals serious shortcomings. First, the identified MDMA users hardly appear to have abnormally low-serotonin transporter levels at all. Looking at the data chart provided, it is clear that there is relatively little difference between the subject group and the control group. Only one of the *Ecstasy* users falls well outside the range of the rest of the subjects. Excluding that particular individual (with a reported lifetime total of 150 *Ecstasy* ingestions), all of the remaining presumed MDMA users' scores are within the same range as the non-MDMA users. As 2 of the 14 MDMA users are actually near the top of the non-MDMA user range (and above the majority of controls), confidence that these data support the findings remains lacking. Indeed, if one removes the one outlier subject and the 15 controls who had been included to weight the correlation curve, a new regression analysis reveals no statistically significant correlation between MDMA use and transporter density. The touted effect correlating low transporter and MDMA use appears to disappear altogether (Erowid, 1998b). Finally, disregard of the possibility that some subjects may have had pre-existing low transporter levels prior to initial *Ecstasy* exposure, perhaps even predisposing them to polydrug abuse to begin with, further erodes the significance of the reported findings.

Doubts have also been raised about the experimental PET approach used in the study, the [11C]-McNeil-5652 serotonin ligand, which has only recently been available to investigators. Only a handful of brain imaging researchers have had access to this developing technology, including two groups of European investigators who have commented critically on the technique used by the Ricaurte group. Professors

Kuikka and Ahonen at the Universities of Kuopio and Oulu in Finland have responded to the original article in *Lancet* that the approach used in that study raises the question of whether the reported reductions in serotonin transporter are in fact actually based on different kinetics of the non-specific radioligand [11C](−)McNeil-5652 between controls and presumed MDMA users (Kuikka and Ahonen, 1999). The other group that has raised questions about Ricaurte's PET methodology, at the University of Zurich under the leadership of Franz Vollenweider, has been at the forefront of the recent resurgence of high level European neuropsychiatric research with hallucinogens and phenethylamines, including MDMA. Having considerable experience with brain imaging and the [11C]-McNeil-5652 ligand, Vollenweider has emphasized that test-retest variability must first be assessed in order to know how stable and reliable the data actually are (Buck *et al.*, 2000; F. X. Vollenweider, pers. com.). The failure of Ricaurte and his colleagues to account for and report the test-retest variability for their technique further underscores the degree to which methodological uncertainty persists with the particular PET scanning approach used.

Finally, there remains the question of what a reduction of serotonin transporters means, if MDMA is capable of inducing such an effect. Does a decrease in measurable transporter density inevitably mean structural damage to the serotonin system? Or, might it simply be a reflection of a functional modulation (pharmacologic downregulation) in response to lower concentrations of the neurotransmitter. Neuronal systems are known to be capable of exhibiting a wide range of adaptive and compensatory responses in response to toxic effects or drug use. In recent years, the classical view of antidepressant drugs as modulators of acute synaptic events has been broadened to include long-term actions that modify neuronal function. Administration of serotonin ligands, including tricyclic and selective reuptake inhibiting antidepressants, have been shown to reduce significantly both the expression of serotonin transporter mRNA as well as the density of serotonin transporter binding sites labeled by [3H]paroxetine in the dorsal raphe nuceus in rats (Lesch *et al.*, 1993; Watanabe *et al.*, 1993; Kuroda *et al.*, 1994). Interestingly, the recreational drug cocaine has also been shown to decrease significantly the abundance of serotonin transporter mRNA (Burchett and Bannon, 1997). To buttress their contention that MDMA is a dangerous human neurotoxin, Ricaurte and his

colleagues have charged that the failure to observe severe short-term negative clinical sequelae is deceptive, and that it might take years for neuropsychiatric signs of serotonin to manifest (the "Time Bomb" theory of MDMA neurotoxicity). They introduce the example of the dopamine neurotoxin MPTP into the argument, and describe how with age the functional dopamine reserve must be progressively depleted before individuals become symptomatic with Parkinsons Disease. What they fail to acknowledge, however, is that unlike the dopamine system, which clearly declines with advancing age in humans and animals, the serotonin neurotransmitter system appears to maintain relative stability over time with significantly lesser degrees of chronological decline than the case of dopamine (McEntee and Cook, 1991). Although legitimate concerns remain that heavy *Ecstasy* users may have caused long-standing alterations in their central nervous system function by their life style and drug taking habits, the Ricaurte PET data sheds little light on the range of MDMA's effects on humans.

CURRENT STATUS

During the concluding years of the 20th Century and into the 21st Century, *Ecstasy* use has continued to spread throughout the United States and Europe. Increasing numbers of youth, at younger ages, are attending *raves* where the vast majority ingest a variety of drugs. The reliability of *Ecstasy* supplies has continued to deteriorate, highlighting the poor quality control which exists on the illicit drug market. The trend for drugs other than MDMA to be used as substitutes for *Ecstasy* has intensified, typified by a recent report from the French *rave* scene identifying that only 25% of *Ecstasy* pills analyzed by *Medicins du Monde* representatives actually contained MDMA (Inciyan, 2000). A variety of different drugs, often but not necessarily disguised as *Ecstasy*, are now in wide circulation on the youth recreational drug market, including methamphetamine, cocaine, opiates, hallucinogens, inhalants, PCP, ketamine, dextramethorphan and GHB. To fully appreciate the degree of public health risk, it is essential for investigators to acknowledge the polydrug context of *Ecstasy* culture. To mistake the cumulative consequences of multiple drug

use for the effects of MDMA alone obfuscates our understanding of this complex phenomenon.

The implications to millions of youth world-wide frequently self-administering these powerful psychoactive drugs remain unclear. Virtually all research efforts to date have been directed at establishing through laboratory animal investigations and retrospective human *Ecstasy* user models the neurotoxic dangers of MDMA. After 15 years, however, the case has yet to be made. Although long-term alterations of neuronal architecture in animals ranging from rats to non-human primates have been consistently demonstrated, the functional consequences have remained obscure. Furthermore, efforts to extrapolate evidence of MDMA induced neuropathology from retrospective examinations of heavy *Ecstasy* users have consistently manifested serious methodological flaws. Although laboratory experimentation in particular has provided fertile ground for the advancement of our knowledge of brain neurotransmitter systems, the MDMA neurotoxicity research model, media hype aside, has demonstrated limited clinical utility.

While the dangers youth expose themselves to while engaged in the activities of *Ecstasy* culture should by no means be written off lightly, more objective appraisal of risk for the long neglected low dose MDMA treatment model needs to be examined. Relying on evaluation of youth with extensive polydrug histories, extreme lifestyles and often comorbid psychopathologies to inform us of the effects of MDMA imposes an inadequate and misleading perspective. The only way to rigorously establish true risk (and safety) parameters is to utilize prospective human research models. Only by administering known quantities of pure drug in a research setting controlling for extraneous factors (including though not limited to ancillary drug use), will we be able to establish an accurate profile of MDMA's effects. In spite of the compelling need to utilize human administration research models, however, only a handful of studies have been conducted. For years, fears aroused by the publicization of neurotoxicity concerns have stalled the development of alternative research paradigms. Although a limited number of prospective investigations have been permitted, recent efforts to expand such research programs (Vollenweider *et al.*, 1998; Vollenweider *et al.*, 1999; Lieberman and Aghajanian, 1999) have come under dubious attack (Gijsman *et al.*, 1999; McCann and

Ricaurte, 2000). While clearly strong human subject protection procedures must be assured for all investigations of this sort, a process of truly objective risk assessment should allow for the cautious elaboration of these optimal research models.

With the brief and isolated exception of the Swiss psycholytic group experience ten years ago, there has been no authorized treatment since MDMA was classified as a Schedule 1 drug in the mid-1980s. The regulatory decision to allow a formal program to investigate the safety and efficacy of MDMA as a treatment modality has not as yet been reached, although there have been hopeful signs for the future. Indeed, a growing consensus is beginning to recognize the need to conduct prospective research with pharmaceutical grade MDMA on subjects who are neither denizens of *Ecstasy* culture nor severe polysubstance abusers. There is no doubt that recreational *Ecstasy* users are exposing themselves to greater and more unusual risks than were ever anticipated by the early explorers of MDMA's putative therapeutic effects (Jansen, 1998, Brody *et al.*, 1998; Harrington *et al.*, 1999). And yet, what is the genuine relevance to the clinical treatment model of such poorly controlled data collected from populations of young polydrug users who have frequented for extended periods of time the fast lane of the contemporary *rave* scene? Hopefully, the time has arrived where it will be possible to undertake sanctioned studies which will finally and honestly elucidate the true risk/benefit ratio for this misunderstood drug.

The world of contemporary *Ecstasy* use poses many dangers for our youth. Exposed to the vagaries of the underground drug trade, and misguided by the omnipotence and naivete of their age, millions of young people experimenting with today's panoply of substances have ignored their elders' admonitions of caution and have continued to pursue the activities of *Ecstasy* culture. Denied the safeguards provided to youth initiates of traditional cultures, young *ravers* in our own contemporary world continue to incur unnecessary degrees of risk (Grob and DeRios, 1992; DeRios and Grob, 1994). Clearly, new models for assessing the unique properties of MDMA, both positive and negative, are called for. The old models which have stalled the development of alternative paradigms, have also unfortunately impeded the flow of open and honest dialogue on these critical issues. The long-neglected treatment model of MDMA augmented

psychotherapy has to date neither been disproven nor proven. Particularly in patients with severe refractory conditions, including the psychological distress associated with end-stage cancer and the spectrum of chronic post-traumatic stress disorder, rigorous and well controlled research assessment of safety and efficacy deserves investigation. Utilizing thorough and comprehensive informed consent procedures, strict standards of medical ethics should be satisfied. Hopefully, the opportunity now exists to develop and implement those research models which will finally address not only the pressing public health concerns implicit within modern *Ecstasy* culture, but also the never answered questions of MDMA's potential as a therapeutic medicine.

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