maps • volume IX number 3 • 1999

MAPS

Bulletin of the Multidisciplinary Association for Psychedelic Studies

MAPS' long-standing efforts to conduct MDMA psychotherapy research have recently become much more difficult. You might expect that this is due to political obstacles restricting opportunities to conduct research. In the past, this has been the major source of difficulty MAPS has faced. However, after lengthy and persistent struggles, the FDA recently wrote to Dr. Charles Grob, Harbor-UCLA Medical Center, stating that it plans to approve a MAPS-sponsored protocol to investigate the use of MDMA-assisted psychotherapy in cancer patients, with the exact details of the protocol still to be determined and awaiting final FDA approval. Opportunities for MAPS-supported research into the use of MDMA psychotherapy in the treatment of post-traumatic stress disorder, though not approved, are looking promising in Spain and Israel.

Letter from Rick Doblin, MAPS President

MAPS' new difficulties result not from political obstructionism but rather from the success of the efforts to obtain FDA permission to conduct research! Now we have to address the inherent complexity of conducting rigorous scientific research into the specific methods by which MDMA can be used to treat clearly defined and meticulously measured aspects of psychological dysfunction. It is relatively easy to stand outside the scientific arena and proclaim that one has a wonder drug useful for this or that purpose, if only the powers that be would permit the necessary research. It is much harder to back up those claims with rigorously gathered scientific data when the doors to the laboratory are finally unlocked.

Naturally, it is a great relief to face these more difficult challenges after struggling for years and decades simply to obtain scientific freedom. Still, it is somewhat befuddling to be in such a position of opportunity. MAPS has been working since its founding in 1986 to obtain permission to study the therapeutic use of MDMA in cancer patients. On June 24, 1999, a teleconference took place between several FDA officials and a group working with MAPS. According to the memorandum of that teleconference prepared by the FDA, "The Center [FDA's Center for Drug Evaluation and Research, which is in charge of research on all new drugs for humans] has decided to allow the sponsor [MAPS] to undertake a proof of principle study..." Now we are faced with the exceedingly difficult question of how to measure exactly what MDMA can do to help cancer patients cope with their illness and impending death. Are we going to show change on standard measures of anxiety and depression, even though these tests have not been created to evaluate people facing death? How do we respond to the fact that the most appropriate measure of Quality of Life in terminal patients—the measure that explicitly evaluates a transcendent dimension related to changes in fear about and acceptance of death—is not yet scientifically validated for use in clinical research? Fortunately, the FDA is willing to let us start with a small pilot study with controls to determine what changes we are able to produce in a variety of measures.

Another promising development is that the FDA Office of Orphan Products Development approved MAPS' application to have marijuana declared an Orphan Drug for AIDS wasting (p. 19). As MAPS moves to initiate long-delayed research projects, your continued support will make all the difference. What a pleasure it will be to work together to address the difficulties that success has placed before us. — **Rick Doblin, MAPS President**

2015 Robinson Avenue • Sarasota, FL 34232 • phone 941/924.6277 • fax 941/924.6265 • internet: info@maps.org • www.maps.org

MAPS (Multidisciplinary Association for Psychedelic Studies) is a membership-based organization working to assist psychedelic researchers around the world design, obtain governmental approval, fund, conduct and report on psychedelic research in humans. Founded in 1986, **MAPS is an IRS approved 501 (c)(3) non-profit corporation funded by tax deductible donations.** MAPS has previously funded basic scientific research into the safety of MDMA (3,4, methylenedioxymethamphetamine, Ecstasy) and has opened a Drug Master File for MDMA at the U.S. Food and Drug Administration. MAPS is now focused primarily on assisting scientists to conduct human studies to generate essential information about the risks and psychotherapeutic benefits of MDMA, other psychedelics, and marijuana, **with the goal of eventually gaining government approval for their medical uses.** Interested parties wishing to copy any portion of this publication **are encouraged** to do so and are kindly requested to **credit MAPS** including name and address. The *MAPS Bulletin* is produced by a small group of dedicated staff and volunteers. **Your participation,** financial or otherwise, **is welcome.**

Multidisciplinary Association for
Psychedelic Studies, Inc. (MAPS)
2105 Robinson Avenue
Sarasota, FL 34232 USA
Phone: **941/924.6277**
Fax: 941/924.6265
E-mail: **info@maps.org**
URL: **http://www.maps.org**

ISSN 1080-8981
Printed on recycled paper

MDMA Neurotoxicity Research: Methodological Concerns

Charles S. Grob, M.D.
Harbor-UCLA Medical Center

CONSIDERABLE MEDIA ATTENTION has been given recently to investigators purporting to demonstrate neurotoxic brain damage in humans who had self-administered large amounts of the polymorphous drug Ecstasy. There is insufficient evidence, however, to extrapolate these findings to single dose effects of MDMA. Furthermore, methodological weaknesses in the humans studies call into question data interpretation attempting to assert that MDMA damages neurons after single or even a few multiple doses. Although animals given large dosages of MDMA appear to undergo extensive loss of 5-HT axons and terminals, evidence for functional sequelae has been scant. There is no evidence demonstrating conclusively that therapeutic doses of pure MDMA given under controlled conditions lead to neuron degeneration or that users who experimented only with a few modest doses of MDMA have suffered any sort of neurological deficit.

INTERPRETATIONS OF HUMAN DATA also contain severe methodological limitations. All subjects were heavy users of the street drug, Ecstasy, a term encompassing a variety of substances other than MDMA, sometimes including ketamine and other adulterants. Furthermore, these Ecstasy-MDMA subjects also had histories of considerable cocaine and methamphetamine use, while non-MDMA using controls were often highly motivated graduate students free of other drugs as well. Although demonstrations of minor cognitive deficits and suspect personality traits have been variable, little can be concluded because of the variety of drugs used and the poorly matched controls.

THERE IS A PRESSING NEED to conduct prospective human research with MDMA. Unfortunately, public apprehension fueled by sensationalist and often inadequately informed media have constricted scientific dialogue. Pressing public health concerns of long-term effects to an increasing percentage of European and American youth remain unanswered. Persistent interest in MDMA's possible therapeutic role must also be addressed. MDMA's potential to cause harm as well as capacity to facilitate healing when used under optimal conditions can only be answered using well-controlled prospective research designs. •

Reference
Grob, C.S. and Poland, R.E. MDMA. In: *Substance Abuse: A Comprehensive Textbook, Third Edition*, Lowinson, J.H, Ruiz, P, Millman, R.B, Langrod, J.G. (Eds), Williams & Wilkins, Baltimore, pp. 269-275, 1997.

MDMA **neurotoxicity** discussed

Rick Doblin

There are several issues related to MDMA neurotoxicity:

1. Do persistent reductions in serotonin levels in humans result from taking MDMA? If so, from what doses and frequency?
2. If there are persistent reductions, are they temporary or permanent?
3. If there are persistent reductions in serotonin levels in humans under any circumstances, do these reductions have any functional or behavioral consequences?

In other words, does MDMA cause lowered serotonin levels and, if so, does it matter?

The answer to the first question is that there is some suggestive evidence that there are serotonin reductions in a group of people who have taken MDMA an average of 90 or more times.[1,2,3]

HOWEVER, this evidence is not conclusive, since MDMA users were compared to matched control groups, which may or may not be matched on all factors that impact on serotonin levels. The most persuasive evidence would come from studies in which MDMA-naive subjects were tested, then given multiple exposures to MDMA, then tested again. Unfortunately, no studies of this sort have been conducted. MAPS recently donated $6,000 toward the costs of a pilot study being conducted under the direction of Dr. Franz Vollenweider, University of Zürich. In this study one dose of MDMA was given to several MDMA-naive subjects, who were evaluated with PET scans before and after the MDMA. The results should be available in a few months.

It is also as yet unknown whether the reductions in serotonin as suggested in some MDMA human studies are linked to damage or to down-regulation, in which neurons adapt to lower levels of serotonin, or to some other factor unrelated to MDMA.[4]

The extent of MDMA-related "damage" would depend—among other factors—on the frequency of use and the doses used. The present state of knowledge does not allow us to tell at which frequency and dosage to draw the line between non-neurotoxic and neurotoxic use in humans. The line would certainly have to be individually drawn at different dosages and frequencies in different users, due to individual variability. Of course, the best way to avoid the risk of MDMA-related neurotoxicity is to avoid MDMA. The balancing of risk and benefit is a decision that each individual must make for themselves.

An unpublished MAPS-funded study by Ricaurte, in which oral 2.5 mg/kg MDMA was administered to non-human primates once every two weeks for four months (8 administrations) showed no effect in levels of serotonin. This is at or above the normal therapeutic or recreational dose level. However, the relative sensitivity to MDMA's effects on serotonin of non-human primates as compared to human beings is unknown.

In animal studies, there is evidence that an SSRI taken acutely (once) even a few hours after MDMA will provide

"neuroprotection" against the possibility of toxicity to serotonin neurons. This suggests that a person who ingests MDMA could take a Prozac for neuroprotection within six hours after ingestion. It is obviously not clear if this holds true for humans, not only because a prospective study has not been done, but also because it is still controversial whether MDMA induces structural changes which can be considered "neurotoxic."[5]

As to the second question, whether reductions are temporary or permanent, there is clear evidence of regeneration of serotonin neurons. However, this regeneration pattern does not restore the pattern exactly to the original state.[6]

The answer to the third question is that there is a lot of circumstantial evidence, and no convincing evidence to the contrary, that serotonin reductions, if there are any, make no difference. There is a frequently repeated claim that MDMA users may show no problems at present but will show such problems in the future, as they age. This delayed effect will supposedly take place when the combination of MDMA and the normal aging process has reduced serotonin levels below a certain threshold. This hypothetical time bomb theory ignores that fact that there are already quite a few people over 60 or 70 who have taken substantial amounts of MDMA and seem fine. Furthermore, the serotonin system does not decline much with age, certainly not as much as the dopamine system, the decline of which can contribute to Parkinsonism.

One should certainly note from the analyses of "Ecstasy" tabs conducted by Nicholas Saunders that most MDMA tablets are not pure and can easily contain drugs which are harmful when taken acutely or on a chronic basis (e.g. atropine, ephedrine). These drugs may be harmful but there is no evidence they reduce serotonin levels. MAPS sponsored an MDMA Analysis Project of U.S. samples in 1996.

Finally, fenfluramine, a drug with actions identical to those of MDMA with respect to effects on serotonergic neurons, does not appear to have toxic effects on these neurons in humans taking the drug twice daily for several years, nor is there evidence of functional or behavioral problems in fenfluramine users. However, no thorough studies have been conducted searching for such effects. Nevertheless, the absence of reported neurotoxic effects from fenfluramine suggests that such effects, if any exist, are likely to be subtle. For example, the dramatic neurotoxic effects of MPTP, the synthetic heroin that caused Parkinson's-like symptoms and for which the term "designer drug" was originally used, were noticed after only a handful of people had taken the drug. In contrast, MDMA has been used for over two decades and millions of people have taken it, some excessively so. Some people have had problematic psychological reactions but there is still no clear evidence of any functional or behavioral consequences linked to MDMA neurotoxicity. While subtle changes can still be important, perhaps crucially so to what it means to be fully human, no such changes have yet been demonstrated from the yet unproven mechanism of MDMA neurotoxicity. At the same time, many people report long-term benefits from their use of MDMA. As a result of these reports of long-term benefits, MAPS focuses on the development of clinical studies designed to scientifically investigate the therapeutic applications of MDMA. •

MDMA has been used for over two decades and millions of people have taken it, some excessively so. Some people have had problematic psychological reactions but there is still no clear evidence of any functional or behavioral consequences linked to MDMA neurotoxicity.

References:

1-McCann U, Hatzidimitriou G, Shaham Y, and Ricaurte G. Serotonin neurotoxicity after 3,4- methylenedioxymethamphetamine (MDMA, "Ecstasy"): a controlled study in humans. *Neuropsychopharmacology* 10:129-138, 1994.

2-Ricaurte, GA, Finnegan, KT, Irwin, I and Langston, JW: Aminergic metabolites in cerebrospinal fluid of humans previously exposed to MDMA: Preliminary observations. *Ann NY Acad Sci* 600:699-710, 1990.

(MAPS played a major role in recruiting volunteers for the first two of the studies referenced above and in covering travel expenses involved in bringing many of the volunteers to be tested in the study referenced as #2.)

3-Peroutka, SJ, Pascoe, N and Faull, KS: Monoamine metabolites in the cerebrospinal fluid of recreational users of MDMA. *Res Comm Substance Abuse* 8:125-138, 1987. [This study found no serotonin reductions.]

4-O'Callaghan JP, Miller DB, Jensen KF and Schmidt CJ: Serotonin depletions are not predictive of neurotoxicity: evidence from increases in glial fibrillary acidic protein induced by methylenedioxymethamphetamine (MDMA) and 5,7-dihydroxytryptamine (5,7-DHT) [abstract] *Society for Neurosciences Abstracts*, 16 (part 1):256,1990.

5-Schmidt CJ; Abbate GM; Black CK; Taylor VL. Selective 5-hydroxytryptamine receptor antagonists protect against the neurotoxicity of methylenedioxymethamphetamine in rats. *J Pharmacol Exp Ther* 255 (2): 478-83, 1990.

6-Fischer C, Hatzidimitriou G, Wios J, Katz J, Ricaurte G. Reorganization of Ascending 5-HT Axon Projections in Animals Previously Exposed to the Recreational Drug (+-) 3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy"). *J of Neuroscience* 15 (8):5476-5485, 1995.

MDMA and Memory Impairment: **Proven or Not?**

Critique of the article:
Bolla, McCann and Ricaurte (1998)
Memory impairment in abstinent MDMA ("Ecstasy") Users,
Journal of Neurology. 51:1532-1537.

K. Thomas Nelson, Ph.D.

THIS RECENT STUDY CLAIMED to have discovered evidence suggesting that MDMA use above certain amounts is linked to memory problems. Much has been said critically about this study on the Internet (see erowid.org). On the one hand, the authors do seem to be implementing the study with state of the art neuropsychological measures, as well as with physiological measures which appear appropriate (CSF 5-HIAA levels to measure 5-HT depletion and Urine Drug Screens to establish current abstinence). Nevertheless, there are serious statistical and methodological weaknesses which undermine the credibility of the conclusions, which are themselves overstated. In addition, the procedures are not explained clearly enough for the study to be replicated, and the statistics used to report the main effects and interactions are confusing and probably inappropriate. [Editors's Note: For more information about this statistical analysis, please contact the author directly.] Furthermore, the magnitude of the purported MDMA-related deficits is not clearly stated in the paper as published, making any interpretation of the clinical significance of those deficits impossible.

K. Thomas Nelson, Ph.D.
nelsontx@ix.netcom.com

AN APPRAISAL of the clinical implications of the study became possible once I had been supplied with Table 6: *Means and Standard Deviations for the Memory Tests*, which was not included in the article as published in the *Journal of Neurology*. I was provided with Table 6 by Rick Doblin who, in turn, had been supplied with that table by principal investigator, Dr. Karen Bolla.

I was motivated to write this critique because I think that there is a lot of research being published in mainstream journals which makes statistically unwarranted conclusions about the dangerousness of MDMA and other entheogens. Because the FDA relies in part on such studies, obtaining permission for research into the possible benefits and applications of entheogens has been and continues to be more difficult than the existing data seem

to warrant. Worse yet, the popular media take such unsound research and publicize it widely to an audience which has very little knowledge on how to evaluate the soundness of the studies. This leads to the use of "scare tactics," which tends eventually to undermine the credibility of drug abuse prevention efforts and increases the extent to which valid warnings are ignored by the public.

Presentation and Interpretation of Results

To quote the authors:

"...when memory functioning in the two groups was compared without taking the average monthly MDMA dose into account, differences were not found." (p.1534).

The authors are flatly admitting that there was no significant difference between the MDMA-User and Control subjects on any of the memory measures. In addition:

"...no significant associations were found between the Memory factors and other estimates of exposure, including duration of MDMA use or the cumulative lifetime use of MDMA." (p.1534)

The results section would ordinarily have stopped right there, since the main hypotheses have been tested and the results found to be non-significant. While the interactions are of secondary interest, the statistical testing of memory factors in Table 4 of the article and the statistical testing of variables (actual test scores) comprising the memory factors is nothing more than what we used to call "data-sifting" or "data-milking" when I was in graduate school.

From my point of view as a clinical psychologist who does a lot of functional neuropsychological assessment, my initial "take" on Table 6 was that the differences between Low Dose/Control and High Dose subjects was pretty trivial. Since no scores on any of the test variables were broken down by age, I decided to take the mean age of the whole sample of 48 subjects (28.5 years) and look up the percentiles for those raw scores which are tabled in the manual for the *Wechsler Memory Scale-Revised* (WMS-R), (Wechsler, 1987, pp. 138-141). These tables provide percentiles for each age group. I used the 25-34 year group and came up with following percentiles (after having to round Bolla et al.'s reported raw scores).

Selected Percentile Equivalents from Scores

Prepared in Table 6:

	Low Dose/Control	High Dose
Logical Memory (Immediate)	62nd	55th
Logical Memory (Delayed)	67th	45th
Visual Reproduction (Immediate)	90th	74th
Visual Reproduction (Delayed)	80th	74th

This is how well the subjects scored who were tested compared to the American adult population matched for age. Fiftieth percent is the midpoint, scores above 50% are better than average, scores below are below average. The "Normal" range is 16th-84th percentile.

These percentile differences between the High Dose and Low Dose/Control groups really amount to practically nothing. When I am evaluating patients for disability or for forensic purposes, I ordinarily consider a score in the 10th percentile to represent "borderline" impairment of memory and scores at or below the 5th percentile to represent clinically significant impairment. I have encountered a majority of people with memory scores in the 15th to 40th percentile who are fully employed, sometimes affluent, and often owning their own homes.

Control and MDMA User Groups

The authors report no significant differences between MDMA and control subjects in overall memory scores and no significant associations between memory and total MDMA consumed or duration of use when comparing all 24 MDMA users with all 24 controls. However, as (unpublished) Table 6 reveals, in order to demonstrate memory impairment, the subjects had to be divided into "Control Group" which included all 24 subjects and the 13 low dose MDMA subjects (N=37) and "High Dose" N=11. The low dose MDMA users were defined in the study as persons who consumed less than an average of 400 milligrams per month for the entire period of time they had been using MDMA, with a cumulative lifetime minimum of 25 doses.

Neither the number of MDMA subjects in the high and low dose groups, nor the inclusion of the 13 low dose MDMA subjects into a larger control group, were mentioned in the paper. This is significant information that should not have been omitted. Lumping those 13 Low Dose

MDMA subjects into the Control group clearly implies that the authors considered low dose MDMA users and people who had never used MDMA to be equivalent neuropsychologically. Such a position would support the notion that low dose MDMA use is relatively harmless and that research involving the administration of MDMA to human subjects is of relatively low risk from the perspective of memory impairment.

Lumping Low Dose MDMA subjects into the Control group clearly implies that the authors considered low dose MDMA users and people who had never used MDMA to be equivalent neuropsychologically.

The authors took great pains to assure that the MDMA users and Control subjects were matched for age, gender, and verbal intelligence. However they had vastly different histories of prior drug use in general. For example, the MDMA User group had five times as many cocaine-experienced subjects (20 as opposed to four in the Control group) and five times as many people with prior amphetamine experiences (10 as opposed to two).

There are also twice as many solvent abusers in the MDMA User group (four as opposed to two) and four times as many past users of PCP (four vs. one). The groups are clearly not equivalent in terms of non-MDMA "street" drug use as reported by Bolla et al. I also suspect that the two groups may not be equivalent in their frequency of prior drug and alcohol use, but the authors provide no data on such frequencies. The effects reported later (especially since they are small) could easily have resulted from the other drugs previously used by the MDMA group. Further, while the prior drug use patterns reported in Table 2 (p. 1534) compare the 24 Subject "Control" and "MDMA User" groups, the effect sizes reported in (unpublished) Table 6 were based upon a comparison between the 37 subject low MDMA dose group and the 11 subject high dose group. One wonders how many of the four past inhalant users and how many of the four past PCP users were among the small High Dose MDMA group. Since inhalants and PCP are among the most indisputably memory impairing substances, any disproportionate representation of these subjects in the 11-subject High Dose group could in and of itself have accounted for the (relatively modest) effects reported. The 11-subject High Dose group may also have had significantly higher rates of other prior drug use than the 24 subject MDMA User group. I am of the opinion that the multiple contamination of the Control and MDMA User groups is the most disturbing flaw in this study. •

Tom is a consulting and forensic psychologist who is gradually phasing out an unsatisfying private practice and leaving Arizona for California. His main interests are schizophrenia and cognitive flexibility. He is presently looking for a clinical/research position. He had the tremendous good fortune to have been taught research design by Professor Glenn E. Tagatz, Ph.D. of Marquette University.

Reference

Wechsler, D. *Wechsler Memory Scale—Revised Manual.* San Antonio: The Psychological Corporation, 1987.

Reviewing the Latest Research with **MDMA and MDE**

A conference organized by the Multidisciplinary Association for Psychedelic Studies

August 30 — September 1, 1999 • Dead Sea Hyatt - Israel

MAPS sponsored an international conference on the clinical use of MDMA, August 31 and September 1, 1999, attended by representatives from every team in the world that has administered MDMA to human subjects, as well as several researchers in the planning stages of such studies. The conference provided information to Israeli regulators needed in determining whether to grant permission for a pilot study of MDMA in the treatment of Post-Traumatic Stress Disorder. MAPS is seeking to sponsor this study at Ben-Gurion University of the Negev, in association with Dr. Moshe Kotler and Dr. Adam Darnell. The conference encouraged the exchange of information and collaboration between research teams around the world. Further reports about this important event will appear in future *MAPS Bulletins.* Speakers presented on the following topics:

Therapeutic Uses

George Greer, MD
Pioneering the use of MDMA in psychotherapy in the United States

Juraj Styk, MD and Sonja Styk, MD
Swiss Society of Physicians for Psycholytic Therapy
Review of clinical issues in MDMA-assisted psychotherapy,
based on their use of MDMA with patients from 1988-1993 in Switzerland

Deborah Mash, Ph.D.
University of Miami, Florida.
Ibogaine research in cocaine addicts, United States, St. Kitts and Israel
(This talk is included since there are some issues common to the therapeutic use of MDMA and ibogaine.)

Raphael Mechoulam, MD
Hebrew University, Israel.
Clinical research with cannabinoids
(This talk is included because there are some policy and protocol design issues common to the therapeutic use of MDMA and cannabinoids.)

Phase 1 Studies

Charles Grob, MD — Harbor UCLA Medical Center.
University of California, Los Angeles.
MDMA dose-response Phase 1 safety study

Jordi Cami, MD, Ph.D.
Institut Muncipal d'Investigacions Mediques - Barcelona, Spain.
Phase 1 MDMA safety study

Phase 1 Studies (cont'd)

Franz Vollenweider, MD — University of Zürich, Switzerland.
Phase 1 MDMA Safety study in MDMA-naive subjects

Alex Gamma — University of Zürich, Switzerland.
MDMA PET Studies - Acute Effects

Reese Jones, MD — University of California, San Francisco.
MDMA Pharmacokinetics

John Henry, Ph.D. — Imperial College School of Medicine.
MDMA clinical research in England

Drug Discrimination and Focused Safety Studies

Efi Gouzoulis, MD — Psychiatric Department of the Technical University (RWTH) - Aachen, Germany.
Evidence from MDE research showing MDE, MDMA, etc. could belong to a new class of substances, the entactogens, and studies of memory in MDMA users v. controls

Twenty-five speakers presented at a recent conference held in Israel and sponsored by MAPS. This event encouraged collaboration between research teams around the world.

Manny Tancer, MD — Wayne State Medical School - Michigan.
MDMA drug discrimination studies

Magi Farré, MD, Ph.D. — Institut Muncipal d'Investigacions Mediques.
Study of MDMA and alcohol

Alex Gamma — University of Zürich, Switzerland.
MDMA and EEG and other measures

Wim Riedel, Ph.D. — University of Maastricht, The Netherlands.
Proposed study of MDMA and driving, cognitive and psychomotor performance

Neurotoxicity

Franz Vollenweider, MD — University of Zürich, Switzerland.
MDMA PET scan study results

Pacale Gucker, Ph.D — University of Zürich, Switzerland.
MDMA PET scan study results

Matt Baggott — University of California, San Francisco.
Review of MDMA neurotoxicity literature

Jon Cole, Ph.D. — University of Liverpool, United Kingdom.
Review of research with MDMA users in England

Lew Seiden, Ph.D. — University of Chicago, Illinois.
Preclinical neurotoxicity research

Proposed Therapy Protocols and Policy Issues

Charles Grob, MD — Harbor UCLA Medical Center.
Proposed study of MDMA in the treatment of anxiety and depression in cancer patients

Jose Carlos Bouso, Ph.D. candidate
Universidad Autónoma de Madrid, Spain.
Proposed MDMA/Post Traumatic Stress Disorder study

Moshe Kotler, MD and Adam Darnell, MD
Ben-Gurion University of the Negev, Israel.
Proposed MDMA/Post Traumatic Stress Disorder study

Mark Kleiman, Ph.D. — UCLA School of Public Policy
Policy issues in clinical research with MDMA, risk/benefit analysis

Proposal for a Study with **MDMA and Post Traumatic Stress Disorder**

By Jose Carlos Bouso Saiz
jcbouso@correo.cop.es

Principal researchers:
Pedro Antonio Sopelana Rodríguez, Psychiatrist. Hospital Psiquiátrico de Madrid
Jose Carlos Bouso Saiz, Ph.D. Candidate. Departamento de Psicología Biológica y de la Salud
Facultad de Psicología, Universidad Autónoma de Madrid
Collaborating researchers:
M. Angeles Corral y Alonso. Intern Psychiatrist, H.P.M.
Dr. Valentín Corcés Pando. Psychiatrist, H.P.M.
José María García del Valle. Cardiologist, Hospital de Cantoblanco
M. Jesús Vico Barranco. Clinical Pharmacologist, H.P.M.
Beatriz de la Luz Navarro, Nurse. H.P.M.
Ludgerio Espinosa Gil. Professor of Methodology, Facultad de Psicología, U.A.M.

Posttraumatic Stress Disorder (PTSD) is one of the most common psychological disorders today. It is estimated that approximately 25% of the victims of any crime, accident, act of violence or catastrophe can develop this syndrome.[1] The current prevalence rate of PTSD is between 1.3% and 9% for normal populations (a higher rate than that of schizophrenia) and 13% for psychiatric populations.[2] According to the DSM-IV, there are three main symptoms of PTSD: 1) Persistent re-experiencing of the traumatic incident; 2) Persistent avoidance of stimuli associated with the trauma; 3) persistent symptoms of hyperarousal.[3] These symptoms are accompanied, in approximately 80% of the cases, by high levels of associated conditions such as depression, drug abuse, anxiety, manias, personality disorders, anger, low self-esteem, etc.[4] Many people who decide to look to a specialist for help do so because of the associated symptoms rather than for the disorder itself, due to fear and the inability to recall and to face the traumatic incident.[5] This sometimes hinders the intervention of the specialist, particularly if he/she does not discover that the reported symptoms hide a deeper disorder. Symptoms tend to lead the PTSD sufferer to psychological discomfort and significant negative effects on social, occupational or other important areas of life.

FURTHERMORE, the most immediate consequences of these symptoms tend to destabilize the cognitive and emotional aspects of people suffering from PTSD.[6] Subjects experience an emotional numbness or affective dullness, demonstrated by an incapacity to express or experience affection, intimacy and feelings of tenderness.[1] This also causes subjects to lose interest in the activities in which they participated before the appearance of the trauma, leaving their social, professional and interpersonal relations substantially limited.

Although PTSD has always been a disorder associated with war (the first descriptions of the syndrome appeared during the Napoleonic Wars) it is no longer considered solely characteristic of war veterans. There are other groups assumed to suffer from it, such as victims of natural catastrophes, traffic accidents, incurable illnesses, physical abuse, victims of other violent crime and, above all, victims of sexual assault.[7] This last group, as well as survivors of war, have been the most studied.

In this research proposal we intend to administer MDMA to women suffering from chronic PTSD as a consequence of sexual assault. We believe that MDMA can help people who suffer PTSD as it allows them to re-experience the trauma in a secure context, with reduced fear and anxiety, and therefore provides them an opportunity to restructure the consequences that the trauma had in their personal lives. Some research shows that the re-experience of the traumatic incident in a secure context, where victims can recall the trauma without the usual distressing feelings, neutralizes the fear structures and allows a better adaptation in the long term.[8,9] Anecdotal cases of patients treated with MDMA before its prohibition show that the re-experience of the traumatic incident under the effects of MDMA can take place.[10] Furthermore, the fact that MDMA acts selectively on the emotions and feelings could help people afflicted with PTSD to get rid of the affective dullness that they suffer, allowing them gradually to recover their emotional balance. Those were basically the two reasons that led us to propose this study to explore the efficacy of MDMA in PTSD.

There were two reasons for choosing female victims of sexual assaults as a study population. On the one hand, important experimental research with this population has been conducted in Spain.[11,12,13] and therefore there are reliable and valid psychological assessment instruments to measure therapeutic outcome. On the other hand, unfortunately, it is estimated that between 15% and 25% of women have suffered a sexual assault, and that between 50% and 60% of those women develop PTSD.[1] This high rate should facilitate access to an appropriate study sample. The fact that symptoms become stable once they become chronic (there are no significant differences in the symptoms, for example, between the third month and the fourth year) will allow us to correlate the results of the study to the treatment, more than to the simple progress of PTSD due to the passage of time.[14] We have decided to focus on chronic cases of victims of sexual assault, which will enable us to obtain as homogeneous a sample as possible, although it is obvious that there are always variables that researchers can not control.

Anecdotal cases of patients treated with MDMA before its prohibition show that the re-experience of the traumatic incident under the effects of MDMA can take place

This research proposal was approved by the Doctorate Commission of the Department of Biological Psychology and Health Psychology (Departamento de Psicología Biológica y de la Salud) of the Psychology Department (Facultad de Psicología) of the Universidad Autónoma de Madrid in November 1998. This permission is needed to present the study as my doctoral thesis. In May 1999 the clinical trial's protocol was approved by the Teaching, Research and Training Committee (Comité de Docencia, Investigación y Formación Continuada) of the Psychiatric Hospital of Madrid, and it allows us to carry out the research in said Hospital. Finally, in July 1999 the protocol was approved by the Ethics Committee for Clinical Research (Comité Etico de Investigación Clínica) of the Hospital Universitario "La Paz" (to which the Psychiatric Hospital of Madrid belongs), an essential requirement to be able to present the protocol to the Ministry of Health, which has the last word and whose decision is expected in November 1999. MAPS has pledged $22,000 in support of this research.

Objectives of the proposed study

1. Test the therapeutic effectiveness of MDMA in a psychotherapeutic context, in women who are victims of sexual assault and who have developed chronic PTSD.

2. Test the therapeutic effectiveness of MDMA in reducing the secondary symptoms generated as a consequence of chronic PTSD in said women.

3. We will evaluate on which specific PTSD symptoms

the MDMA treatment acts.

4. Determine the most effective therapeutic dose (dose finding pilot study).

We propose to carry out two pilot studies. The first one would be a dose finding study and the second one a therapeutic effectiveness study. We outline in the first pilot study a range of several different doses to determine the most effective one. The most effective dose will be administered in the therapeutic effectiveness study. All participants are volunteers and will pass rigorous medical examination to be sure that none of them has previous illnesses which could lead to potential risk situations. The psychiatric inclusion criterion is to suffer from PTSD as a consequence of a sexual assault, according to the DSM-IV criteria.

Two psychotherapy sessions will be carried out before and after each session with MDMA or placebo. In the pre-session we intend to prepare the subjects for the MDMA session, and in the post-session we intend to facilitate the integration of the MDMA experience. There will be two psychotherapists, a man and a woman, both psychiatrists. The therapists will stay with the women during the MDMA experience to hear and support them with a phenomenological/existential approach.

In this research proposal

we intend to administer

MDMA to women

suffering from chronic PTSD

as a consequence of sexual assault.

MAPS has pledged

$22,000 in support

of this study.

The treatment will consist of the re-experience of the trauma under the effect of the drug or the placebo, in a psychotherapeutic context. As we have already mentioned, some research shows that the re-experience of the trauma in a secure context is a good predictor for the therapeutic outcome for the subject in the long term.[8] However, some drugs have turned out to be ineffectual in inducing this re-experience.[16] The hypothesis is that MDMA in a clinical context: 1) allows the re-experience of the trauma without the usual feelings of anxiety, fear and psychological distress; 2) modifies in the subjects the implications of the trauma, and 3) enhances the therapeutic alliance, a factor that has proven to be the best predictor of the therapeutic change.[17]

STUDY DESIGN

Dose finding pilot study

We suggest a pilot study with 20 subjects, five groups of four subjects each, and three different MDMA doses. This study will determine the most effective therapeutic dose, as well as the usefulness of the assesment scales. The dose for the subsequent subjects would only be increased when and if it was demonstrated that the previous dose could be administered safely. The clinical experience of some therapists when MDMA was used in psychotherapy has suggested that it can be effective to give a booster dose of half the initial dose after two hours, when the initial effects start to subside. The effect of the booster is to increase the duration of the psychoactive effects and to facilitate a gradual descent of the effects.[15] This would allow therapists to work with the subjective experiences of the subject during the sessions for a longer period of time than with a single administration and may contribute to the therapeutic effectiveness. The design of the pilot study explores the value of a booster dose.

Dose finding pilot study outline

Group 1 (4 subjects): 75 mg of MDMA followed by a placebo two hours later (3 subjects); placebo followed by a placebo two hours later (1 subject).

Group 2 (4 subjects): 75 mg followed by 50 mg of MDMA two hours later (=125 mg) (3 subjects); placebo followed by a placebo two hours later (1 subject).

Group 3 (4 subjects): 125 mg of MDMA followed by a placebo two hours later (3 subjects); placebo followed by a placebo two hours later (1 subject).

Group 4 (4 subjects): 125 mg followed by 50 mg of MDMA two hours later (=175 mg) (3 subjects); placebo followed by a placebo two hours later (1 subject).

Group 5 (4 subjects): 175 mg of MDMA followed by a placebo two hours later (3 subjects); placebo followed by a placebo two hours later (1 subject).

According to this schedule, subjects will receive a dose of MDMA followed after two hours by either an additional MDMA dose or a placebo dose. A subject from each group will receive a placebo dose followed after two hours by another placebo dose. This way we can compare three different dose levels administered with and without a booster. We will therefore explore which dose and which method of administration is more effective.

Therapeutic effectiveness pilot study

Twenty four subjects will participate in this study. All subjects will undergo two experimental sessions separated by a two-week interval. They will be divided into two groups. The first group will be administered the dosage of MDMA that was most effective in the dose-finding pilot study, either in a single dose or in two doses (a booster dose two hours after the initial dose). The second group will

receive a placebo dose under the same conditions as the subjects in group one. The study will be double-blind and assignment to the treatment will be random.

Therapeutic effectiveness pilot study outline

Group 1 (12 subjects):
2 sessions with the most effective dose of MDMA.
Group 2 (12 subjects):
2 sessions with placebo.

Proposed evaluation measures, validated for the Spanish population

Scale of Gravity of the Symptoms of PTSD (Echeburúa et al., 1997).
Semi-Strutured Interview About Sexual Aggressions (Echeburúa et al., 1995).
The State-Trait Anxiety Inventory (STAI). State version. (Spielberger et al., 1970).
The Beck Depression Inventory (BDI) (Beck et al., 1961).
The Hamilton Rating Scale (HRS) (Hamilton, 1960).
The Modificate Fears Scale (MFS-III) (Veronen and Kilpatrick, 1980).
Maladjusment Scale (Echeburúa et al., 1998).
The Rosenberg Self-Esteem Scale (Rosenberg, 1965).
The Penn Helping Alliance Questionnaire (HAq) (Alexander y Luborsky, 1984).
Hallucinogen Rating Scale (HRS). Version 3.06P (Strassman et al., 1994).
The UKU Side-Effects Rating Scale (Lingjaerde et al., 1987).
The Penn Helping Alliance questionnaire (HAq) (Alexander y Luborsky, 1984).

The experimental research will take place in the Psychiatric Hospital of Madrid, where subjects will have to undergo the treatment. Because of the characteristics of this hospital (an institution reserved for the chronically and acutely "mentally ill"), the subjects in this study will not be formally hospitalized, in order to avoid the possible fearful connotations of admittance to a psychiatric ward. Subjects will leave the hospital once the effects of the drug have worn off, accompanied by a relative or by taxi.

There will be a follow up of the progress of the subjects at one, three, six, nine and twelve months. The outcome measures will be administered by a blind rater, who will be the same person to do the follow up testing.

The design of the dose-finding pilot study explores the value of a booster dose.

Acknowledgments

In the first place, I want to thank Rick Doblin for the continous help he has offered me since the moment when I decided to get involved in this project. From the first day he supplied useful information and has given me valuable comments, above all during the experimental design phase, which is his in good part.

Dr. Magí Farré (IMIM) who has advised me of the bureaucratic steps to be taken, as well as about the formal preparation of the protocol. He also read the protocol before it was presented to the Ethics Committee and made an essential last-minute improvement in the experimental design.

Of course, I personally made all decisions regarding the protocol, so any existing errors can only be attributed to me.

I want to thank as well the generous help from Dr. Valentín Corcés and above all the help from Dr. Pedro Sopelana, who offered to participate in the project as principal researcher, when I thought I was not going to find anyone to do so.

I appreciate the support and useful comments of Manuel Díez and Miguel Angel Alcázar and of other friends and colleagues. And lastly, my partner Maite Muñoz for her encouragement and valuable comments. •

References

(1) Corral, P; Echeburúa, E; Sarasua, B; Zubizarreta, I. (1992): "Estrés Postraumático en Ex Combatientes y en Víctimas de Agresiones Sexuales: Nuevas Perspectivas Terapéuticas." *Boletín de Psicología*, 35: 7-24.

(2) Van der Kolk, B.A.; Van der Hart, O.; Burbridge, J. (1995): "Approaches to the Treatment of PTSD." Bookshelf.

(3) American Psychiatric Association (1994): *Diagnostic and Statistical Manual of Mental Disorders* (4th. ed.). Washington DC: A.P.A.

(4) Helzer, J.E; Robins, L.N.; Mcevoy, L. (1987): "Post-traumatic Stress Disorder in the General Population: Findings of the Epidemiologic Catchment Area Survey." *New England Journal of Medicine*, 317 (24): 1630-1634.

(5) *The Harvard Mental Health Letter*, June-July,1996: "Post-traumatic Stress Disorder."

(6) González de Rivera, J.L. (1990): "El Síndrome de Estrés Post-traumático." *Psiquis*, vol. 11: 11-24.

(7) Echeburúa, E.; Corral, P. (1997): "Avances en el Tratamiento Cognitivo Conductual del Trastorno de estrés Postraumático." *Ansiedad y Estrés*, 3(2-3): 249-264.

(8) Meichenbaum, D. (1994): "Tratamiento de Clientes con Trastornos de Estrés Post-Traumático: Un Enfoque Cognitivo Conductual." *Revista de Psicoterapia*, 5 (17): 5-84.

(9) Echeburúa, E.; Corral, P. (1995): "Trastorno de Estrés Postraumático." En: Belloch, A.; Sandín, B; y Ramos, F. (Eds.): *Manual de Psicopatología*. Madrid: McGraw Hill.

(10) Greer, G.; Tolbert, R. (1998): "A Method of Conducting Therapeutic Sessions with MDMA." *Journal of Psychoactive Drugs*, vol. 30 (4), Oct-Dec: 371-379.

(11) Corral, P; Echeburúa, E; Sarasua, B; Zubizarreta, I. (1995a): "Tratamiento Cognitivo-Conductual del Trastorno por Estrés Postraumático Agudo en Víctimas de Agresiones Sexuales: Un Estudio Piloto." *Psicología Conductual*, 3(2): 195-210.

(12) Corral, P; Echeburúa, E; Zubizarreta, I.; Sarasa, B. (1995b): "Tratamiento Psicológico del Trastorno de Estrés Postraumático Crónico en Víctimas de Agresiones Sexuales: Un Estudio Experimental." *Análisis y Modificación de Conducta*, 21(78): 455-482.

(13) Sarasa, B; Echeburúa, E; Corral, P. (1993): "Tratamiento Psicológico del Trastorno de Estrés Postraumático en una Víctima Reciente de Violación." *Análisis y Modificación de Conducta*, 19 (64): 189-213.

(14) Kilpatrick, D.G. (1992a): "Etiología y Factores Predictivos de Estrés Postraumático en Víctimas de Agresiones Sexuales." En: Echeburúa, E. (Ed.): *Avances en el tratamiento psicológico de los trastornos de ansiedad*. Pirámide: Madrid.

(15) Greer, G and Tolbert, R (1986): "Subjective Reports of the Effects of MDMA in a Clinical Setting." *Journal of Psychoactive Drugs*, vol. 18 (4): 319-327.

(16) González de Rivera, J.L. (1994): "El Síndrome Post-traumático de Estrés: Una Revisión Crítica." En: Delgado Bueno, S. (Dir.): *Psiquiatría Legal y Forense*. Madrid: Colex.

(17) Poch, J.; Avila, A. (1998): *Investigación en Psicoterapia*. Barcelona: Paidós.

MDMA in a couple struggling with cancer: Two years later

August 7, 1999

In the Autumn 1997 *MAPS Bulletin*, Sue and Shane wrote about the difficulties of dealing with his cancer and how they saved their relationship with the help of MDMA. Here, Sue writes about their continuing struggle.

MEETING SHANE SIX YEARS AGO was a dream that fluttered into a nightmare state many times. I knew that I was in love, but the fears that we both faced since Shane was diagnosed with renal cell cancer in 1995 made a constructive, blossoming relationship nearly impossible.

In 1997, MDMA and proposed studies with cancer patients were brought to our attention by a good friend. After much research on our end, we decided to try it. I'm not exaggerating when I claim that it was the best event of our relationship and of our lives. It changed how we looked at life, how we looked at love and how we felt love. Our channels of communication opened fully and three years after this event, we still utilize the knowledge we gained that night. We were allowed to live a lifetime full of love in an evening. With Shane's cancer and the uncertainty of our time together, this was the most wonderful blessing. It allowed us to address issues involving his cancer—a formerly taboo subject with us, and to be able to learn to cope. We were allowed to learn how to open up to each other with such a painful subject coming between us. We have learned since we wrote in the *MAPS Bulletin* about our two MDMA sessions in 1997 that Shane's cancer has spread.

It has not only gone to his lungs, but is now in his brain along with the new tumor in his kidney area. He also has a golf ball-sized nodule on his neck. He went through an agonizing six weeks of radiation to his head trying to kill the tumor on his brain. The radiation succeeded in making his gorgeous mane of chestnut hair fall out.

As for the tumor we were attempting to evict from its new home, well... it defied our direct orders to leave and decided it liked its location. Believe it or not, once it defied us and didn't leave, we decided that while it's there to stay, we're not only making the best of it and accepting it, we have named the tumor and made "friends" with it. If Shane ever has a time where he begins to babble incoherently—we try to decide if it's the drugs he is on, or if it's "Steve" talking to us. Yes, we try to take this as good-naturedly as we can despite our fear.

My own health

Due to the circumstances of what Shane and I are going through, I have been to my breaking point and back quite a few times. I have friends who say that I'm

In 1997, Sue wrote:

We still fall back on our first MDMA session together when one of us feels like we are closing down emotionally on the other...

handling the potential loss of the man I love more than life like a trooper. I have been called courageous. But I feel like a scared little girl inside that just has no choice but to survive and be brave. Having three kids who depend on my strength has brought me to where I will always be able to pick myself up and continue. God knows, there are days when I feel that I just can't do it anymore, days where the fear inside threatens to consume me and then spit me out. But I manage. When I lose Shane to the cancer, I am afraid of walking through life as a mere shell of a human.

Recently my doctor became concerned when he saw that I have been losing a lot of weight. He prescribed Paxil for me in addition to the Klonopin that he had already prescribed to me for the really taxing times where the stress gets unbearable. Researching Paxil on the Net scared me. The terms bi-polar and neurosis jumped off the screen and made me think that maybe, just maybe, I was worse off than I thought. Then Paxil was explained to me by a friend. Taking it daily has allowed me to breathe again. I still have a cloud over my head, but it's dissipating.

Poor prognosis

Our fears have been coming to a head lately. Shane's cancer is progressing and there is nothing that can be done to stop it. His doctor is now using the words "pain management" instead of treatment. Oh, how that hurts the both of us. He is no longer the vibrant, full of life man that I fell deeply in love with so many years ago. My love has grown for him tenfold since his conditioned has worsened. He has shown me a vulnerable side and I have gotten fiercely protective of him. This same man who used to put on his roller-blades and gripe at me to get off the computer to go blading with him, has a hard time getting up off the couch to do a simple task such as going to the bathroom. The man who used to have bulging muscles is now going through a wasting syndrome and getting bedsores from laying down constantly. His weight has dropped drastically and he takes 2200-calorie weight gainer drinks along with the drink Boost nightly to try to keep weight on. His belly is very bloated due to where they removed his cancerous kidney five years ago. There is a tumor replacing it that is bigger than the original kidney. It is pressing on his internal organs, causing the belly to be distended drastically. A standing joke is for me to hand him a bowl and have him go ask the neighbors for rice. Yes, his belly is that bad. Recently we have discovered that his remaining kidney is being affected and from this, he is retaining water so badly that his feet and ankles are swollen and he can no longer wear his once loose-fitting slippers. His ankles are almost as big as the bottom of my thigh.

Pain management

Blessed words indeed. For the longest time while he was still up and around, Shane was only taking Vicodin for the pain and was able to still be up on a roof 8 to 10 hours a day shingling (his job). Those days are a distant memory. The list of meds he is on is a long one:

1. MS Contin - 90 mg. taken twice daily - 12 hour intervals.
2. Roxanol-T - 1 mL taken every 3-4 hours for breakthough pain as needed.
3. Oxycodone - 5 mg taken every 3-4 hours for breakthrough pain. This is sometimes taken instead of the Roxanol if the pain isn't excessive.
4. Lasix - 40 mg taken twice a day to try to relieve some of the horrible water retention from the malfunctioning remaining kidney.
5. K-Dur - taken twice a day as a potassium supplement needed from taking the Lasix.
6. Restoril - 30 mg taken as needed for sleep. The morphine for some reason makes it difficult for him to sleep, so these are needed occasionally.
7. Vicodin - 5/500 - these aren't taken very often anymore due to the increase in pain, and they just aren't as good as the other things that he is on for pain management.

All of the medications that he is on have robbed him of a quality life, but allow him to manage the pain somewhat. He nods

off regularly—we deem this the "Morphine Nods"—he will be sitting there in a conversation and suddenly his head will drop to his chest and he's out for the count, momentarily. He snaps back out of it after a few moments only to do it again shortly there after.

Have I mentioned that life is too short and to live it and love it to the fullest?

A third MDMA session?

Since there has been such a progression in his illness, we have been wanting to have another MDMA session. Luck has been with us and we have procured enough for a session for the both of us. We can now be open and talk about nearly anything, thanks to the sessions we had in 1997 and that we've adapted into everyday life. But there are still issues that are so painful that we don't want to talk about them. Funeral... life afterwards... last wishes... and I will admit, we are just plain greedy. We want one more night of barrier-free love and closeness. We want all walls of pain to be dropped if only for a night. To share what others write about in fairy tales and dream about in the most beautiful nights of slumber. When we had our second MDMA session in 1997, we walked to the field at the end of our street and lay in the grass watching the stars. I can't really describe how it felt, but to sum it up to the best of my ability, we were immortal. Cancer, death and anything bad had no place in our lives that night. No clouds over either of our heads. We felt like normal people. We have been coping with the cancer so long that it has become second nature to us and we don't think anything out of the ordinary of it. Oh, to be normal for a night. To feel love without fear, to feel life without pain.

Facing loss

WALKING hand-in-hand through life with your soul-mate... this is something that most only dare dream of. Finding that one person that knows you better than you know yourself, someone that you are positive was your destiny... I was one of the lucky ones.

Walking through life anticipating losing your soul-mate is something that masks itself as a nightmare. I'm afraid of never waking up from this. I'm terrified of becoming a mere shell of a person, going through the motions of life without feeling... without daring to care again for fear of the pain coming back once I begin to heal.

I'm not afraid to admit that I'm bitter. I try not to be, but there are days that I can't help how I feel. I'm only human. But I am, I'm bitter because of what Shane and I are going through and the closeness that is going to be ripped from us in the not-so-distant future. I have days where I feel so much animosity towards others who are in relationships as they tell me how happy they are. I don't feel it's fair that I find the love of my life, and can't keep him for what society deems "forever." From this though, I'm able to tell people to love to the fullest extent of their capabilities. Life is too short.

I recall one incident where a woman that I work with and I were watching a movie one night at work, "Stepmom." She came up with the comment of "Can you imagine living your life knowing that you're going to die?" This thought actually floored her! I had to laugh inside because I live with this every minute of every day of my life. I have a cloud of death over my head due to Shane's cancer. I've discovered that the average person that hasn't been exposed to a terminal person seems to think that they are immortal. Death isn't an issue with most people. They shed a tear when they hear of a tragic incident, maybe they have lost a distant relative... but still seem to think that life goes on forever. I hate to tell them (so I don't) but life doesn't go on indefinitely. We are all mortal and will all be affected by the death of someone close to us eventually. •

We can now be open and talk about nearly anything, thanks to the sessions we had in 1997 and that we've adapted into everyday life. But there are still issues that are so painful that we don't want to talk about them.

Cannabis in Migraine Treatment Project Close to FDA Approval

The future of medical marijuana research is uncertain, though looks promising. In late July 1999, the FDA informed Dr. Ethan Russo, University of Montana, that his MAPS-supported protocol to study marijuana in the treatment of migraines was fully approved. However, the protocol was placed on hold until NIDA decides if it will supply the marijuana. NIDA's new policy is to submit FDA-approved projects to a special Public Health Service (PHS) review before agreeing to sell marijuana for a yet-to-be-determined price to non-government funded projects. Whether this PHS review will be conducted in a fair and timely manner remains to be seen.

Dear Friends,

I received word today from FDA that my revised protocol for the *Cannabis in Acute Migraine Treatment Project* has been accepted by that agency, but remains on "clinical hold" pending receipt of a letter from NIDA authorizing access to the Drug Master File on cannabis. I have previously been in contact with personnel at NIDA in regard to obtaining that letter. Thus it appears that my protocol is ready for the PHS review that has been mandated by NIDA, although seemingly without any legislative basis.

Although I would repeat my opinion that this process is redundant in view of FDA acceptance, I have willingly submitted the protocol to NIDA. Inasmuch as FDA assesses its IND applications in 30 days from receipt, I would expect similar treatment for this protocol from NIDA. I understand that NIDA has said that a price for the cannabis will not be available until December 1999, but that should not delay this process, since I am willing to pay any price that is required for the 200 grams of cannabis, and 200 grams of acetone-treated cannabis placebo. Thus, I would hope to hear from NIDA expeditiously as to plans and disposition of the project.

This application process began in early 1997 when FDA refused to review a first protocol due to lack of an approved supply of cannabis from NIDA. A subsequent application to NIH for funding was denied. The process repeated itself in 1998 with an FDA refusal, and subsequent NIH denial of an amended protocol.

In 1999, the protocol was submitted a third time, but received the mandated 30 day review with request for certain clarifications and supplementation. These were recently returned, and apparently were sufficient to allow FDA approval pending NIDA cooperation. I am hoping that a "thaw" has occurred in NIDA philosophy on provision of cannabis for clinical studies. If so, an additional hurdle will remain in the fund-raising for performance of the study. What was originally envisioned as a simple clinical trial has grown into a budget of some $250,000 to study effects of cannabis, Marinol (synthetic THC), and their placebo equivalents vs. injected sumatriptan (the current "gold standard") in 40 patients over five months.

We will provide additional news of developments as they become available. •

Ethan Russo, MD
Department of Neurosciences
18717 Highway 200 East
Western Montana Clinic
Bonner, MT 59823-9722
Phone: 406-329-7315 FAX: 406-329-7453
ptm5739@montana.com

MAPS Succeeds in Securing an **Orphan Drug Designation** for Marijuana

Rick Doblin

TWO AND A HALF YEARS AGO, MAPS submitted an application to the Food and Drug Administration's Office of Orphan Drug Products requesting that marijuana be designated an Orphan Drug for the treatment of AIDS wasting syndrome. The Orphan Drug program was created by Congress to facilitate development of drugs for rare diseases, defined as fewer than 200,000 patients per years. Drugs for such rare diseases have not been considered sufficiently profitable for pharmaceutical companies and research has been minimal, leaving drugs for rare diseases "orphans." Orphan Drug designation provides a package of incentives for research and development, culminating in seven years of patent protection (exclusive right to market) should convincing data about safety and efficacy ever be submitted to the FDA and the drug be approved for marketing. Marinol, the oral THC pill, was approved for AIDS wasting under the Orphan Drug program.

the FDA Office of Orphan Products Development approved MAPS' application to have marijuana declared an Orphan Drug for AIDS wasting.

On May 25, 1999, the FDA wrote a letter announcing that MAPS' application, which had already been rejected five times and each time sent back to MAPS for a response, had finally been accepted. This designation is a demonstration of good faith on the part of the FDA and represents a major milestone in MAPS' efforts to support research into the medical uses of marijuana.

As MAPS members and other readers of the *Bulletin* probably know, MAPS began working in 1992 with Dr. Donald Abrams, UC San Francisco, in an effort to obtain permission for his study of the use of marijuana in AIDS patients. Dr. Abrams' study was eventually approved, received a $970,000 grant from NIDA, and treated its first subject in 1998. Dr. Abrams' study is the first FDA-approved investigation of the medical use of marijuana in a patient population in 15 years. Dr. Abrams will complete the dosing phase of the study in early 2000. MAPS' successful effort to have marijuana declared an Orphan Drug will make it easier to continue to research the medical use of marijuana for AIDS wasting syndrome, if the data gathered by Dr. Abrams demonstrates that marijuana can be administered safely to AIDS patients.

Another benefit of having marijuana declared an Orphan Drug by the FDA is that it will theoretically be easier for MAPS to obtain a DEA license to establish a domestic medical marijuana production facility to produce high-quality marijuana for FDA-approved research. In late July 1999, MAPS received a grant of $20,000 from Peter Lewis to explore whether it really will be possible to obtain a DEA license to establish a domestic medical marijuana production facility. MAPS is currently searching for the appropriate personnel with whom to prepare an application to the DEA, preferably partnering with an already existing botanical medicine company with expertise in developing plant-based medicines for pharmaceutical research.

MAPS is the first organization to use the Orphan Drug program to help facilitate research into any medical use of marijuana. The way the program is structured, other entities can also seek Orphan Drug designation, either for AIDS wasting or for other rare diseases that marijuana may be useful in treating. Congress intended Orphan Drug designation to be the starting point for scientific research that would culminate in an informed decision regarding the potential safety and efficacy of each designated drug for the treatment of the specific indication so designated.

The growth of political support for scientific research into the medical use of marijuana has resulted in several for-profit firms initiating research into various forms of marijuana extracts and isolated cannabinoids administered in non-smoking delivery systems such as vaporizers and aerosol sprays. MAPS supports all of these efforts to develop needed medicines for patients. MAPS' work on behalf of research into the plant itself is intended to ensure that an accurate risk/benefit ratio can be determined for the use of marijuana when smoked or used in a vaporizer. Profit-making firms with obligations to shareholders have powerful incentives to abandon efforts to study and obtain approval for the plant itself, which is likely to be the least expensive, least profitable dosage form and is certainly the most politically controversial. As a non-profit organization, MAPS does not face such pressure and will therefore focus on facilitating research with the marijuana plant.

Orphan Drug designation is merely the first step in a very long process. Whether any additional progress will be made remains to be determined. •

Medical Cannabis Potency Testing Project

Dale Gieringer, Ph.D.

Given the rapidly growing use of medical cannabis for a wide variety of indications and the manifold different underground sources currently supplying patients, there is a natural interest in investigating the potency, purity, and chemical content of the available supplies of medical cannabis. While the availability of medical cannabis has increased in the wake of the passage of California's Proposition 215 and other state medical marijuana initiatives, scientific research on its content remains frustrated by the continued federal ban on medical cannabis research.

Forty-seven samples of medical cannabis were submitted By over a half-dozen providers and patients' cooperatives ranging from California to the East Coast.

In an effort to cast light in this obscure area, a research project was undertaken by a group of us, including researchers, growers, and medical cannabis buyers' clubs, with support from California NORML and MAPS, to analyze samples of medical cannabis from various patients' cooperatives and providers around the country. This effort proved to be a lesson in the difficulties and uncertainties of cannabis research in a society where freedom of pharmacological research has been stifled by an effectively totalitarian drug bureaucracy.

From the outset, our project was frustrated by a lack of access to qualified research labs with expertise in analysis of cannabis. The leading research lab in the country declined to do business with us for fear of compromising government contracts, while the other likely candidates were all foreign and thus not legally accessible to us because of DEA regulations. In the end, we were fortunate to obtain the services of a laboratory that had the requisite DEA license and equipment (a gas chromatograph mass spectrometer, or GCMS), but no prior experience in cannabis analysis—in fact, its primary business was drug urinalysis! The analysis of our samples was accordingly a learning process for both the lab and ourselves.

Our original aim had been to obtain a broad-spectrum quantitative analysis of as many of the 60-plus naturally occurring cannabinoids as possible, in the hope of detecting differences that might produce differing therapeutic effects among the samples. To our disappointment, however, our lab could obtain laboratory standards only for the three most common cannabinoids, delta-9-THC, cannabidiol (CBD), and cannabinol (CBN).

A total of 47 different samples of medical cannabis were submitted by over a half dozen different providers and patients' cooperatives ranging from California to the East Coast. Included were 42 samples of sinsemilla bud, three samples of hashish or resin; one liquid sample of a milk-based cannabis drink ("Mother's Milk"), and one capsule of an oral whole leaf preparation.

Upon analysis by GCMS, the potency of the 42 sinsemilla samples was determined to range from 10.2% to 31.6% THC, with a mean of 19.4%. These results were surprisingly high, given that the average potency of marijuana in the U.S. has been typically estimated at around 3% to 4% by

Dale Gieringer, Ph.D.
California NORML, 2215-R Market St. Suite 278
San Francisco CA 94114 tel: (415) 563-5858
E-mail: canorml@igc.apc.org

NIDA, with higher grade sinsemilla ranging towards 10% - 15%. The highest potency recorded came from a sample of hashish, which registered 68.6%. Yet even a sample of Mexican commercial grade registered a surprisingly high 11%, twice what we had expected. All of this cast a troubling shadow of doubt on our test results, although it appeared likely that we were dealing with highly potent varieties.

In contrast, the CBD levels observed were surprisingly low. Only four of the sinsemilla samples had more than 0.3% CBD, and 35 of them had only trace amounts (<0.1%). However, one sample had an astoundingly high CBD content of 28.0% (plus 11.6% THC). Another registered 5.6% CBD and 13.4% THC. Aside from these two anomalies, the CBD results were frankly disappointing, as we had hoped to discover significant variations in the content of the samples, with accompanying variations in medical activity. Because CBD is suspected to have peculiar efficacy for control of muscle spasms and for damping anxiety and "panic reactions" caused by THC, we had hypothesized that certain patients would tend to prefer high-CBD varieties. In fact, however, it appears that few patients are ever exposed to high-CBD cannabis. Unfortunately, we were unable to procure additional specimens of the high-CBD varieties for further testing.

As for CBN, the majority of samples showed only trace amounts. The highest level detected was 1.4%, and only one other sample tested above 1%. CBN is a breakdown product of THC, so high CBN levels are expected in old, degraded samples. This was confirmed by the fact that one of the samples above 1% CBN was known to be a year old. The prevalence of low CBN in the samples was evidence that most available medical cannabis tends to be fresh and well-preserved. Otherwise, these results were of limited interest, as there are few if any known medical effects of CBN.

Another disappointing surprise was the failure to detect more than trace levels of THC or CBD in the liquid "Mother's Milk" sample. Upon further investigation, the lab determined that this was because it is impossible to extract cannabinoids from fat-based liquids using standard methanol extraction techniques. Consulting with other researchers, we found that there is no known method for isolating THC from fat-based liquids.

Later, we located a lab that claimed to have developed a secret, proprietary method for extracting cannabinoids from fat. With considerable difficulty, we arranged to have the lab test the Mother's Milk. To our disappointment, however, once again only trace amounts of THC and CBD were detected. Just to make sure, one of us swallowed a sample of the Mother's Milk (which by now had spent several

Included were 42 samples of sinsemilla bud, three samples of hashish or resin; one liquid sample of a milk-based cannabis drink, "Mother's Milk," and one capsule of an oral whole leaf preparation.

Table: THC and CBD Test Results (Round 1 vs. Rounds 2 and 3)

	1st Round		2nd Round		3rd Round (New Lab)	
Sample name	THC -1	CBD-1	THC-2	CBD-2	THC-3	CBD-3
High CBD	11.6%	28.0%	4.0%	16.2%	2.8%	8.8%
Sinsemilla BB 006	25.2	<.1	18.2	<.1	14.9	<.1
Sinsemilla BB 008	27.4	<.1	35.1	<.1	21.0	0.07
Sinsemilla MR001	18.0	<.1	11.7	<.1		
Sinsemilla BB 009	10.2	1.3	7.6	2.8		
Sinsemilla SCJ	14.2	<.1	14.1	<.1		
Sinsemilla BB 007	21.1	<.1			12.8	<.1
Sinsemilla Tri 501	27.2	<.1			20.0	<.1
Sinsemilla BB 010	18.0	0.3			8.7	<.1
Sinsemilla BB 004	18.6	<.1			13.0	<.1
Sinsemilla AQ	23.7	<.1			17.6	<.1
Hashish	68.6	0.1			44.0	<.1
Mother's Milk	<.1	<.1			<.1	
NIDA Leaf			3.9%	<.1		
Low-grade Leaf			2.1	<.1		

months in the freezer) and found it to be delightfully potent. Evidently, the lab's technique had failed. It appears that further advances in testing technology will be needed in order to properly analyze fat-based oral cannabis products such as Mother's milk, bhang, ghee, and possibly baked goods such as brownies.

The extraordinarily high THC potency in the sinsemilla samples raised troubling doubts about the reliability of the test results. The lab director expressed concern about the sample preparation, saying that he had noted a tendency for the oils to separate from the rest of the liquid during extraction. We therefore decided to re-submit some of the samples for a second round of testing. We selected six samples, including the one with anomalously high CBD. As a check, we added two new samples with presumably low potency: a sample of low-grade leaf, and some of the government's own marijuana, grown for NIDA, whose potency is known to be in the 2.9 - 3.9 % range.

In the second round of testing, the average THC potency for the seven samples declined slightly to 15.1% from 17.8% in the first round. For the six low-CBD samples, second-round potencies varied between 65% and 128% of their first-round values (see table). The high CBD sample registered a precipitous decline of 60 - 65% in both THC and CBD, bolstering suspicions of some kind of irregularity in the sample. NIDA's marijuana came in at 3.9%, at the high end of its expected range, and the low-grade shake came in at 2%. One sinsemilla sample registered a record 35% on re-testing.

The second round of testing failed to dispel our uncertainty about the results. Overall, the trend of the data seemed to confirm our suspicions that the first round results had been systematically too high. However, the wide variation in individual test results between the two rounds undermined confidence in any firm conclusions. While it seemed reasonable to infer that we were dealing with some genuinely potent cannabis, the high-range results for NIDA's pot suggested that the second round might still be too high.

After some months of head-scratching, we stumbled upon the opportunity to re-check our test results via a circuitous route to a second lab. This lab, recognized for its expertise in cannabis potency testing, was the same one that tested the Mother's Milk. In addition to the Mother's Milk, we submitted seven sinsemilla samples, the high-CBD sample, and the high-potency hashish. The potencies were uniformly lower in the third round than the first, by proportions ranging from 25 - 50%. All of this clearly implied that our first round test results had been systematically on the high side. Still, the average potency of the seven sinsemilla samples was an impressive 15.4%, four or five times greater than NIDA's marijuana.

we can safely conclude that the marijuana currently being provided by underground cannabis clubs is far superior in quality to that currently provided by NIDA to the eight legal medical marijuana patients.

From this, we can safely conclude that the marijuana currently being provided by underground cannabis clubs is far superior in quality to that currently provided by NIDA to the eight legal medical marijuana patients. Due to its higher THC content, patients need consume only a fraction of the harmful, non-medically-active tars and gases in cannabis smoke in order to achieve the same effective dose. This is of course especially significant in light of the recent Institute of Medicine report, which singled out smoking as the major adverse health hazard of medical marijuana. Aside from THC, we could find no significant presence of the other tested cannabinoids, CBN and CBD, except in one or two anomalous samples. There is thus little evidence that patients are currently making use of differing varieties of cannabis to treat different medical conditions, although it is possible that other, untested cannabinoids remain lurking in the background. Finally, our experience shows that laboratory measurements of cannabinoid content can vary widely from test to test and lab to lab, and are entirely undependable in the case of fat-based cannabis liquids. •

Reprinted with permission from *Advances in Mind-Body Medicine*, 15 (1999)

Do entheogen-induced mystical experiences boost the immune system?
Psychedelics, peak experiences, and wellness

Thomas B. Roberts, Ph.D.

Abstract:

DAILY EVENTS THAT BOOST THE IMMUNE SYSTEM (as indicated by levels of salivary immunoglobulin A), some instances of spontaneous remission, and mystical experiences seem to share a similar cluster of thoughts, feelings, moods, perceptions, and behaviors. Entheogens — psychedelic drugs used in a religious context—can also produce mystical experiences (peak experiences, states of unitive consciousness, intense primary religious experiences) with the same cluster of effects. When this happens, is it also possible that such entheogen-induced mystical experiences strengthen the immune system? Might spontaneous remissions occur more frequently under such conditions? This article advances the so called *"Emxis hypothesis"* — that entheogen-induced mystical experiences influence the immune system.

Thomas B. Roberts, Ph.D. is a Professor of Educational Psychology at Northern Illinois University, DeKalb, Illinois, where he has taught courses on transpersonal, mind-body, psychedelic, and consciousness topics.
E-mail: P30TBR1@WPF.CSO.NIU.EDU

COMBINED OBSERVATIONS from biology, medicine, religion, psychology, and psychotherapy point to the possibility of a fascinating relationship among entheogens (psychoactive plants and chemicals used in a religious context), mystical experiences, and the immune system — that entheogen-induced mystical experiences may strengthen the immune system. I call this proposition the "Emxis hypothesis" - "emxis" being a partial acronym of sorts for "Entheogen-induced Mystical eXperiences Influence the immune System."

This article summarizes the observations that contribute to the Emxis hypothesis, and it explores some possible connections among these observations and their academic disciplines. In skeletal form, the Emxis hypothesis is based on the following observations: the immune system is boosted by a number of emotionally positive events in people's daily lives; these events are weaker forms of similar experiences that occur during mystical states; and under the right psychological state and physical location—known in the literature as "set and setting"—entheogens induce mystical states. To be clear, it is not my contention that the Emxis hypothesis is proved but rather that it offers leads worth investigating. There are many unknowns here, as suggested by my own varied entheogenic experiences: powerfully overwhelming states of unitive consciousness probably occurred about one-sixth of the time, while brief, more diluted episodes of a feeling of sacredness occurred over half the time.

These mixed results prompt the first of several caveats I want to note. First, the Emxis hypothesis does not apply to all

psychedelic usage or to all religious uses but only to those occasions when entheogens bring about states characterized by profound experiences of oneness. Some religions use marijuana sacramentally (see, for example, Chevannes 1995), but this usage does not seem to produce states of unitive consciousness, and thus falls short of the mystical state that is an essential element of the Emxis hypothesis.[1]

Again, the hypothesis does not apply to psycholytic psychotherapy (Grof 1975/1993, 1980/1994; Passie 1997), which uses small doses of LSD in multiple sessions as a way to help bring otherwise blocked material to consciousness. Since the small doses, used as an adjunct to usual psychotherapeutic practices, do not produce a mystical experience, this is outside the Emxis hypothesis, too.

On the other hand, psychedelic psychotherapy (Grof 1975/1993, 1980/1994; Passie 1997), in contrast to low-dose psycholytic psychotherapy, uses single, heavy-dose sessions that have the intent of providing psychotherapeutic mystical experiences. In the instances in which this goal is reached, the Emxis hypothesis would look for boosts to the immune system. The fact that psychedelic therapy does not always produce a state of unitive consciousness could be useful in studying the hypothesis. Conceivably, if the predominant emotions raised by the therapy were negative and if the patients' stress were unresolved, such "unsuccessful" sessions would provide a control to mystical-experience sessions: both would be high-dose but with opposite emotional tones.

Finally, a caution: Even if entheogen-induced mystical experiences strengthen immune functions, they might not be strengthened enough to influence health or may be strengthened only marginally. As Stone et al. (1996) found in a study of salivary immunoglobulin A (IgA), the role of positive emotions may be primarily to counteract negative emotions; the positive emotions may not actually add strength to the immune system beyond its normal capacity. The whole issue of the possible immune effects of exceedingly positive experiences is not clear because all scientific research done to date has been within the range of normal daily events. The immune effects of exceedingly strong positive affect have yet to be studied.

Such cautions and caveats notwithstanding, this article argues three main points: that entheogens sometimes produce mystical experiences, that mystical experiences contain exceedingly powerful positive affects and cognitions, and that in daily life-events, lesser instances of these feelings and thoughts strengthen the immune system somewhat. It then pursues two related questions: Do the powerful positive affects and cognitions during mystical experiences strengthen the immune system a great deal? Is it possible to find anecdotal and clinical reports of unusual cures that are associated with mystical experiences and/or the typical thoughts and feelings that accompany them? We begin our investigation by taking a closer look at entheogens and mystical experiences.

Entheogens and mystical experiences

What are entheogens? Because psychedelics select certain emotional and cognitive processes, focus one's attention on them, and magnify subjective awareness, they produce a great variety of effects —sometimes conflicting effects. In this article, we are interested in the occasions that psychedelics produce states of unitive consciousness, or mystical experiences. When causing this kind of experience, they are called "entheogens."

The literature on psychedelics and mystical experiences occurs predominantly in two disciplines, religion and psychotherapy. The word "entheogen" comes from the religious literature. The term, which literally means "realizing the divine within" or "generating the experience of god within," was coined in 1979 (Ruck et al.) specifically to denote the religious experiences of psychedelic use. The Native American Church's use of peyote as a sacrament is probably the most widely recognized example.

The classification of a psychedelic as an "entheogen" comes from its use, not its chemical structure or any other drug taxonomy. The process of labeling a psychedelic as an entheogen is similar to classifying the wine in a religious ceremony as a sacrament, in other words by its use,

1 - Of course, it would be interesting to know whether less intense strengthening of the immune system occurs under these less intense conditions—that is, whether there is a gradual, dose-related strengthening or a step-function that suddenly occurs.

rather than by its chemical structure or its possible use as a food, medicine, or recreational drug.

The scholarly writings on entheogens occur in religion, theology, psychology, archeology, anthropology, sociology, history, law, literature, and a scattering of related fields. Taken as a whole, but still with widespread disagreement, there is general consensus that, under the right conditions, entheogens may induce experiences that are identical with, or closely resemble, mystical experiences that can be attributed to religious practices such as fasting, prayer, meditation, an ascetic life, or "the grace of God."

Religious writings on entheogens contain a large number of complex arguments about whether entheogen-induced mystical experiences are genuine religious experiences and a large number of considerations about how one goes about interpreting these experiences as religious phenomena. As important as these religious issues and distinctions are, in this article we are going to side-step them, and focus rather on the existence of entheogen-induced mystical experiences and the effects of mystical experiences on the immune system.

That entheogens do produce mystical experiences that are akin to religious experiences is indicated by two respected but by no means universally accepted scholarly investigations. One is Forte's anthology *Entheogens and the Future of Religion* (1997), and the other, an earlier work, is the chapter "Psychedelic Drugs and the Human Mind" in Grinspoon and Bakalar's *Psychedelic Drugs Reconsidered* (1979/1997). As for the Forte anthology, the well-known philosopher of religion, Huston Smith, evaluates it as "the best single inquiry into the religious significance of chemically occasioned mystical experiences that has yet appeared." With various flavors to their answers, the contributors maintain that entheogens sometimes produce religious experiences.

This outlook echoes Grinspoon and Bakalar's analysis two decades earlier in their comprehensive review of psychedelic research. The evidence, they argue, demonstrates "that psychedelic drugs produce experiences that those who undergo them regard as religious in the fullest sense." In addition, "drug-induced religious and mystical experience is often reported to be unusually intense."

Additional support for the proposition that psychedelics can induce mystical experiences comes from a more recent review, Hood's The Facilitation of Religious Experience (1995). Hood judges "that somewhere between 35 and 50 percent of psychedelic participants report religious experiences of a mystical or numinous nature, even without religious contexts." This number rises to about 90% if one includes reports with any religious imagery or religious vocabulary.

Thus, the literature abounds with instances of entheogen-occasioned mystical experience. The next question is: do these events share characteristics with experiences that are known to strengthen the immune system?

Characteristics of mystical experiences

It is important to distinguish between the different ways that the term "mystical experience" is used in common language and in philosophy and religion. In the former, it is associated with parapsychology, the occult, cultic practices and with television shows about "the unexplained." In philosophy, religious studies, and the psychology of religion, "mystical experience" denotes a specific experience or a group of similar experiences. (There is considerable discussion on this point.) Typically, mystical experiences are characterized by subjective qualities. Pahnke and Richards (1966) list nine: (1) a feeling of oneness, that is, ego transcendence; (2) objectivity and reality—noetic quality or sense of truth; (3) a transcendence of time and space; (4) a feeling of sacredness; (5) deeply felt positive mood; (6) an awareness of paradoxicalness—an awareness that is anomalous in the Western scientific paradigm; (7) a feeling that the experience is ineffable; (8) transiency; and (9) positive changes in attitude and/or behavior. As will be discussed below, these subjective characteristics resemble those that are associated with a strengthened salivary IgA levels and, indeed, with spontaneous remissions.

Thanks to Hood's construction of a *Mysticism Scale* in 1975 and its subsequent

Frequently, high-dose psychedelic sessions are a mixture of extreme emotions, both positive and negative. How these would effect immune indicators such as salivary immunoglobulin A or cortisol is anybody's guess. My guess is that the final emotional state will be most influential.

modifications and also to the concurrent growth of transpersonal psychology (*Journal of Transpersonal Psychology* 1969+), there is a substantial amount of empirical research on mystical experiences. Three summaries of the literature (Council on Spiritual Practices 1997, Hruby 1996, Lukoff & Lu 1988) contain many findings relevant to our discussion here. To begin, these summaries show that mystical experiences tend to be associated with indicators of positive mental health. Further, as compared with people who have not had mystical experiences, those who have experienced them report lives that are more meaningful and hopeful and more often report that they feel a purpose or direction in their lives. They have higher levels of education and income and rate themselves higher in levels of personal talent and capabilities, self-sufficiency, intelligence, and ego strength. They picture themselves as more psychologically mature, less motivated by personal fame and a desire for high income, and as more altruistic. They say their mystical experiences were more conducive to mental health than to mental illness.

Now, because most of these findings come from correlational studies, it is not clear whether mystical experiences help produce these characteristics, intensify already existing traits, or occur because of a third factor such as personality traits. Future experimental studies with entheogens might help clear up this theoretical ambiguity. In any event, for us the critical question is whether the characteristics of mystical experiences correlate with improved functioning of the immune system.

IgA "is the major immunoglobulin in the fluids that bathe the mucosal surfaces of the body and the surfaces that are the paths of entry to invading bacteria and viruses into the body (e.g. tears, saliva, gastrointestinal, vaginal, nasal, and bronchial secretions)" (Valdimarsdottir & Stone 1997).

The immune system and salivary immunoglobulin A

Here we will focus specifically on increased levels of salivary IgA—sIgA—as a presumed indicator of overall immune strengthening. Salivary IgA is, of course, only one measure of immune function. I select it for the many advantages listed below. Other immune indicators presumably could show similar effects and deserve attention, too.

Because one of its locations in saliva, IgA is especially easy to sample. Since one hope behind this article is to encourage research into positive emotional experiences induced by entheogens, salivary IgA has the advantage of being readily obtainable while causing a minimum of interruption to an on-going entheogenic session. Its use is additionally appropriate during a situation when suggestibility is heightened and subjects may be easily frightened or stressed by blood-taking procedures, which, further, would be beyond the professional qualifications and personal preferences of many potential researchers into this area, including theologians and sociologists.

A prime reason for using salivary measures, and specifically IgA, as indicators of the immune system's health is the large number of studies that form a theoretical and empirical base. In their 1992 review *Saliva as a Diagnostic Fluid*, Glock, Heller, and Malamud list 2298 citations from over 7500 that were initially retrieved. Of these, 174 consider immunoglobulins. From 1993 through September 1998, Medline lists 6486 IgA citations, some salivary, some not. Thus, in all, salivary IgA studies are embedded in a widely recognized research base with established methods and professional practices.

From the perspective of the Emxis hypothesis, a problem with these sIgA studies is that many of them do not use human subjects, and of these only a small fraction address wellness, positive health, or positive experiences. However, if we assume that positive emotions have the reverse effect of negative emotions, the Emxis hypothesis is supported by a large database of illness-related studies, showing that stressors reduce salivary IgA and other immune functions.

A final reason to focus on salivary IgA is that there are intriguing research leads that link stressful daily events in one's life with lower salivary IgA levels and positive events with higher levels. For example, in a series of studies by Stone et al. (1987, 1994, 1966), desirable and undesirable daily events are found to influence IgA up or down respectively, and as the Emxis hypothesis assumes, mood mediates the effects. We shall return to these studies.

Psychospiritual and psychosocial boosts for the immune system

Might mystical experiences (peak experiences) be an intervening variable between entheogens and increased im-

mune system functioning? If mystical experiences share characteristics with events that enhance salivary IgA, it is entirely reasonable to hypothesize that they could serve such mediating roles.

In exploring the data, we need to keep in mind that most of the treatments tried so far as interventions to enhance sIgA are presumed to reduce stress—that is, reduce negative emotions rather than increase positive emotions and boost the immune system (a general strategy that, of course, is in keeping with contemporary medicine's orientation to illness rather than wellness). Coping with negative mood may not be the same as increasing positive mood, especially increasing positive mood to the great extremes occurring during some kinds of mystical experiences. Nevertheless, the reduction of unpleasant emotions, depression, and other stressful daily events that weaken the immune system as measured by sIgA is, in essence, an increase in positive mood.

In "Psychosocial Factors and Secretory Immunoglobulin A," Valdimarsdottir and Stone (1997) select and summarize about two dozen research studies on the relationships between sIgA and both stressful events and stress-reduction interventions. Although the authors caution that "methodological refinements are needed before more definitive conclusions can be made," they maintain that the studies indicate that various stress-reduction interventions are associated with increases in salivary IgA levels. The question that concerns us is whether the interventions that increase salivary IgA exhibit in some form the characteristics of mystical experiences?

Among the stress-reduction techniques that have been tried, we find relaxation response, progressive relaxation, guided visualization, imaging powerful immune functions, back massage, music combined with self-induced state of appreciation (McCraty et al 1996), self-hypnosis, suggestions, and humorous movies (McClelland & Cheriff 1997). These interventions are consistent with the decreased need for ego defensiveness that accompanies ego-transcendent states and with feelings of belonging and unity, deeply felt positive mood—all characteristics of mystical experiences. Further, on the basis of the assumption that human abilities vary in strength from one mind-body state to another (Roberts 1989), it is likely that the abilities of visualization suggestion, hypnosis, and imaging are more powerful in some altered states of consciousness, an important possibility considering that entheogens alter consciousness.

In short, although these interventions do not investigate the hypothetical relationship between mystical states and improved immune function, as a whole they are in the expected direction. Perhaps these stress-reduction interventions can best be considered as mild examples of more powerful entheogenic interventions. The most common feature of both types of interventions is positive emotions.

Studies of social support offer another possible link to the characteristics of mystical experiences For example, Jemmott and Magloire (1988) found that high levels of sIgA are associated with social support. One can argue that, for people who have had mystical experiences, the feelings of unity, belonging in the universe, and "coming to one's ultimate home" provide feelings of extreme support, even cosmic support. For people who have experienced these states, cosmic belonging may substitute—more than substitute—for ordinary, interpersonal social support.

Studies of social support, positive psychological mood, and desirable daily events show all three are correlated with increased sIgA. These studies also provide some general support for the Emxis hypothesis, especially the link between positive experience and increased sIgA, or they are at least consistent with this hypothesis.

Mystical state and spontaneous remission

Let us ratchet up the importance of the possible significance of the Emxis hypothesis. If positive day-to-day experiences strengthen the immune system somewhat, might powerfully positive experiences—mystical states, states of unitive consciousness, or ego-transcendent states—strengthen the immune system to the point of being associated with unusual cures? We can raise this question because some suggestive data prompt it.

Here we will focus specifically on increased levels of salivary IgA as a presumed indicator of overall immune strengthening. It has the advantage of being readily obtainable while causing a minimum of interruption to an on-going entheogenic session.

if we assume that positive emotions have the reverse effect of negative emotions, the Emxis hypothesis is supported by a large database of illness-related studies, showing that stressors reduce salivary IgA and other immune functions.

In *Spontaneous Remission: An Annotated Bibliography*, O'Regan and Hirshberg (1993) present a table of "Psychospiritual Correlates of Remission." Resembling both the characteristics of mystical experiences and the daily events, moods, and attitudes that are associated with increased levels of sIgA, many of their list of 27 correlates seem like old friends: group support, hypnosis/suggestion, meditation, relaxation techniques, mental imagery, psychotherapy/psychoanalysis, behavioral therapy, group therapy, miraculous spiritual phenomena, prayer/spiritual belief, religious/spiritual conversion, autonomous behavior/increased autonomy, faith/positive outcome expectancy, fighting spirit, denial, lifestyle/attitude/behavioral (changes), social relationships/interpersonal relationship/family support, positive emotions/acceptance of negative emotions, environmental/social awareness/altruistic, expression of needs/demands /self-nurturing, sense of control/internal locus of control, desire/will to live, increased or altered sensory perception, taking responsibility for the illness, sense of purpose, placebo effect, diet /exercise.

Many of these 27 psychospiritual correlates are characteristics of both mystical experiences and events that boost salivary IgA. Others, such as sense of belonging, discarding ego-centeredness, reorienting one's life, and altered states of consciousness are typical of mystical experiences but do not appear in sIgA research. The correlates that emphasize insights into one's personal life and social relationships parallel the results of decreased ego-attachment that often follow ego transcendence, both psychedelic and non-psychedelic. One cluster of correlates is composed of experiences of altered-states phenomena—the very nature of mystical experience.

Taking such parallels into consideration, might it be reasonable to say that there is a persistent cluster of feelings, thoughts, moods, and behaviors that recur in mystical experiences, daily events associated with increased sIgA levels, and spontaneous remission?

At this point, an inclination toward a positive answer can be only a surmise. O'Regan and Hirshberg report disappointingly few findings that show a relationship between mystical states and unaccountable cures. (Given that both spontaneous remissions and mystical experiences occur at certain low rates in a population, this may not be so surprising.) Still, they provide some suggestive clinical observations.

They note that at the first conference on spontaneous regression held at Johns Hopkins in 1974 (see *Medical World News* 1974), "Dr. Renee Mastrovito of the neuropsychiatric service at Memorial Sloan Kettering Cancer Center alluded to historical references to cures following religious conversion or prayer." They also point to a study of five selected cases "who made a narrow escape from cancer," by Ikemi at al. (1975). According to O'Regan and Hirshberg, the authors claim that the patients' spontaneous cures were "supported and encouraged by their religious faith or favorable change of human environment [social relationship]" and suggest "that the background of Oriental thought also might help them reach such a blessed state of mind." In three of the five cases, "the unchanged or rather elevated immunological capacity which was usually lowered in cancer patients has been confirmed."

A comment on another survey of 18 cases of cancer regression (Weinstock 1983) can also be aligned with the typical feelings of hope, purpose, and meaning that follow mystical experiences. "All 18 definitely did not have anything for which to live before the favorable psychosocial change, and all found life very much worth living afterwards."

O'Regan and Hirshberg cite clinical reports by Meares of 12 cases of spontaneous regression of cancers associated with intensive meditation. In the discussion of one case, Meares (1979) writes, "*It may well be that the extreme reduction of anxiety in these patients triggers off the mechanism which becomes active in the rare spontaneous remissions. This would be consistent with the observation that spontaneous remissions are often associated with some kind of religious experience or profound psychological reaction.*"

We can suppose that the religious conversion experiences, blessed states of mind, and marked favorable psychosocial change reported by researchers probably indicate strongly felt positive moods and

possibly peak or ego-transcendent mystical experiences. From a transpersonal perspective, a consistent source of psychological anxiety and its resulting physical stress is over-identification with the ego. As the saying goes: The ego has problems, and the ego is a problem. Might it be that ego transcendence or dis-identification during meditation helps account for instances of spontaneous remission?

Ego transcendence is also a common experience during intense psychedelic sessions. While using psychedelics with cancer patients not to cure cancer but as an adjunct to psychotherapy, Richards et al. (1977) reported that the most significant variable in psychedelic psychotherapy is "the peak experience variable."

Taking up unfinished work

In their summary of psychosocial factors effecting sIgA, Valdimarsdottir and Stone (1997) conclude that both negative and positive affect mediate between daily events and sIgA levels. This "indicates that researchers should not only focus on the role of negative affect but should also consider the contribution of positive affect." The Emxis hypothesis might add, "Especially extremely powerful positive affect!"

Twenty years ago in *Psychedelic Drugs Reconsidered*, the book-length review of the scientific and scholarly literature (over 1000 studies), Grinspoon and Bakalar (1979) summarized their position:

After more than ten years of almost total neglect, it is time to take up the work that was laid down unfinished in the sixties. We need to arrange a way for people to take psychedelic drugs responsibly under appropriate guidance within the law, and a way for those who want to administer them to volunteers for therapeutic and general research to do so.

They wrote this after examining and compiling nearly the whole corpus of psychedelic research in psychotherapy, religion, creativity, psychology, and related fields. Now, two decades later, little progress has been made, but the Emxis hypothesis gives a new rationale to restart this research: Entheogen-induced mystical experiences may boost the immune system. •

References

Chevannes B (1995) *Rastafari and Other African-Caribbean Worldviews*. Basingstoke, Hants, England: Macmillan and The Hague: Institute of Social Studies.

Council on Spiritual Practices (1997) *States of Unitive Consciousness: Research Summary*. San Francisco ® www.csp.org/docs/unitive.html

Forte R (Ed.) (1997) *Entheogens and the Future of Religion*. San Francisco: Council on Spiritual Practices.

Glock MH, Heller PA, Malamud D (1992) *Saliva as Diagnostic Fluid: January 1982 through April 1992*. Bethesda, MD: National Library of Medicine, National Institutes of Health.

Grinspoon L, Bakalar J (1979) *Psychedelic Drugs Reconsidered*. New York: Bantam Books. (Reprint edition 1997 by Lindesmith Center, New York).

Grof S (1975/1993) *Realms of the Human Unconscious: Observations from LSD Psychotherapy*. London Souvenir Press (E & A).

Grof 5 (1980/1994) *LSD Psychotherapy*. Pomona, CA Hunter House.

Hood R W Jr. (1995) The facilitation of religious experience.
In: Hood R W Jr. (Ed.) *Handbook of Religious Exp*. Birmingham, AL: Religious Education Press.

Hruby PJ (1996) *The Varieties of Mystical Experience, Spiritual Practices, and Psychedelic Drug Use Among College Students*. DeKalb, IL: Northern Illinois University (Unpublished doctoral dissertation).

Ikemi Y, Nakagawa S, Nakagawa T, Mineyasu S (1975) Psychosomatic consideration of cancer patients who have made a narrow escape from death. *Dynamiche Psychiatry* 31: 77-92.

Jammott J B, Magloire K (1988) Academic stress, social support, and secretory immunoglobulin A. *Journal of Personality and Social Psychology* 55: 803-810.

Journal of Transpersonal Psychology (1969+). Palo Alto CA: Institute for Transpersonal Psychology.

Lukoff D, Lu F (1988) Transpersonal psychology research review. Topic: Mystical experiences. *Journal of Transpersonal Psychology* 20(2): 161-184.

McCraty R, Atkinson M, Rein G, Watkins A D (1996) Music enhances the effect of positive emotional states on salivary IgA. *Stress Medicine* 12(3): 167-175.

McClelland D, Alexander C, Marks E (1982) The need for power, stress, immune function, and iliness among male prisoners. *Journal of Abnormal Psychology* (91): 61-70.

McClelland DC, Cheriff A D (1997) Immunoenhancing effects of humor on secretory IgA and resistance to respiratory infections. *Psychology and Health* 12: 329-344.

Meares A (1979) Regression of cancer of the rectum after intensive meditation. *Medical Journal of Australia* 2 (Nov.17): 539-540.

Medical World News (1974) Spontaneous cancer regression—First World Conference asks: How does it work? June 7: 13-15.

O'Regan B, Hirshberg C (1993) *Spontaneous Remission: An Annotated Bibliography*. Sausalito, CA: Institute of Noetic Sciences.

Pahnke W N, Richards (1966) Implications of LSD and experimental mysticism. *Journal of Religion & Health* 5:17-208. [Reprinted in: Tart CT (1969) *Altered States of Consciousness: A Book of Readings*. New York: John Wiley].

Passie T (1997) *Psycholytic and Psychedelic Therapy Research 1931-1995: A Complete International Bibliography*. Hannover, Germany: Laurentius Publishers.

Richards W, Rhead J, DiLeo F, Yensen R, Kurland A (1977) The peak experience variable in DPT-assisted psychotherapy with cancer patients. *Journal of Psychedelic Drugs* 9(1): 1-10.

Roberts T (1989) Multistate education: metacognitive implications of the mindbody psychotechnologies. *Journal of Transpersonal Psychology* 21(1): 83-102.

Roberts T, Hruby P (1997) *Psychoactive Sacraments: An Entheogen Chrestomathy*. San Francisco: Council on Spiritual Practices. Online: http://www.csp.org/chrestomathy.

Roberts T, Hruby P (1998) Toward an entheogen research agenda. *Under submission*.

Ruck C A P, Bigwood J, Staples R, Wasson R G, Ott J (1979) Entheogens. *Journal of Psychedelic Drugs* 11(1-2): 145-146.

Scotton B W, Chinen A B, Battista J R (Edss) (1997) *Textbook of Transpersonal Psychiatry and Psychology*. New York: Basic Books.

Stone A A, Macro C A, Cruise C E, Cox D A, Neale I M (1996) Are stress-induced immunological changes mediated by mood? A closer look at how both desirable and undesirable daily events influence sIgA antibody. *International Journal of Behavioral Medicine* 3:1-13.

Stone A A, Neale J M, Cox D S, Napoli A, Valdimarsdottir H, Kennedy-Moore E 1994 Daily events are associated with a secretory immune response to an oral antigen in men. *Health Psychology* 13(5): 440-446.

Stone A A, Valdimarsdottir H, Jandorf L, Cox D S, Neale J M 1987 Evidence that secretory IgA antibody is associated with daily mood. *Journal of Personality and Social Psychology, 25(5)*: 988-993.

Valdimarsdottir H B, Bovbjerg D H 1997 Positive and negative mood: association with natural killer cell activity. *Psychology and Health* 12: 319-327.

Valdimarsdottir H B, Stone A A 1997 Psychosocial factors and secretory immunoglobulin A. *Critical Reviews in Oral Biology and Medicine* 8(4): 461-474.

2105 Robinson Avenue
Sarasota, FL 34232
phone: 941-924-6277
fax: 941-924-6265
e-mail: info@maps.org
Web: www.maps.org

Secure website transactions

Complete Set of Back Issues – $120 U.S. ($160* non-U.S.)

☐ **YES, I would like to renew my support of MAPS and receive the quarterly Bulletin.**

☐ Basic Member **$35** ☐ Supporting Member **$100**

☐ Patron **$250 or more** ☐ Student/Low-income **$20**

☐ Members outside the U.S., please add **$15** per membership

☐ Payment is included for the book(s) I have ordered (see below)

☐ Donation is included for a Gift Membership: **$** _____

Name and address of recipient:

NAME

ADDRESS

CITY STATE OR COUNTRY POSTAL CODE

TOTAL $ _____ enclosed. Donations to MAPS are tax-deductible.

☐ Enclosed is my check or money order payable to MAPS

☐ Please charge my credit card: ☐ Mastercard ☐ Visa

CARD NUMBER EXPIRATION DATE

SIGNATURE PHONE NUMBER E-MAIL

☐ Check here for change of address.

AVAILABLE **FROM MAPS**

1. THE SECRET CHIEF: CONVERSATIONS WITH A PIONEER OF THE UNDERGROUND PSYCHEDELIC THERAPY MOVEMENT, Myron Stolaroff – 144 pp: $10/$14* special price for current & new MAPS members. $13.95/$19.95* for non-member orders.
2. THE SECRET CHIEF, hardback (extremely limited supply) – $25.95/$28.95*
3. THE SECRET CHIEF, limited edition hardback signed by Myron Stolaroff, Stanislav Grof, Albert Hofmann, Ann & Alexander Shulgin (only 14 of 100 remain) – $250/$256*
4. ECSTASY–DANCE, TRANCE AND TRANSFORMATION, Nicholas Saunders – 281 pp: $18/$24*
5. COMPLETE SET OF MAPS BULLETIN BACK ISSUES: 1988-1999 – 1000 pp: $120/$160*
6. THE GOOD FRIDAY EXPERIMENT FOLLOW-UP, *article on psychedelics & experimental mysticism*, Rick Doblin, originally published in Aug. '91 Journal of Transpersonal Psychology: – $8/$11*
7. THE HEFFTER REVIEW OF PSYCHEDELIC RESEARCH – 77 pp: $12.95/$15.95*

** Indicates price for orders from outside the U.S. Please do not send checks on foreign banks.*

MAPS MEMBERSHIP INFORMATION

MAPS IS A MEMBERSHIP-BASED organization working to assist psychedelic researchers around the world design, obtain governmental approval, fund, conduct and report on psychedelic research in humans.

Founded in 1986, MAPS is an IRS approved 501 (c)(3) non-profit corporation funded by tax-deductible donations from 1,800 members.

MAPS' founder and current president, Rick Doblin, is currently in the Ph.D. program in Public Policy at Harvard's Kennedy School of Government and has previously graduated from Stan and Christina Grof's Holotropic Breathwork 3-year training program.

Sylvia Thyssen is responsible for editing the *Bulletin* and oversees MAPS' website and outreach efforts. She is a graduate of the University of North Carolina at Chapel Hill, where she majored in Art History and French.

Carla Higdon coordinates MAPS member services and the marketing and distribution of the *MAPS Bulletin* and *The Secret Chief.* She is a graduate of Western Carolina University and certified art educator with a Bachelor of Science in Education.

MAPS has previously funded basic scientific research in both humans and animals into the safety of MDMA (3,4-methylenedioxymethamphetamine, *Ecstasy*) and has opened a Drug Master File for MDMA at the U.S. Food and Drug Administration. MAPS is now focused primarily on assisting scientists to conduct human studies to generate essential information about the risks and psychotherapeutic benefits of MDMA, other psychedelics, and marijuana, with the goal of eventually gaining governmental approval for their medical uses.

ALBERT EINSTEIN WROTE: **"Imagination is more important than knowledge."** If you can even faintly imagine a cultural reintegration of the use of psychedelics and the states of mind they engender, please join MAPS in supporting the expansion of scientific knowledge in this area. Progress is possible with the support of individuals who care enough to take individual and collective action. In addition to supporting research, your contributions will return to you the following benefits:

The *MAPS Bulletin:*

Each *Bulletin* will report on MAPS research in progress. In addition to reporting on research both in the United States and abroad, the *Bulletin* can include feature articles, reports on conferences, book reviews, Heffter Research Institute updates, and the Hofmann Report. Issues raised in letters, calls and e-mail from MAPS members may also be addressed, as may political developments that affect psychedelic research and usage.

General Members: $35

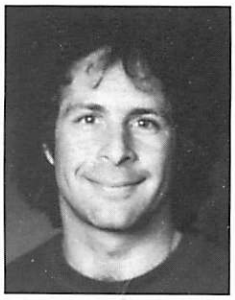
(If outside U.S. add $15 postage.)
General members will receive the *MAPS Bulletin,* which appears on a quarterly basis.

Supporting Members: $100

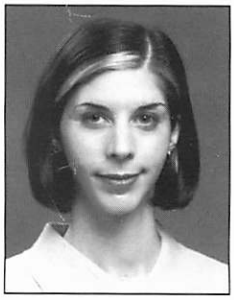
(If outside U.S. add $15 postage.)
Supporting members will receive the *MAPS Bulletin* plus a copy of the MAPS-published book *The Secret Chief: conversations with a pioneer of the underground psychedelic therapy movement*, by Myron Stolaroff.

Patron: $250 or more

Patrons members will receive the *MAPS Bulletin* plus a copy of *The Secret Chief,* by Myron Stolaroff. Patrons may also request copies of back issues and research updates on matters of personal interest.



Rick Doblin,
MAPS President



Sylvia Thyssen,
Director of Communications

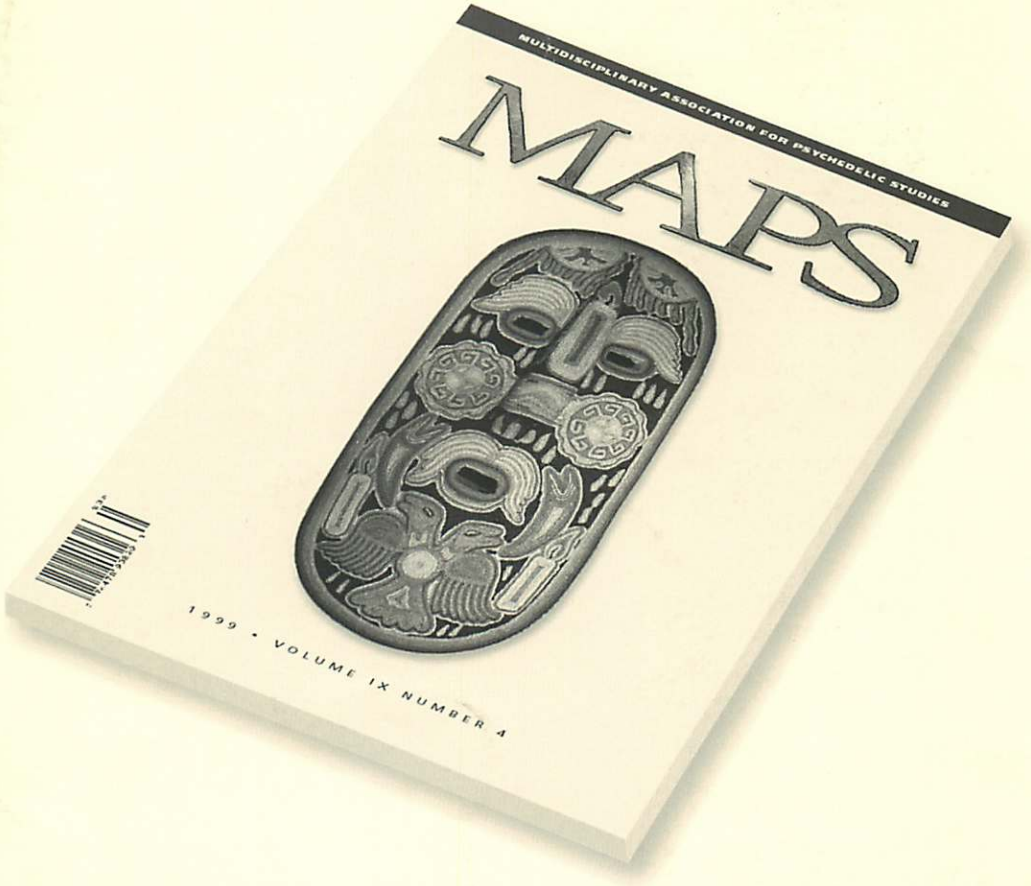
Carla Higdon,
Projects Coordinator

Did you know...

You can renew your MAPS membership on-line?

Visit our secure server at **www.maps.org/memsub.html**
or call 888/868.MAPS (in the U.S.)

If we don't support the
cultural reintegration
of psychedelics and marijuana
through good science,
who will?



WHY Why do some issues of the MAPS Bulletin have color covers... and others don't?

The *MAPS Bulletin* is produced by a small group of dedicated staff and volunteers on a limited budget. We produce two issues per year which are quite long (64 to 72 pages) and those have color covers. The interim Bulletins are like this one... brief, but full of the latest information from the world of psychedelic research. Here is a preview of articles featured in upcoming issues:

Winter 1999

Dr. Leary's Concord Prison Experiment: A 34-Year Follow-Up Study by **Rick Doblin**
Reflections on the Concord Prison Project and the Follow-up Study by **Ralph Metzner**
From Eleusis to PET scans: the mysteries of psychedelics by **David Nichols**
Aspects of a New German Study on Psilocybin by Thomas Heinz

...and next year!

Stan Grof interview with Albert Hofmann
Essay by Nicholas Sand, Pioneering Psychedelic Chemist and Prisoner of the War on Drugs
The Year 2000 Creativity Issue of the *MAPS Bulletin*

We always welcome your comments and suggestions.