TESTIMONY BY RICK J. STRASSMAN, M.D.

INTRODUCTION:

Methylene dioxymethamphetamine (MDMA) is an N-methyl derivative of methlenedioxyphenylisopropylamine (MDA). They are both synthesized from compounds related to safrol, an aromatic compound found in high concentrations in nutmeg (1). MDMA was first synthesized by Merck, in Germany, in the early part of this century (2, 3).

MDMA was first investigated as a potential psychotoxic compound by the Army, in the middle 1950's. Like mescaline, one of the most psychoactive compounds in peyote cactus, MDMA is a phenylisopropylamine, and as such, was considered a "mescaline analog" (4). By implication, then, MDMA was considered among the so-called "psychedelic" drugs.

TERMINOLOGY

There is significant liability involved in labeling MDMA as a true psychedelic compound. Perhaps it may be of some use, then, to diverge here, in order to address this particular issue of nomenclature before proceeding much further in this discussion. "Psychedelic" is a term that has been associated primarily with the "LSD-like" compounds, as described by Martin and Sloane (5). They can be distinguished from other centrally acting drugs that can also under certain conditions, induce perceptual distortions (e.g. anticholinergic compounds such as atropine), paranoid and other

delusions (e.g. as in chronic, high-dose amphetamine administration), and other alterations of cognition, behavior and affect (e.g. bromides and opiates). They are capable of, when pathological effects are absent or minimal, "reliably inducing or compelling states of altered perception, thought and feeling that are not (or cannot be) experienced otherwise, except in dreams or at times of religious exhaltation" (6). Psychedelic compounds include the indolealkylamines (lysergic acid diethylamide--LSD, diethyltryptamine--DET, dimethyltryptamine--DMT, and psilocybin and psilocin--in the psilocybian mushrooms), and the phenylisopropylamines (MDA, mescaline, DOM, DOET). "Psychedelic," however, as much as describing particular psychological effects elicited by these drugs, also has partaken of an association with the subculture out of which their use emerged in the 1960's. Osmond defined psychedelic as "mind-manifesting," (7, pg.8), a purposefully vague term, and at the time, the most value-free. Others, however, stuck by these drugs' primarily perceptual effects, labelled them "hallucinogenic" or "illusogenic." "Psychotomimetic" or "psychotogenic" are other terms used by investigators attempting to relate drug-induced states to functional psychotic illness, an attempt that has consistently been unsuccessful (see 8, for details).

MDMA does not appear to be a true psychedelic compound, by virtue, primarily, of the psychological effects ascribed to its use in humans, as will be detailed later in this presentation. Therefore, labeling MDMA as a psychedelic obscures the relevant issues that need be addressed in determining abuse and use potential for this compound.

What, then, to call MDMA? I do not know. But its continued investigation should provide data sufficient to appropriately classify it. Based on its subjective effects (see below), a term like "feeling-enhancer," "empathy-catalyst," or "introspection/insight aid," all may capture part of the experience brought on by this drug.

PHARMACOLOGY

Nervous tissue studies of MDMA are at the most rudimentary stage. Only one paper has been published regarding this issue, by Nichols, et al (9). This group found that MDMA was a potent releaser of serotonin from rat whole brain synaptosomes. The relevance of this finding is unknown. The psychedelic drugs (e.g. LSD) have generally been found to inhibit serotonergic cell-firing via either pre- (10) or post- (11) synaptic mechanisms. Amphetamines, on the other hand, primarily release dopamine and norepinephrine from synaptic regions (12).

BEHAVIORAL EFFECTS IN ANIMALS

MDMA has been studied somewhat more from a behavioral pharmacologic point of view, but still, this work can only be described as preliminary.

It is important to keep in mind the caveats regarding behavioral studies of psychoactive compounds in animals. LSD was found to be nonspecifically active in animal models run by Sandoz Laboratories, and was initially abandoned as not having any noteworthy effects. The most appropriate manner of understanding clinical effects of drugs in man, especially psychological effects, is in man. Further evidence for this is in Hardman's report (4), wherein massive doses of

mescaline in monkeys produced no "hallucinogenic behavior." Mescaline is clearly a psychedelic compound in man. MDMA, on the other hand, produced "hallucinogenic behavior" in monkeys, in contradistinction to its clinically described effects, wherein no hallucinations are experienced.

Glennon (13) has attempted to demonstrate that the "discriminative properties" paradigm is an effective way of predicting psychedelic effects of compounds. In this model, animals are starved to 80% of their body weight, trained to press a bar for food in association with a psychedelic drug (in this case, DOM), and then studied to see what other drugs will elicit bar-pressing at the same rate as DOM (compared to saline placebo). MDMA was not found "psychedelic" in this paradigm. In a later paper (14), Glennon describes generalization of MDMA to MDA, although their statistical handling of the data is not described. MDMA was also found to generalize to amphetamine. The significance of these findings is unclear, although the authors speculate that N-methylation of MDA (to MDMA) decreases its "hallucinogenic" (i.e. generalizability to DOM) properties, while making it more similar to amphetamines (i.e. generalizing to amphetamine).

Even Glennon, however, with Nichols, sum up this research appropriately with the following comment: "It is unlikely that any non-human model will be developed which can reliably predict (psychedelic) properties in advance (of human research). This is simply due to the large number of possible component processes involved...." (15, pg 100). Shulgin also remarks concerning the difficulty in generalizing