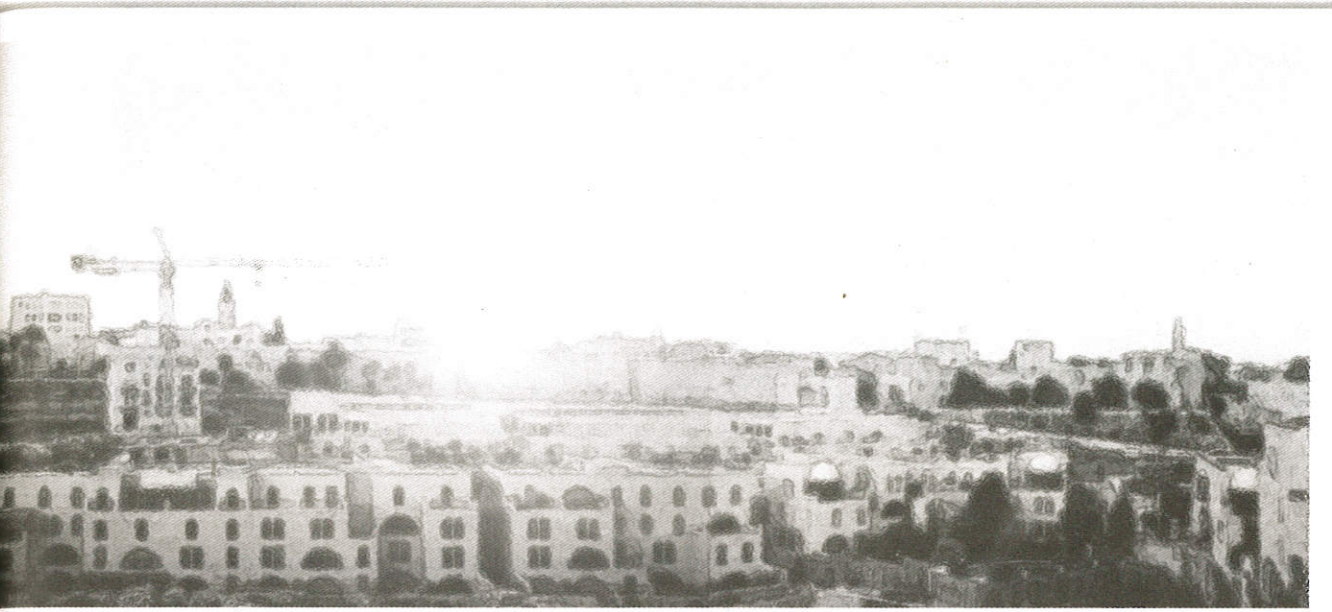


Clinical Research with MDMA and MDE

A MAPS' Conference: Dead Sea, Israel

Rick Doblin

IT HAS TAKEN ME SOME TIME to reflect on the enduring accomplishments of MAPS' international scientific conference on clinical research with MDMA and MDE. The conference took place August 30-September 1, 1999 at the Dead Sea, Israel. Attending the conference were representatives of every team in the world that has administered MDMA or MDE to human subjects, along with three teams (from Israel, Spain and the US) proposing to initiate MAPS-sponsored MDMA psychotherapy research (for a list of speakers, see *MAPS Bulletin* Vol. IX No. 3, p. 9). In addition to the conference, MAPS organized a six-day pre-conference tour of Israel for 33 people, paid for by tour participants. I'll first discuss the accomplishments of the conference and pre-conference tour, then report on some of the new data that was presented about MDMA, particularly about MDMA neurotoxicity.



MAPS arranged for the entire conference to be recorded on digital video. We are working to place selected video and audio recordings on the MAPS web site, as well as edited transcripts of several talks and associated question and answer periods. In addition, Dr. Julie Holland, who attended the conference and the pre-conference tour, is editing a book on MDMA with chapters from many of the conference speakers.

Purpose of the conference

MAPS has been working since March 1998 to sponsor a study into the use of MDMA-assisted psychotherapy in the treatment of patients suffering from post traumatic stress disorder (PTSD), to take place in Israel at Ben-Gurion University of the Negev, under the direction of Dr. Moshe Kotler and Dr. Adam Darnell. MAPS has pledged \$50,000 for this study, \$12,500 of which has already been paid. MAPS' long-term strategy prioritizes the effort to open the door to MDMA psychotherapy research in several countries in

addition to the United States. In this way, we have the greatest chance that at least one such study will be approved and will yield data that can then be shared with other regulatory agencies. In the best of circumstances, MAPS will be able to sponsor and coordinate MDMA-assisted psychotherapy research in several locations around the world.

The primary purpose of the conference was to present the latest scientific information about the risks and benefits of MDMA to Drs. Kotler and Darnell, and to officials in the Israeli Ministry of Health and Anti-Drug Authority. MAPS' goal was to fully inform the protocol design and approval process in Israel regarding the proposed MAPS-sponsored MDMA/PTSD study, in the belief that a balanced assessment of the research data would lead to approval of the study. The secondary purpose of the conference was to foster the exchange of data and international collaborations between research teams involved in all aspects of the study of MDMA in human subjects, thereby

The building and rebuilding of Jerusalem has been going on for over 5,000 years, and shows no signs of letting up. Here the sun rises over the ancient walls of the Old City. MAPS' visiting scientists and guests spent several days touring numerous shrines and the Holy Places of three major world religions as they prepared for the MDMA summit conference.



The landscape of the Dead Sea shoreline is an unforgiving place of heat and rocks, where only the heartiest survive.

expediting the pace and quality of research.

The conference was budgeted at \$50,000. MAPS was able to raise \$45,500 in new funds specifically for the conference, from Tim Butcher, Ami Shinitzky, Robert Barnhart, Jeremy Tarcher and the S. Family Foundation. This large investment and the support MAPS obtained from funders demonstrates the importance we all place on obtaining permission to conduct research into the psychotherapeutic benefits of MDMA.

The pre-conference tour

I've come to realize that scientists frequently need to meet each other in person before they come to fully believe what they read in scientific journals. Research, particularly at the advancing frontiers of knowledge, is still as much art and ambiguity as it is fact and clarity. In order to give MDMA researchers a chance to visit with each other in an informal setting, and to make coming to the conference potentially more attractive, MAPS organized a six day pre-conference tour of Israel, with participants charged a break-even cost. The tour involved four days in Jerusalem, one day in the Galilee and the final day in desert areas on the way to the Dead Sea Hyatt, where the conference was held.

I am proud to say that 33 people participated in the tour; 28 adults, 4 children and one nine-month old infant (my daughter, Eliora). Tour participants were primarily from the US and Spain, with one person from the Swiss MDMA research team. I was particularly glad that three of the people involved in the Spain MDMA/PTSD project and their families came along for the tour. I have been engaged for some time in an e-mail discussion with Jose Carlos Bouso, a Ph.D. candidate who is developing the MDMA/PTSD study in Spain, and actually committed \$22,000 to his project before ever meeting him in person. The opportunity to get to know Jose Carlos and his



Left to right: Deborah Mash, Rick Doblin and Alex Gamma discussing MDMA research onboard a Sea of Galilee water taxi.

medical advisors was one of the most important aspects of the tour.

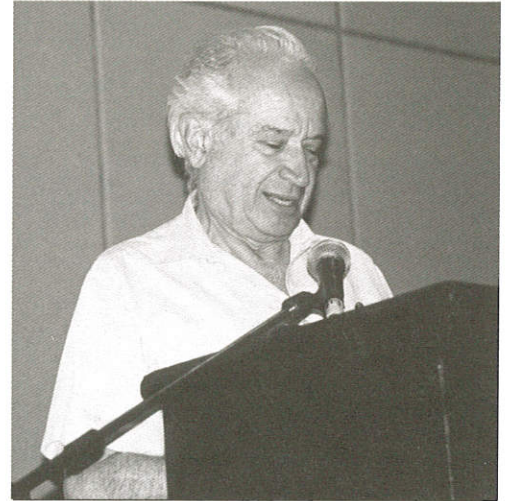
One participant in the tour, Lew Seiden, Ph.D., University of Chicago, needed to use a wheelchair. Not surprisingly, the Old City of Jerusalem was not built to accommodate wheelchairs, which didn't exist when the city was founded or when it was rebuilt after being destroyed numerous times. It was therefore necessary to carry Lew around the Old City, which is built into a hill, with a shifting team of four people around each corner of the wheelchair. This was actually a bonding experience for us all. I was reminded of Jerusalem in days of old, with the Kings being carried about in their chairs. Fortunately, Lew's laborers were permitted ice cream, water and rest breaks.

Accomplishments – Israeli perspective

On the first night of the conference, the only event on the schedule was an opening dinner. Dr. Carmi Margolis, an administrator at Ben-Gurion University of the Negev, welcomed everyone to Israel on behalf of the University. In his talk, he explained that one of the goals of the Medical School at Ben-Gurion University was to foster international scientific exchange. He also pointed out that, though he still needed to be convinced, he had an open mind about the possible therapeutic benefits of psychedelics. Dr. Kotler and I enjoyed dinner with Dr. Margolis, his wife and his daughter. After a spirited and well-received discussion of the use of MDMA and LSD in treating PTSD, I gave Dr. Margolis a copy of *Shivitti: A Vision*, an autobiographical story about the LSD-assisted psychotherapy of a concentration camp survivor suffering from PTSD. The author of *Shivitti* has also written several other powerful books about his experiences during the Holocaust and is well known in Israel. Dr. Margolis appreciated the gift and offered a short description of the Kabbalistic meaning of



The Dead Sea Scrolls were found in caves much like this one in the cliffs overlooking En Gedi between Qumran and Masada on the western shores of the Dead Sea.



Dr. Raphael Mechoulam is internationally famous for his research into the constituents of marijuana.

Shivitti, which is sort of an incantation making the spiritual world manifest physically. I think our dinner made Dr. Margolis more comfortable with Dr. Kotler's efforts to initiate MDMA/PTSD research.

Rather than start with my own impressions of the impact of the conference itself, I'd like to quote from an e-mail message I received after the conference from Dr. Jorge Gleser, Director of the Department for the Treatment of Substance Abuse, Israeli Ministry of Health, who attended the conference along with several other staff members from his Department. Dr. Gleser remarked:

"I would like to thank you and MAPS again for the meeting and for allowing and supporting the participation of other Israeli colleagues. The meeting did change our point of view towards MDMA and similar substances and served to reduce the stigma. We will try to advance some of the projects like the treatment of PTSD with MDMA, the treatment of opiate [withdrawal] with Ibogaine and possibly with Ketamine."

The reference to the ibogaine project refers to a study in heroin addicts that Dr. Kotler is trying to obtain approval for in Israel, to be funded by Humatech, a company founded by Bob Sisko (see *MAPS Bulletin* Vol. IV, No. 2, pp. 15-23). To support the case for the approval of the Israeli ibogaine study, I invited Dr. Deborah Mash, University of Miami, to speak at the conference about her experience studying the use of ibogaine in the treatment of heroin addicts. Dr. Mash's talk was inspiring. She made a strong argument for the expansion of ibogaine research. Dr. Kotler's protocol is now being reviewed by the Israeli Ministry of Health, with eventual approval considered likely.

Dr. Gleser's comments about ketamine research need a bit of elaboration. At the conference, I handed Dr. Gleser and his associates copies of Dr. Evgeny Krupitsky's latest

paper about his three year MAPS and Heffter Research Institute (HRI)-funded study investigating ketamine-assisted psychotherapy in the treatment of heroin addicts, conducted at the Leningrad Regional Center for Alcoholism and Drug Addiction Therapy. Dr. Krupitsky's study shows promising results at the six-month follow-up (see p. xx, this issue). Dr. Gleser was interested in learning more about the ketamine research, even though there is no effort being made at present to start such a study in Israel.

As a result of the conference, Dr. Gleser invited MAPS to organize a series of presentations on psychedelic research, especially related to the treatment of addiction and to drug policy, at a large international conference on addiction scheduled for November 6-9, 2000, in Jerusalem. The conference is being sponsored and organized by the Israeli Ministry of Health's Department for the Treatment of Substance Abuse, the Anti-Drug Authority, the International Society of Addiction Medicine, and the Israel Society of Addiction Medicine. I have already sent Dr. Gleser a proposal for seven speakers that MAPS would like to sponsor at the conference, with the proposal currently under review by the conference organizing committee.

One unexpected benefit of the conference was the opportunity to offer international support from the assembled scientists for the Department for the Treatment of Substance Abuse's plans for a heroin maintenance study in Israel. In this proposed study, which builds on the pioneering Swiss heroin maintenance program, heroin will be administered to heroin addicts in an effort to see if health problems and crime can be reduced. Also to be investigated is the extent to which the treatment team is able to motivate and assist addicts to quit their habits entirely.

Also present at the conference was Dr. Rachel



Alex Gamma, University of Zürich, discussed EEG data from MDMA-naïve subjects given 1.7 mg/kg of MDMA.



The most important new data about MDMA neurotoxicity was presented by Dr. Franz Vollenweider, University of Zürich.

Hamberger, the chief scientist for the Israeli Anti-Drug Authority. She seemed quite interested in the presentations at the conference and offered encouragement for the protocol. I introduced Dr. Hamberger to Dr. Franz Vollenweider, University of Zürich, who spoke to her about the research opportunities at his world-class lab, his need for more staffing, and his interest in offering internships to Israeli scientists/physicians in training who could go to Zürich for six months to assist in research. I mentioned to Dr. Hamberger that Drs. Kotler and Darnell had wanted to send some psychiatrists they train to Switzerland to fulfill their six-month research requirement, but hadn't been able to find anyone who was fluent in German, required to understand and sensitively assist subjects undergoing psychedelic experiences. Dr. Hamberger felt she might be able to find a qualified German-speaking scientist/physician and indicated an interest in trying to find out whether the Israeli's expenses could be paid for by some combination of the Israeli Ministry of Health, the Swiss National Science Foundation, and MAPS, if need be.

Another Israeli present at the conference was Dr. Raphael Mechoulam, Professor at Hebrew University. Dr. Mechoulam is internationally famous for his research into the constituents of marijuana. He was the first to isolate THC from marijuana and the first to identify the endogenous cannabinoid neurotransmitter, which he named anandamide. Dr. Mechoulam spoke about clinical research with cannabinoids, reinforcing the idea that clinical research with Schedule I drugs like marijuana and MDMA is important and can be conducted safely. Dr. Mechoulam has also been involved in Israel in determining which scientific studies can ethically be conducted in humans. In the US, these decisions are made by committees called Institutional Review Boards (IRBs) and in Israel by Helsinki Committees, after the Helsinki Accords

which were drafted after the Nazi concentration camp experiments. As a result of the conference, Dr. Mechoulam now has a more comprehensive and accurate view of the risks of MDMA to human subjects.

Near the conclusion of the conference, Dr. Moshe Kotler told me that he thought the conference was very impressive and a major success. His final words to me were, "Let's move forward." Coming from an Israeli with the rank of General (Moshe was chief psychiatrist for the Israeli Defense Forces), I feel confident that our forward motion will eventually lead to approval for the study.

One major goal of the conference was to improve the chances of approval for the MDMA/PTSD protocol. That goal was clearly accomplished.

Accomplishments - Spain

Three MDMA researchers from Spain participated in the conference and came on the pre-conference tour with their spouses, and one daughter. After meeting the Spanish team in person, I am more enthusiastic than ever about their proposed study into the use of MDMA in the treatment of PTSD in rape victims. They have a long history of sophisticated and important drug research, much of it funded by government grants.

The conference also provided the opportunity for Moshe Kotler, Adam Darnell and Jose Carlos Bouso to meet informally to discuss protocol design issues and scientific collaboration between the two teams working to obtain permission to conduct MDMA/PTSD studies.

The meetings between the Israeli and Spanish teams were a very important benefit of the conference, and hopefully are just a beginning in a long relationship.

Jose Carlos' study, one of MAPS' highest priority projects, has already been submitted to the Spanish Ministry of Health for review. We are all hoping for the best.



Jose Carlos Bouso (Spain) presents his MDMA/PTSD study, with some translating help from Christopher Ryan. Bouso, Charles Grob and the Israeli team received invaluable feedback on their studies from colleagues.



Matt Baggott presented a new analysis designed to extrapolate from animal data what dose in humans would cause the first signs of long-term reductions in serotonin levels.

Additional accomplishments— my perspective

On a personal note, the complex logistics worked smoothly for bringing together 33 people for the six-day tour, 15 more people for from 1-3 days in Jerusalem, and scientists from 8 countries for the conference. In a delightful moment, the people on the pre-conference tour met up at the top of Masada with the 15 other people who came from Jerusalem in a separate bus, just as I had hoped. In my hopefully accurate estimation, I was Exhibit A for ability to perform complex tasks after taking lots of MDMA, instead of being Exhibit A for MDMA brain damage.

MDMA neurotoxicity: new data

The most important new data about MDMA neurotoxicity was presented by Dr. Franz Vollenweider, University of Zürich. Franz reported on a study of MDMA neurotoxicity in MDMA-naive subjects, to which MAPS donated \$6,000. The study involved the use of PET scans to measure serotonin uptake sites, which are reduced by MDMA neurotoxicity. Dr. Vollenweider's team and Dr. Ricaurte's team at Johns Hopkins are the only groups in the world using PET scans to measure serotonin uptake sites. However, there is a crucial difference between the methodology of the two groups. Dr. Vollenweider studies the effects of the actual administration of pure MDMA to MDMA-naive subjects. Dr. Ricaurte does not administer MDMA but studies people with extensive use of Ecstasy (which is sometimes MDMA and sometimes not), frequently taken in rave environments. Dr. Ricaurte then compares the results of the Ecstasy users to that gathered from matched controls. Methodologically, Dr. Vollenweider's study design is more reliable in that it eliminates problems related to inexact matching between

MDMA and control subjects. Furthermore, Dr. Vollenweider's study directly relates to determining the risk to research subjects in studies examining the therapeutic use of MDMA, where one or several doses of MDMA will be administered to MDMA-naive patients. Dr. Ricaurte's studies in polydrug users who have taken MDMA from 75 to thousands of times are valuable because this sort of study is most likely to show reductions in serotonin nerve terminals, since subjects have such high exposure to MDMA. However, this study is of less relevance to understanding the risks of exposure to a few doses of MDMA in a clinical research context.

Dr. Vollenweider reported on data gathered from several subjects who were given three PET scans, before, during and one-month after the administration of 1.5 mg/kg of MDMA. No reduction of serotonin uptake sites were found at the one-month follow-up. Dr. Vollenweider actually reported a slight increase, which he said was not statistically significant and represented normal variation in the PET scanning technique.

Dr. Vollenweider also reported on the results of a series of other biological and psychological tests administered to a total of about 50 MDMA-naive subjects, with the tests administered to subjects before and after one MDMA session and before and after one placebo session. There was no evidence of functional or behavioral consequences due to MDMA, either between the tests given before and after the administration of MDMA or between the people whose first session was MDMA or whose first session was the placebo.

Lew Seiden, Ph.D., University of Chicago, presented data from animal research that showed conclusively that serotonin reductions are related to core body temperature, with higher ambient temperatures producing hyperthermia which makes one vulnerable to serotonin reductions. This research calls into question risk assessments for



Conferees attended a rigorous series of informative presentations lasting well into late evening... This symposium enlarged the Israeli researchers' point of view toward MDMA and similar substances and served to reduce the stigma associated with them.

clinical research subjects based on data from rave-goers who take MDMA in high-ambient temperatures, exercise vigorously, and sometimes do not consume sufficient fluids. In contrast, clinical research contexts involve the administration of MDMA in temperature-controlled settings, to people who are resting in bed and are supplied with fluids. This data about the importance of ambient temperature requires a revision of the understanding of the mechanism of MDMA-related neurotoxicity. Some drugs which we previously thought blocked neurotoxicity through a specific pharmacological mechanism turn out to actually block neurotoxicity through non-specific blocking of hyperthermia.

Matt Baggott, researcher on the UC San Francisco MDMA research team, presented a complicated new analysis designed to compare human and animal data in order to extrapolate from animal data what dose in humans would cause the first signs of any long-term reductions in serotonin levels. Matt's approach is based on comparing similar blood levels of MDMA, as determined in pharmacokinetic studies, as opposed to basing comparisons on body weight or body surface area. According to this analysis, 5 mg/kg in humans is the equivalent of the lowest dose that has been shown to cause any long-term reductions in serotonin levels in rats. This is not necessarily the same as the highest dose that will not cause neurotoxicity, which is not known. This is only a preliminary approach and there are lots of assumptions in this model that are based on incomplete data. Most of the rat neurotoxicity data was collected before the importance of hyperthermia was appreciated. Therefore, these doses may cause serotonin reductions only in certain environments, or with certain behaviors. Significant amounts of individual variability also need to be taken into account. A 5 mg/kg amount of MDMA is the same as taking more than twice as many milligrams as pounds of body weight,

for example 5 mg/kg in a 150 pound person is 340 milligrams. A standard therapeutic dose of MDMA is 100-125 milligrams.

According to Baggott's estimates, Dr. Vollenweider's preliminary finding of no apparent long-term reductions in serotonin uptake sites in humans from a dose of 1.5 mg/kg was not surprising and is consistent with the animal neurotoxicity data.

Dr. Efi Gouzoulis-Mayfrank presented data from a study comparing MDMA-using ravers with two control groups, one with subjects who had used cannabis but not MDMA and another with control subjects who did not use drugs. The mean estimated cumulative total dose of the MDMA-using group was 93 pills, the mean duration of regular use was 27 months. The only differences found were in certain subsets of memory and executive functions, with the MDMA-using group performing somewhat lower. According to Dr. Gouzoulis-Mayfrank, these differences were statistically significant but clinically insignificant, meaning that neither the subjects nor the testers could tell the groups apart in normal social situations or in life performance. Dr. Ricourte and Dr. Bolla's studies of memory function in MDMA users (*MAPS Bulletin* Vol. IX No. 3 pp. 6-8) are also statistically significant but clinically insignificant. Possibly confounding any causal role of MDMA in the memory findings is that these studies may be measuring effects of the Ecstasy raver lifestyle (lack of sleep, poor nutrition, heavy use of other drugs not matched by the controls groups) or of possible preexisting factors. However, the study of Dr. Gouzoulis-Mayfrank included no unusually heavy or poly-drug users. At present, the only evidence in humans for functional consequences from regular exposure rates to MDMA is from data that are not clinically significant and are not conclusively proven to be due to MDMA. The minimal findings in these studies of Ecstasy users is



Ripples in the viscous waters of the Dead Sea. Like these expanding waves, the after-effects of the 1999 international symposium on MDMA will be felt for years to come. Collegial relationships among scientists were forged and solidified across national boundaries, a development which augers well for both research quality and chances of approval. In all, it was one of MAPS' finest moments.

reassuring. In summary, there are no data showing that one or few doses of MDMA in a clinical research context bear substantial risks for long-term harms from possible neurotoxicity.

Conclusion

The consensus of the conference was that MDMA research in humans is important, that it can be conducted safely, that there are sufficient anecdotal reports and case histories of the therapeutic use of MDMA to justify research into the therapeutic use of MDMA, and that the risk of neurotoxicity is clearly outweighed by potential benefits in patients who are either terminal or have failed on conventional medications. Studies in MDMA-naive subjects or in patients who are not terminal or have not already failed on conventional medications were sup-

ported by most but not all conference participants.

MAPS' Israel MDMA conference helped improve the chances that the MDMA/PTSD study will be approved in Israel, fostered international collaboration and data sharing, provided an opportunity for MDMA psychotherapy protocols to receive thoughtful critiques, and generated a willingness among several researchers to provide letters of support to national regulatory bodies for MDMA psychotherapy protocols.

After reflection, I believe that the many months of MAPS' staff time that were invested in this conference, along with roughly \$50,000, will prove to be an excellent investment that has played a major role in bringing us into the promised land of MDMA psychotherapy research. •