AN ANNOTATED BIBLIOGRAPHY OF THE SCIENTIFIC LITERATURE REFERRING TO MDMA

(including a sampling of the popular literature)

ALEXANDER T. SHULGIN
1483 SHULGIN ROAD
LAFAYETTE, CA
94549

JULY 1, 1988

TABLE OF CONTENTS

(1) CHEMISTRY

Anon: Verfahren zur Darstellung von Alkyloxyaryl-, Dialkyloxyaryl- und Alkylendioxyarylamino-propanen bzw. deren am Stickstoff monoalkylierten Derivaten. German Patent, 274,350; Filed December 24, 1912, issued May 16, 1914. Assigned to E. Merck in Darmstadt.

A chemical process is described for the conversion of several allyl- and propenyl-aromatic compounds to the corresponding beta- or alpha-bromopropanes. These, in turn, react with ammonia or primary amines to produce the corresponding primary or secondary propylamines. Specifically, safrole was reacted with aqueous HBr, and the impure reaction product reacted with alcoholic methylamine to produce MDMA in an unstated yield. Also described and characterized are MDA and DMA, as well as the corresponding 1-phenyl-1-aminopropanes. No pharmacology.

Anon: Formyl Derivatives of Secondary Bases. German Patent 334,555, assigned to E. Merck. 1920. CA: 17:1804a.

A chemical conversion of MDMA to its formyl derivative, and the properties of the latter, are described.

Biniecki, S. and Krajewski, E. Preparation of DL-1-(3,4-Methylenedioxy)-2-(methylamino)propane and DL-1-(3,4-dimethoxyphenyl)- 2-(methylamino)propane. Acta Polon. Pharm. 17 pp. 421-425 (1960). CA: (1961) 14350e.

A chemical procedure is given for the conversion of safrole to the beta-bromopropane with HBr, and its subsequent conversion with alcoholic methylamine to MDMA. 4-Allylveratrole was similarly converted to 3,4-dimethoxy- methamphetamine.

Braun, U., Shulgin, A.T. and Braun, G., Centrally Active N- Substituted Analogs of 3,4-Methylenedioxyphenylisopropylamine (3,4-Methylenedioxyamphetamine), J. Pharm. Sci., 69 pp 192-195 (1980).

Twenty two homologs and analogs of MDA were synthesized and their physical properties presented. Twelve of them were assayed in man as psychotomimetic agents. Three of them were found to be active: MDMA with a human potency of between 100 and 160 mg orally; MDE somewhat less potent at a dosage requirement of 140-200 mg orally; and MDOH, which was similar to MDMA in potency. Some animal pharmacology is reviewed, and a comparison between MDMA and MDA (toxicology, CNS pharmacology, and human effectiveness) is tabulated.

Fujisawa, T. and Deguchi, Y. (Concerning the Commercial Utilization of Safrole). J. Pharm. Soc. Japan 74 975 (1954). CA: 49: 10958i.

The conversion of safrole to piperonylacetone is described, using formic acid and hydrogen peroxide, in acetone. The yield is satisfactory, and this is probably the most direct and efficient conversion of a natural product to an immediate precursor to MDMA.

Janesko, J.L. and Dal Cason, T.A. Seizure of a Clandestine Laboratory: The N-Alkyl MDA Analogs. Paper presented at the 39th Annual Meeting of the American Academy of Forensic Sciences, San Diego,

CA Feb. 16-21 (1987). See Microgram, 20 52 (1987).

Several clandestine laboratories have been seized, revealing the illicit preparation of not only MDMA, but the N-ethyl (MDE), the N-propyl (MDPR), the N-isopropyl (MDIP) and the N,N-dimethyl (MDDM) homologues. These were all synthesized by the $NaCNBH_3$ reduction method from the appropriate amine salt and piperonylacetone. Also, the N- ethyl-N-methyl, and the N,N-diethyl homologs were found, prepared by catalytic hydrogenation.

Nichols, D.E., Synthesis of 3,4-Methylenedioxymethamphetamine Hydrochloride. FDA Master File on MDMA. 1986.

A detailed synthesis of MDMA from piperonylacetone is presented, including all the spectroscopic and physical detail, bibliographies, CVs, and such that define the final product for medical needs.

Shulgin, A.T. and Jacob III, P., Potential Misrepresentation of 3,4-Methylenedioxyamphetamine (MDA). A Toxicological Warning. J. Anal. Tox., 6, pp 71-75 (1982).

The commercial availability and overt misrepresentation of 3,4-methylenedioxybenzyl-acetone as 3,4-methylenedioxyphenylacetone might well suggest that an unsuspecting attempt to synthesize MDMA may yield a new and unexplored base, 1-(3,4-methylenedioxy-phenyl)-3-(methylamino)butane. This compound was synthesized, and characterized in comparison to MDMA. The analogous relationship between MDA and its comparable homolog, 1-(3,4-methylenedioxyphenyl)-3- aminobutane, was also explored.

(2) IN VITRO STUDIES

Brady, J.F., Di Stephano, E.W. and Cho, A.K., Spectral and Inhibitory Interactions of (+/-)-3,4-Methylenedioxyamphetamine (MDA) and (+/-)-3,4-Methylenedioxymethamphetamine (MDMA) with Rat Hepatic Microsomes. Life Sciences 39 1457-1464.

> Both MDA and MDMA were shown to form complexes with cytochrome P-450 that were inhibitory to its function as to demethylation of benzphetamine and carbon monoxide binding. Liver microsome studies showed the metabolic demethylation of MDMA and the N-hydroxylation of MDA.

Frye, G. and Matthews, R. Effect of 3,4-methylenedioxymethamphetamine (MDMA) on Contractive Responses in the G. Pig Ileum. The Pharmacologist 28 149 (#318) (1986).

> Using the longitudinal muscle of the guinea pig ilium, MDMA evoked dose-related, transient contractions, but failed to reduce contractions produced by serotonin, acetylcholine, or GABA. The MDMA contractions were blocked by atropine, and do not appear to involve serotonin receptors.

Gehlert, D.R., Schmidt, C.J., Wu, L. and Lovenberg, W., Evidence for Specific Methylenedioxymethamphetamine (Ecstasy) Binding Sites in the Rat Brain. Europ. J. Pharmacol. 119 135-136 (1985).

> Evidence is presented from binding to rat brain homogenate studies. The use of the serotoninergic re-uptake inhibitor, active in vivo, does not antagonize this binding, nor in studies with uptake into striatal microsomes.

Levin, J.A., Schmidt, C.J. and Lovenberg, W. Release of [^{3}H]- Monoamines from Superfused Rat Striatal Slices by Methylenedioxymethamphetamine (MDMA). Fed. Proc. 45 1059 (#5265) April 13-18, 1986.

> The release of tritiated serotonin and dopamine from superfused rat striatal slices was observed for three amphetamine derivatives. MDMA and p-chloroamphetamine were equivalent, and about 10x the potency of methamphetamine. This last compound was, however, some 10x more effective than MDMA in the relase of dopamine.

Lyon, R.A., Glennon, R.A. and Titeler, M. 3,4-Methylenedioxymethamphetamine (MDMA): Stereoselective Interactions at Brain 5- HT_1 and 5-HT_2 Receptors. Psychopharmacology88 525-526 (1986).

> Both MDMA and MDA, and their respective optical isomers, were assayed as to their affinity at radio-labelled serotonin (5-HT_1 and 5-HT_2) and dopamine (D_2) binding sites. The "R" isomers of both drugs showed a moderate affinity at the 5-HT_2 receptor (labelled with ^{3}H ketanserin), and the "S" isomers were lower. Affinities for the 5-HT_1 site were similar, but that for D_2 sites were very low. Since the "S" isomer of MDMA is the more potent in man, it may not work primarily through a direct interaction at 5-HT receptors.

Nichols, D.E., Lloyd, D.H., Hoffman, A.J., Nichols, M.B. and Yim, G.K.W. Effects of Certain Hallucinogenic Amphetamine Analogues on the Release of [^{3}H] Serotonin from Rat Brain Synaptosomes. J. Med. Chem. 25, pp 530-535 (1982).

The optically active isomers of MDMA (as well as those for MDA, PMA) and the corresponding phentermine analogs, have been evaluated as to their effect on the release of serotonin from rat brain synaptosomes. The (+) isomer of MDMA was the more effective (this is the active isomer in humans) suggesting that serotonin release may play some role in the psychopharmacological activity. The alpha-alpha dimethyl homologues were inactive even at the highest concentrations studied.

Steele, T.P., Nichols, D.E. and Yim, G.K.W. Stereoselective Effects of MDMA on Inhibition of Monoamine Uptake. Fed. Proc. 45 1059 (# 5262) April 13-18 1986.

In the investigation of the optical isomeric difference of activities seen for amphetamine, MDMA, and DOM (the more potent isomers being the "S", "S" and "R" resp.) their abilities to inhibit the uptake of radio-labelled monoamines into synaptosomes were studied. The findings are discussed, and it is concluded that MDMA exhibits stereoselective effects similar to those of amphetamine on monoamine uptake inhibition, a parameter that is unrelated to the mechanism of action of the hallucinogen DOM.

Steele, T.D., Nichols, D.E. and Yim, G.K.W. Stereochemical Effects of 3,4-Methylenedioxymethamphetamine (MDMA) and Related Amphetamine Derivatives on Inhibition of Uptake of [^{3}H]Monoamines into Synaptosomes from Different Regions of Rat Brain. Biochem. Pharmacol. 36 2297-2303 (1987).

MDA, MDMA, and the alpha-ethyl homolog MBDB were found to inhibit serotonin uptake in brain synaptosomes. The conclusions to a broad series of studies were that MDMA and its homologs are more closely related to amphetamine than to DOM in their biochemical actions.

Wang, S.S., Ricaurte, G.A. and Peroutka, S.J., [^{3}H] 3,4 Methylenedioxymethamphetamine (MDMA) Interactions with Brain Membranes and Glass Fiber Filter Paper, Europ. J. Pharmacol. 138 439-443 (1987).

Tritiated MDMA appears to give a pharmacological "binding profile" in rat brain homogionate studies, even in the absence of brain tissue. This appears to result from an unexpected binding of the radioligand to glass filter paper. Pretreatment with polyethylenimine eliminated this artifact.

(3) BIOCHEMISTRY

Gibb, J.W., Hanson, G.R. and Johnson, M. Effects of (+)-3,4- methylenedioxymethamphetamine [(+)MDMA] and (-)-3,4- methylenedioxymethamphetamine [(-)MDMA] on Brain Dopamine, Serotonin, and their Biosynthetic Enzymes. Soc. Neurosciences Abstrts. 12 169.2 (1986).

> The optical isomers of MDMA were studied in rats, as to the extent of serotonin and dopamine depletion, and the changes in their respective biosynthetic enzymes TPH (tryptophane hydroxylase) and TH (tyrosine hydroxylase). The (+) was the more effective in reducing serotonin levels at several sites in the brain, and was the more effective in reducing the TPH levels at all sites. Striatal TH was not effected by either isomer.

Johnson, M., Bush, L.G., Stone, D.M., Hanson, G.R. and Gibb, J.W. Effects of Adrenalectomy on the 3,4-Methylenedioxymethamphetamine (MDMA)-induced Decrease of Tryptophan Hydroxylase Activity in the Frontal Cortex and Hippocampus. Soc. Neurosci. Abstr., Vol. 13, Part 3, 1987. # 464.6.

> The tryptophan hydroxylase (TPH) activity of rat frontal cortex and hippocampus was found to decrease seven days following an acute large dosage of MDMA. The latter area was spared enzyme loss with adrenalectomy.

Letter, A.A., Merchant, K., Gibb, J.W. and Hanson, G.R. Roles of D_2 and 5-HT_2 Receptors in Mediating the Effects of Methamphetamine, 3,4-Methylenedioxymethamphetamine, and 3,4-Methylenedioxyamphetamine on Striato-Nigral Neurotensin Systems. Soc. Neurosciences Abstrts. 12 1005 (# 277.7) 1986.

> The chronic treatment of rats with methamphetamine, MDA or MDMA leads to a 2-3 fold increase of the neurotensin-like immunoreactivity in the striato-nigral areas of the brain. Efforts to assign neurotransmitter roles led to the simultaneous administration of serotonin and dopamine antagonists. These interrelationships are discussed.

Lim, H.K. and Foltz, R.L. Metabolism of 3,4-Methylenedioxymethamphetamine (MDMA) in Rat. FASEB Abstracts Vol. 2 No. 5 page A-1060. Abst: 4440.

> The metabolism of MDMA in the rat is studied. Seven metabolites are identified from the urine. These are:
>
> 4-hydroxy-3-methoxy methamphetamine
> 3,4-methylenedioxy amphetamine
> 4-hydroxy-3-methoxy amphetamine
> 4-methoxy-3-hydroxy methamphetamine
> 3,4-methylenedioxyphenyl acetone
> 3,4-dihydroxyphenyl acetone
> 4-hydroxy-3-methoxyphenyl acetone

Merchant, K., Letter, A.A., Stone, D.M., Gibb, J.W. and Hanson, G.R. Responses of Brain Neurotensin-like Immunoreactivity to 3,4-methylenedioxymethamphetamine (MDMA) and 3,4-methylenedioxyamphetamine (MDA). Fed. Proc. 45 1060 (# 5268) (1986).

> The administration of MDA and MDMA profoundly alters the levels of neurotensin-like

immunoreactivity (NTLI) concentrations in various portions of the brain of the rat. Increases of up to a factor of 3x are observed in some regions of the brain.

Schmidt, C.J. and Taylor, V.L. Acute Effects of Methylenedioxy- methamphetamine (MDMA) on 5-HT Synthesis in the Rat Brain. Pharmacologist 29 ABS-224 (1987). See also: Biochemical Pharmacology 36 4095-4102 (1987).

Acute exposure of MDMA dropped the tryptophane hydroxylase activity of rats, and this persisted for several days. Subsequent administration of Fluoxethine recovered this activity, but reserpine or alpha-methyl-tyrosine did not.

Stone, D.M., Johnson, M., Hanson, G.R. and Gibb, J.W. A Comparison of the Neurotoxic Potential of Methylenedioxy- amphetamine (MDA) and its N-methylated and N-ethylated Derivatives.

Multiple doses of MDA and MDMA decreases the level of brain tryptophan hydroxylase (TPH). The N-ethyl homolog was without effect. It is argued that although the studies here were well above human exposures, the cumulative effects of repeated exposures, the differences between rat and human metabolism, and increased human sensitivity to this drug, could present a serious threat to human abusers of this drug.

Stone, D.M., Hanson, G.R. and Gibb, J.W. GABA-Transaminase Inhibitor Protects Against Methylenedioxymethamphetamine (MDMA)- induced Neurotoxicity. Soc. Neurosci. Abstr. Vol. 13, Part 3 (1987). # 251.3.

The neurotoxicity of MDMA (in the rat) was protected against by GABA-transaminase inhibitors.

Stone, D.M., Stahl, D.C., Hanson, G.R. and Gibb, J.W. Effects of 3,4-methylenedioxyamphetamine (MDA) and 3,4-methylenedioxymethamphetamine (MDMA) on Tyrosine Hydroxylase and Tryptophane Hydroxylase Activity in the Rat Brain. Fed. Proc. 45 1060 (# 5267) April 13-18, 1986.

The effects of rats treated chronically with either MDA or MDMA on the enzymes involved with neurotransmitter synthesis is reported. The levels of tryptophane hydroxylase (TPH, involved with serotonin synthesis) were markedly reduced, differently in different areas of the brain. The tyrosine hydroxylase (TH, involved with dopamine synthesis) remains unchanged. This is in contrast to the documented reduction of TH that follows high dosages of methamphetamine.

(4) PHARMACOLOGY

Anderson III, G.M., Braun, G., Braun, U., Nichols, D.E. and Shulgin, A.T., Absolute Configuration and Psychotomimetic Activity, NIDA Research Monograph #22, pp 8-15 (1978).

The "R" isomer of most chiral hallucinogenics is known to be the active isomer. This generality includes LSD, DOB, DOM, DOET, and MDA. This assignment has been demonstrated both in rabbit hyperthermia studies as well as in clinical evaluations. With MDMA, however, this assignment is reversed. In both rabbit and human studies, the more potent isomer of MDMA is the "S" form, similar to that of amphetamine and methamphetamine. The summed activity of the individual isomers did not satisfactorally reproduce the activity of the racemic mixture.

Also, the addition of an N-methyl to a known hallucinogenic amphetamine routinely decreases the potency (as with DOB, DOM, TMA and TMA-2). The exception again is with MDA, which produces the equipotent MDMA. The relationship between the stimulants amphetamine and methamphetamine is similar. The two drugs MDA and MDMA appear not to be cross-tolerant in man.

It is argued that the mechanisms of action of MDMA must be different from that of MDA and related hallucinogenics.

Beardsley, P.M., Balster, R.L. and Harris, L.S. Self- administration of Methylenedioxymethamphetamine (MDMA) by Rhesus Monkeys. Drug and Alcohol Dependence 18 149-157 (1986)

In monkeys trained to self-administer cocaine intravenously MDMA was found, in two out of four animals, to be an effective substitute.

Beaton, J.M., Benington, F., Christian, S.T., Monti, J.A. and Morin, R.D. Analgesic Effects of MDMA and Related Compounds. Pharmacologist 29 page ABS 281 (1987).

Analgesia of several compounds (including MDMA and several close homologs) was measured by the tail-flick reponse in mice. All produced analgesia, with the (+) (S) MDMA being the most potent.

Bird, M. and Kornetsky, C. Naloxone Antagonism of the Effects of MDMA "Ecstasy" on Rewarding Brain Stimulation. The Pharmacologist 28 149 (#319) (1986).

The lowering of the reward threshold (REBS, rewarding electrical brain stimulation) by the s.c. administration of MDMA to rats (as determined by implanted electrodes) was blocked by naloxone. This suggests that MDMA affects the same dopinergic and opioid substrates involved in cocaine and d-amphetamine reward.

Braun, U., Shulgin, A.T. and Braun, G. Prufung auf zentral Aktivitat und Analgesie von N-substituierten Analogen des Amphetamin-Derivates 3,4-Methylenedioxyphenylisopropylamin. Arzneim.-Forsch. 30 pp 825-830 (1980).

MDMA, and a large collection of N-substituted homologs, were assayed in mice for both analgesic potency and enhancement of motor activity. MDMA proved to be the most potent analgesic (compared with some 15 homologs) but was not particularly effective as a motor stimulant. The structure and pharmacological relationships to known analgesics are discussed.

Callahan, P.M. and Appel, J.B. Differences in the Stimulus Properties of 3,4-Methylenedioxyamphetamine (MDA) and N-Methyl-3,4- methylenedioxmethamphetamine (MDMA) in Animals Trained to Discriminate Hallucinogens from Saline. Soc. Neurosci. Abstr., Vol. 13, Part 3, p. 1720 (1987) No. 476.2.

The stimulant properties of MDA and MDMA (including the optical isomers) were studied in rats that were trained to discriminate mescaline or (separately) LSD, from saline. "R"-MDA appears similar to both hallucinogens, but the other isomers gave no clear-cut accord to the literature reports of behavioral activity.

Davis, W.M. and Borne, R.F., Pharmacological Investigation of Compounds Related to 3,4-Methylenedioxyamphetamine (MDA), Subs. Alc. Act/Mis. 5 105-110 (1984).

MDA and MDMA, as well as the homologous 3-aminobutanes HMDA and HMDMA, were studied toxicologically in both isolated and aggregated mouse groups. Both MDA and MDMA were of similar lethality in isolated animals (ca. 100mg/Kg i.p.) which was enhanced 3 or 4 fold by aggregation. The homologs HMDA and HMDMA were approximately twice as toxic but showed no such enhancement. The prelethal behavior characteristics and the effects of potential protective agents are described.

Evans, S.M. and Johanson, C.E. Discriminative Stimulus Properties of (+/-)-3,4-Methylenedioxymethamphetamine and (+/-)- Methylenedioxyamphetamine in Pigeons. Drug and Alcohol Dependence 18 159-164 (1986).

Pigeons, trained to discriminate (+) amphetamine from saline. Both MDA and MDMA substituted for amphetamine, and both were less potent.

Fellows, E.J. and Bernheim, F. The Effect of a Number of Aralkylamines on the Oxidation of Tyramine by Amine Oxidase. J. Pharm. Exptl. Therap. 100 94-99 (1950).

There were some animal behavioral studies made on the chain homolog of MDMA, vis., 1-(3,4-methylenedioxyphenyl)-3- methylaminobutane. This is the amine that would result from the use of the "wrong" piperonylacetone in illicit synthesis. In the dose range 10-25 mg/Kg, toxic effects such as tremors and convulsions were seen.

Glennon, R.A. and Young, R. Further Investigation of the Discriminative Stimulus Properties of MDA. Pharmacol. Biochem. and Behavior 20, 501-505 (1984).

In rats trained to distinguish between racemic MDA (and separately, "S"-amphetamine) and saline, MDMA (as well as either optical isomer of MDA) was found to generalize to MDA. Similarly, with rats trained to distinguish between dextro-amphetamine and saline, MDMA and "S"-MDA (but not "R"-MDA or "S"-DOM) produced generalization responses.

Glennon, R.A., Little, P.J., Rosecrans, J.A. and Yousif, M. The Effects of MDMA ("Ecstasy") and its Optical Isomers on Schedule- Controlled Responding in Mice. Pharmacol. Biochem. Behav. 26 425-426 (1987).

The effectiveness of several analogs of MDMA were evaluated in mice trained in a reinforcement procedure. Both (+) and racemic MDMA were 4x the potency of the levo- isomer; all were less potent than amphetamine.

Glennon, R.A., Young, R., Rosecrans, J.A. and Anderson, G.M. Discriminative Stimulus Properties of MDA Analogs. Biol. Psychiat. 17, 807-814 (1982).

In rats trained to distinguish between the psychotomimetic DOM and saline, several compounds were found to generalize to DOM (including racemic MDA, its "R" isomer, and MMDA-2) Others did not generalize to DOM (including MDMA, the "S" isomer of MDA, and homopiperylamine). These results are consistent with the qualitative differences reported in man.

Glennon, R.A., Yousif, M. and Patrick, G. Stimulus Properties of 1-(3,4-Methylenedioxy)-2-Amino-propane (MDA) analogs. Pharmacol. Biochem. Behav. 29 443-449 (1988).

Rats were trained to discriminate between saline and DOM or d-amphetamine. They were challenged with "R" and "S" MDMA, with racemic, "R" and "S" MDE, and with racemic MDOH N-OH-MDA). The amphetamine-trained animals generalized to "S" MDMA, but not to "R" MDMA, nor to any of the MDE isomers nor to MDOH (nor to homopiperonylamine). N-substituted amphetamine derivatives (N-ethyl and N-hydroxy) also gave the amphetamine response, but not of these compounds generalized to DOM. This study supports the suggestion that MDMA represents a class of compounds apart from the stimulant or the hallucinogenic.

Griffiths, R.R., Lamb, R. and Brady, J.V. A Preliminary Report on the Reinforcing Effects of Racemic 3,4-Methylenedioxy- methamphetamine in the Baboon. Document entered into evidence Re: MDMA Scheduling Docket No. 84-48, U.S. Department of Justice, Drug Enforcement Administration, October 16, 1985.

In three baboons trained to respond to cocaine, MDMA maintained self-administration at a somewhat lower level than cocaine, d-amphetamine, and phencyclidine. There was the evocation of distinct behavioral signals, which suggested that MDMA had a high abuse potential.

Harris, L.S. Preliminary Report on the Dependence Liability and Abuse Potential of Methylenedioxy-methamphetamine (MDMA). Document entered into evidence Re: MDMA Scheduling Docket No. 84-48, U.S. Department of Justice, Drug Enforcement Administration, October 16, 1985.

MDMA and amphetamine were compared as to locomotor activity in mice, and in reinforcing activity in monkeys as compared to cocaine. MDMA showed a fraction (20-25%) of the stimulant activity of amphetamine, and was substituted for cocaine in some of the test monkeys.

Kamien, J.B., Johanson, C.E., Schuster, C.R. and Woolverton, W.L. The Effects of (+/-)-Methylene-dioxymethamphetamine in Monkeys Trained to Discriminate (+)-Amphetamine from Saline. Drug and Alcohol Dependence 18 139-147 ((1986),

In monkeys trained to discriminate between amphetamine and saline, MDMA substituted and suggested that there was an amphetamine-like component to its action. This similarity to amphetamine suggests a dependence potential.

Kasuya, Yutaka Chemicopharmacological Studies on Antispasmodic Action. XII. Structure-Activity Relationship on Aralkylamines. Chem. Pharm. Bull. 6 147-154 (1958).

In vitro studies on mouse intestinal segments were carried out for the chain homolog

of MDMA, vis., 1-(3,4- methylenedioxyphenyl)-3-methylaminobutane. This is the amine that would result from the use of the "wrong" piperonylacetone in illicit synthesis. The compound shows weak atropine action.

Kulmala, H.K., Boja, J.W. and Schechter, M.D. Behavioral Suppression Following 3,4-Methylenedioxymethamphetamine. Life Sciences 41 1425-1429 (1987).

Rotation in rats was employed as an assay of the central dopaminergic activity of MDMA. At low doses it acts similarly to amphetamine, but at higher doses it appears to stimulate the dopamine receptor directly.

Lamb, R.J. and Griffiths, R.R. Self-injection of d,l-3,4- Methylenedioxymethamphetamine in the Baboon. Psychopharmacolgy 91 268-272 (1987).

In monkeys conditioned to the self-administration of cocaine, MDMA produced a similar but less potent response. A decrease in food intake was also reported.

Li, A., Marek, G., Vosmer, G. and Seiden, L. MDMA-induced Serotonin Depletion Potentiates the Psychomotor Stimulant Effects of MDMA on Rats Performing on the Differential-Reinforcement-of-Low-Rate (DRL) Schedule. Society of Neurosciences Abstracts 12 169.7 (1986).

This is a study of Serotonin depletion and motor response. The long term depletion following both acute and chronic administration of MDMA to rats, increased activity and decreased serotonin suggests some inhibitory action of this neurotransmitter.

Nichols, D.E., Hoffman, A.J., Oberlender, R.A., Jacob III, P. and Shulgin, A.T. Derivatives of 1-(1,3-Benzodioxol-5-yl-2- butanamine: Representatives of a Novel Therapeutic Class. J. Med. Chem. 29 2009-2015 (1986).

Animal discrimination studies (LSD versus saline) of the alpha-ethyl homologues of MDA and MDMA were performed. No generalization occurred with the N-methyl analogs of either group (MDMA and MBDB), and the latter compound was also found to be psychoactive but not hallucinogenic in man. It was found to be less euphoric than MDMA, but with the same sense of empathy and compassion. The term "entactogen" is proposed for the class of drugs represented by MDMA and MBDB.

Oberlender, R. and Nichols, D.E. Drug Discrimination Studies with MDMA and Amphetamine. Psychopharmacology 95 71-76 (1988).

In rats trained to discriminate saline from either racemic MDMA or dextroamphetamine. The MDMA cue generalized to MDA and to all isomers of MDMA and MBDB, but not to LSD or DOM. The dextroamphetamine cue generalized to methamphetamine, but to none of the forms of either MDMA or MBDB. The "S" isomers of both MDMA and MBDB were the more potent.

Rosecrans, J.A. and Glennon, R.A. The Effect of MDA and MDMA ("Ecstasy") Isomers in Combination with Pirenpirone on Operant Responding in Mice. Pharmacol. Biochem. Behav. 28 39-42 (1987). See also: Soc. Neurosci. Abstr., Vol. 13, Part 3, p. 905 (1987) No. 251.10.

The disruptive effects of the optical isomers of MDA and MDMA were studied for mice trained in a reinforcement schedule, both with and without pretreatment with pirenpirone, a serotonin antagonist. Of the four isomers evaluated, only "R"-MDA behavior responses were

attenuated by pirenpirone.

Schechter, M.D. Discriminative Profile of MDMA. Pharmacol. Biochem. Behav. 24 1533-1537 (1986)

Rats trained to discriminate several psychoactive drugs (against saline) were challenged with MDMA. The findings show that MDMA may act both as a dopamine and a serotonin agonist. This property is related to its abuse potential.

Schechter, M.D. MDMA as a Discriminative Stimulus: Isomeric Comparisons. Pharmacol. Biochem. Behav. 27 41-44 (1987).

Studies with rats trained to discriminate racemic MDMA from saline, showed generalization with both optical isomers of MDMA, with the "S" isomer being more potent. The chronological observations paralleled the reported human responses.

Schlemmer Jr., R.F., Montell, S.E. and Davis, J.M. Fed. Proc. 45 1059 (#5263) April 13-18 (1986).

The behavioral effects of MDMA have been studied in a primate colony, following multiple acute exposures. There was a decrease in activity, grooming, and food-searching, and an increase in staring. There was a disruption of social behavior, that differed from the effects of other hallucinogens.

Thompson, D.M., Winsauer, P.J. and Mastropaolo, J. Effects of Phencyclidine, Ketamine and MDMA on Complex Operant Behavior in Monkeys. Pharmacol. Biochem. Behav. 26 401-405 (1987).

The loss of response to conditioned behavior in monkeys was observed for the title drugs. All were effective i.m., with phencyclidine the most potent, and MDMA the least.

(5) NEUROCHEMISTRY

Ali, S.F., Scallet, A.C.,Holson, R.R., Newport, G.D. and Slikker Jr., W. Acute Administration of MDMA (Ecstasy): Neurochemical Changes Persist up to 120 Days in Rat Brain. Soc. Neurosci. Abstr., Vol. 13, Part 3, p. 904 (1987) No. 251.5.

Rats were given 40 mg/Kg MDMA twice daily for 4 days. After 120 days, some regions of the brain (frontal cortex, hippocampus) still had serotonin depletion. There was fighting behavior noted between rats during the dosing and for up to two weeks following it.

Battaglia, G., Kuhar, M.J. and De Souza, E.B. MDA and MDMA (Ecstasy) Interactions with Brain Serotonin Receptors and Uptake Sites: In vitro Studies. Soc. Neurosciences Abstrt. 12 336.4 (1986).

The receptor site uptake of the optical isomers, as well as the racemate, of both MDA and MDMA were measured by separate, selective labelling with appropriate radioligands. The relationships between the isomers depended on whether uptake sites or receptors were involved, and differed at different locations in the brain.

Battaglia, G., Yeh, S.Y., O'Hearn, E., Molliver, M.E., Kuhar, M.J. and De Souza, E.B. 3,4-Methylenedioxymethamphetamine and 3,4-Methylenedioxyamphetamine Destroy Serotonin Terminals in Rat Brain: Quantification of Neurodegeneration by Measurements of [^{3}H] Paroxetine-Labeled Serotonin Uptake Sites. J. Pharm. Exptl. Therap. 242 911-916 (1987),

Effects of repeated administration of MDMA and MDA on the levels of rat brain monoamines and their metabolites are reported. Only the serotonin-related systems were found to be affected.

Bird, M.P., Svendsen, C.N., Knapp, C., Hrbek, C.C., Bird, E.D. and Kornetsky, C. Evidence for Dopaminergic and Not Serotonergic Mediation of the Threshold Lowering Effects of MDMA on Rewarding Brain Stimulation. Soc. Neurosci. Abstr., Vol. 13, Part 3, p. 1323 (1987) No. 365.13.

An effort is made to determine the rewarding aspect of MDMA by a combination of brain electrodes and specific neurotransmitter inhibitors. It is felt that MDMA reinforcing values may be mediated by the dopamine D_2 receptor rather than the serotonin 5-HT_2 receptor.

Champney, T.H., Golden, P.T. and Matthews, R.T. Reduction of Hypothalamic Serotonin Levels after Acute MDMA Administration. Soc. Neurosciences Abstrts. 12 101.6 (1986).

Cortical, hypothalamic, and pineal levels of catecholamines, serotonin and 5-HIAA were determined shortly following an acute exposure of rats to each of several doses of MDMA. Dose-dependent decreases of serotonin and 5-HIAA were noted in some but not other areas. The catecholamine levels were unchanged.

Commins, D.L., Vosmer, G., Virus, R.M., Woolverton, C.R., Schuster, C.R. and Seiden, L.S. Biochemical and Histological Evidence that Methylenedioxymethylamphetamine (MDMA) is Toxic to Neurons in Rat Brain. J. Pharm. Exptl. Therap. 241 338-345 (1987).

MDMA was chronically administered to rats and guinea pigs , and the neurotransmitter levels were assayed in several portions of the brain. Neurotransmitter levels are related to dosage, and to the extent of exposure. Anatomical morbidity is carefully described.

DeSousa, E.B., Battaglia, G., Shu, Y.Y. and Kuhar, M.J. In Vitro and In Vivo Effects of MDA and MDMA (Ecstasy) on Brain Receptors and Uptake Sites: Evidence for Selective Neurotoxic Actions on Serotonin Terminals. Amer. Coll. of Neuropsychopharm. p. 207 (Dec. 8-12, 1986).

MDA and MDMA both showed a relatively high affinity for both $5HT_2$ serotoninergic and $alpha_2$ adrenergic brain receptors, but low affinities for $5HT_1$ and for the $alpha_1$ and beta adrenergic receptors, as well as for dopamine, muscarinic, and opiate receptors. Chronic administration of either drug decreases the number of $5\text{-}HT_2$ receptors in various brain locations.

Gehlert, D.R. and Schmidt, C.J. Acute Administration of Methylenedioxymethamphetamine (MDMA) Results in a Persistent and Selective Increase in $5\text{-}HT_1$ Receptor Binding in Rat Brain. Pharmacologist 29 ABS-44 (1987)

Acute administration of MDMA in the rat showed an increase in serotonin binding in 24 hours. This occurred in several parts of the brain.

Gold, L.H., Hubner, C.B. and Koob, G.F. The Role of Mesolimbic Dopamine in the Stimulant Action of MDMA. Soc. Neurosci. Abstr., Vol. 13, Part 3, p. 833 (1987) No. 234.13.

The administration of MDMA to rats may involve (like amphetamine) the release of dopamine. Test animals with lesions induced by 6-hydroxydopamine showed less motor activity in response to MDMA than control animals.

Johnson, M., Letter, A.A., Merchant, K., Hanson, G.R. and Gibb, J.W. Effects of 3,4-Methylenedioxyamphetamine and 3,4- Methylenedioxymethamphetamine Isomers on Central Serotonergic, Dopaminergic and Nigral Neurotensin Systems of the Rat. J. Pharm. Exptl. Therap. 244 977-982 (1988).

The difference of the isomers of MDA and MDMA in their ability to induce neurotransmitter changes and neurotensin immunoreactivity are reported. In general the d-isomers of each were the more potent in affecting neurochemical systems.

Glennon, R.A., Titeler, M., Lyon, R.A. and Youssif, M. MDMA ("Ecstasy"): Drug Discrimination and Brain Binding Properties. Soc. Neurosciences Abstracts 12 250.11 (1986).

In rats treated chronically with MDMA (trained to discriminate racemic MDMA from saline), radioligand binding studies were conducted with both serotonin and dopamine sites. The Ki values for both $5\text{-}HT_1$ and $5\text{-}HT_2$ receptors were highest for the "S" isomers of MDMA and MDA, with the racemate lower, and the "R" isomer yet lower. There was no particular affinity for the dopamine receptors studied.

Johnson, M.P., Hoffman, A.J. and Nichols, D.E. Effects of the Enantiomers of MDA, MDMA, and Related Analogues on [^{3}H]Serotonin and [^{3}H]Dopamine Release from Superfused Rat Brain Slices. Europ. J. Pharmacol. 132 269-276 (1986).

The study of a series of MDA homologs (MDA, MDMA, MBDB) showed a dramatic dependence between chain length and dopamine release. The longer the chain, the less the release. It is concluded that dopamine release plays a minor role in the human activity of these compounds.

Kalix, P. A Comparison of the Effects of Some Phenethylamines on the Release of Radioactivity from Isolated Rat Caudate Nucleus Prelabelled with ^{3}H-Dopamine. Arzneim. Forsch. 36 1019-1021 (1986).

A number of phenethylamines were found able to release radioactive dopamine from prelabelled caudate nuclei. MDMA was not spectacular, as the simplest unsubstituted amphetamine derivatives were the most effective.

Kopajtic, T., Battaglia, G. and De Souza, E.B. A Pharmacologic Profile of MDA and MDMA on Brain Receptors and Uptake Sites. Soc. Neurosciences Abstrts. 12 336.1 (1986).

Both MDA and MDMA were studied at various brain recognition sites using radioligand binding techniques. The findings suggest that these drugs may express their effects at serotonin receptors or uptake sites and/or alpha-2 adrenergic receptors.

Lyon, R.A., Glennon, R.A. and Titeler, M. 3,4-Methylenedioxy- methamphetamine (MDMA): Stereoselective Interactions at Brain 5- HT_1 and 5-HT_2 Receptors. Psychopharmacology 88 525-526 (1986).

The assay of the optical isomers of MDA and MDMA with isolated receptors of rat brains, suggested that MDMA does not work primarily through direct interaction with serotonin receptors.

Mokler, D.J., Robinson, S.E. and Rosecrans, J.A. Differential Depletion of Brain 5-Hydroxytryptamine (5-HT) by (+/-) 3,4- Methylenedioxymethamphetamine (MDMA). Pharmacologist 29 ABS-273 (1987).

Specific brain areas have been studied for the serotonin depletion effects of MDMA. The neuron metabolic activity in the specific areas might be involved.

Mokler, D.J., Robinson, S.E. and Rosecrans, J.A. (+/-) 3,4- Methylenedioxymethamphetamine (MDMA) Produces Long-term Reductions in Brain 5-Hydroxytryptamine in Rats. Europ. J. Pharm. 138 265-268 (1987).

Following chronic administration of MDMA to rats, both serotonin and 5-HIAA became depleted in the brain. It is suggested that MDMA can function as a neurotoxin.

Mokler, D.J., Robinson, S.E. and Rosecrans, J.A. A Comparison of the Effects of Repeated Doses of MDMA ("Ecstasy") on Biogenic Amine Levels in Adult and Neonate Rats. Soc. Neurosci. Abstr., Vol. 13, Part 3, p. 905 (1987) No. 251.9.

MDMA was given to both adult and neonate rats in 10-40 mg/Kg doses over several days. The serotonin levels were decreased and the dopamine levels were significantly increased.

Molliver, M.E. Serotonergic Neural Systems: What their Anatomic Organization Tells Us about Function. J. Clinical Psychopharm. 7 3S-23S (1987).

A review of the organization of the serotonin nervous system is presented. The findings associated with the neurotoxic effects of MDMA are used as instructive tools, and speculation is extended as to the role of these neurons in the generation of the affective state.

Molliver, M.E., O'Hearn, E., Battaglia, G. and De Souza, E.B. Direct Intracerebral Administration of MDA and MDMA Does Not Produce Serotonin Neurotoxicity. Soc. Neurosciences Abstrts. 12 336.3 (1986).

The microinjection of either MDA or MDMA directly in to the cerebral cortex resulted in no detectable cytotoxicity. This suggests that the neurotoxicity of both compounds may be due to some metabolite formed peripherally.

Monti, J.A., Beaton, J.M., Benington, F., Morin, R.D. and Christian, S.T. MDMA and MBDB Potentiate Phorbol Ester- Stimulated Catecholamine Release from PC-12 Cells. Society for Neuroscience, Abstract, for November 13-18, 1988.

The "S" isomer of both MDMA and MBDB are potent in stimulating catechol release from PC-12 cells. The norepinephrin and dopamine release was increased in the presence of phorbol dibenzoate. It is suggested that this release may be mediated by protein kinase-C.

O'Hearn, E., Battaglia, G., De Souza, E.B., Kuhar, K.J. and Molliver, M.E. Systemic MDA and MDMA, Psychotropic Substituted Amphetamines, Produce Serotonin Neurotoxicity. Soc. Neurosciences Abstrts. 12 336.2 (1986).

Rats exposed chronically to either MDA or MDMA were found, on sacrifice, to have a reduced number of serotonin axon terminals. This was most evident in cerebral cortex, thalamus, olfactory bulb and striatum, but also occurred in other areas. This may be due to the binding of thse drugs to the uptake sites. The serotonin cell bodies and the preterminal axons are spared.

Peroutka, S.J., Pascoe, N. and Faull, K.F. Monoamine Metabolites in the Cerebrospinal Fluid of Recreational Users of 3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy"). Res. Commun. Subst. Abuse 8 125-138 (1987).

Lumbar punctures from five MDMA users with various histories were assayed (some weeks following the last exposure) for the levels of metabolites from the three major neurotransmitters serotonin, dopamine, and norepinephrine. All assays fell within normal limits.

Ricaurte, G.A., Bryan, G., Strauss, L., Seiden, L. and Schuster, C. Hallucinogenic Amphetamine Selectively Destroys Brain Serotonin Nerve Terminals. Science 229 986-988 (1985).

MDA was studied and found to produce long lasting reductions in the level of serotonin, the number of serotonin uptake sites, and the concentration of 5-HIAA in the rat brain. It was suggested that these deficits were due to serotonin nerve terminal degeneration. This was the research report that had been submitted for publication at the time of the MDMA hearings, and that played a focal role in the emergency scheduling of MDMA.

Ricaurte, G.A., Forno, L.S., Wilson, M.A., DeLanney, L.E., Irwin, I., Molliver, M.E. and Langston, J.W. (+/-) Methylenedioxymethamphetamine (MDMA) Exerts Toxic Effects on Central Serotonergic Neurons in Primates. Soc. Neurosci. Abstr., Vol. 13, Part 3, p. 905 (1987) No. 251.8.

MDMA was given s.q. twice daily for four days to monkeys, at 2.5, 3.75 and 5 mg/Kg. Post-mortum brain analyses showed serotonin reduction (90%) and axon damage. Some was described as "striking" and involved morphological changes.

Scallet, A.C., Ali, S.F., Holson, R.R., Lipe, G.W. and Slikker Jr., W. Neurohistological Effects 120 Days after Oral Ecstasy (MDMA): Multiple Antigen Immunohistochemistry and Silver Degeneration Staining. Soc. Neurosci. Abstr., Vol. 13, Part 3, p. 904 (1987) No. 251.6.

Both silver degeneration procedures (Fink-Heimer) and immunohistochemical techniques have been appled to MDMA- treated rats long after dosing. There are indications of regional differences in recovery, and that some changes may be irreversible.

Schmidt, C.J. Acute Administration of Methylenedioxymethamphet- amine: Comparison with the Neurochemical Effects of its N- desmethyl and N-ethyl Analogs. 136 81088 (1987).

MDMA (and its two immediate homologs, MDMA and MDE) were studied in the serotoninergic systems in the rat brain. There was depletion of cortical serotonin which in the case of MDMA appeared to persist after at least a week.

Schmidt, C.J. and Lovenberg, W. (+/-)Methylenedioxymethamphetamine (MDMA): A Potentially Neurotoxic Amphetamine Analogue. Fed. Proc. 45 1059 (#5264) April 13-18, 1986. Note paper below, Schmidt et al., with this same title.

Rats were administered MDMA s.c. at various doses and sacrificed at three hours. Brain concentrations of dopamine and serotonin, and their major metabolites were determined. The serotonin concentrations were reduced in a dose- dependent manner. Coadministration of a serotonin uptake inhibitor, citalopram, blocked the MDMA-induced decline in striatal serotonin concentrations suggesting a mechanism similar to that of the known serotonergic neurotoxin p- chloroamphetamine.

Schmidt, C.J. and Lovenberg, W. Further Studies on the Neurochemical Effects of 4,5-Methylenedioxymethamphetamine and Related Analogues. Soc. Neurosciences Abstrts. 12 169.5 (1986).

The racemate and optical isomers of MDMA produced depletion of cortical and striatal serotonin. The (+) isomer was the more effective material. MDA was similar to MDMA, but effects produced by the N-ethyl homolog (MDE) were reversed in a week. Whereas all three drugs caused an acute decrease in serotonin concentration, only MDA and MDMA reduced the uptake of tritiated serotonin at the dosages studied (20 mg/Kg).

Schmidt, C.J., Wu, L. and Lovenberg, W. Methylenedioxymethamphetetamine: A Potentially Neurotoxic Amphetamine Analogue. Eur. J. Pharmacol. 124 175-178 (1986). A typewritten draft of this paper was presented to the DEA in conjunction with the legal hearings held concerning the scheduling of MDMA.

Acute administration of MDMA to rats provide selective and long lasting serotonin and 5-HIAA depletion, similar to that produced by p-chlorophenylalanine. There was an elevation of neostriatal dopamine as well as it primary metabolite homovanillic acid.

Seiden, L.S. Report of Preliminary Results on MDMA. Document entered into evidence Re: MDMA Scheduling Docket No. 84-48, U.S. Department of Justice, Drug Enforcement Administration, October 16, 1985.

Rats were treated both acutely and chronically with MDMA, and the study of the decrease of serotonin receptors and the interpretation of neurological staining indicated a neurotoxicity similar to, but less dramatic than, that seen with MDA.

Slikker, W., Ali, S.F., Scallet, A.C. and Frith, C.H. Methylenedioxymethamphetamine (MDMA) Produces Long Lasting Alterations in the Serotonergic System of Rat Brain. Soc. Neurosciences Abstrts. 12 101.7 (1986).

The chronic treatment of rats with MDMA (orally) produced decreased levels of serotonin and 5-HIAA. At high dose levels there was a temporary decrease in homovanillic acid (HVA) but no change in dopamine levels.

Spanos, L.J. and Yamamoto, B.K. Methylenedioxymethamphetamine (MDMA)-induced Efflux of Dopamine and Serotonin in Rat Nucleus Accumbens. Society of Neurosciences Abstr't. 12 p. 609 (#169.6)

Following MDMA adminstration to rats, the efflux of dopamine was decreased but then it quickly recovered. Serotonin depletion does not recover even after 2 hours, thus MDMA may be neurotoxic.

Stone, D.M., Hanson, G.R. and Gibb, J.W. Does Dopamine Play a Role in the Serotonergic "Neurotoxicity" Induced by 3,4- Methylenedioxymethamphetamine (MDMA)? Society of Neurosciences Abstract 12 169.4 (1986).

The possibility that the negative serotonin effects of MDMA might be mediated by dopamine was investigated. Studies involving dopamine synthesis inhibitors and antagonists suggest less involvement of dopamine than is seen with methamphetamine.

Stone, D.M., Hanson, G.R. and Gibb, J.W. Differences in the Central Serotonergic Effects of Methylenedioxymethamphetamine (MDMA) in Mice and Rats. Neuropharm. 26 1657-1661 (1987).

A number of studies as to the brain serotonin responses to MDMA (in rats) suggest that the duration of exposure might be an important factor in the estimation of toxic effects. Mice are shown to be less susceptible, neurotoxicologically, than rats.

Stone, D.M., Merchant, K.M., Hanson, G.R. and Gibb, J.W. Immediate and Long Term Effects of 3,4-Methylenedioxymethamphetamine on Serotonin Pathways in Brain of Rat. Neuropharmacology 26 1677-1683 (1987).

The time course for the decrease of markers of central serotonin function in the rat is reported. Changes were observed at 15 minutes following a 10 mg/Kg s.c. injection, and much recovery was observed at the 2 week point. Following multiple dose administration of MDMA, significant serotonin changes were still evident after 110 days.

Stone, D.M., Stahl, D.C., Hanson, G.R. and Gibb, J.W. The Effects of 3,4-methylenedioxymethamphetamine (MDMA) and 3,4- methylenedioxyamphetamine (MDA) on Monoaminergic Systems in the Rat Brain. Eur. J. Pharmacol. 128 41-48 (1986).

Single or multiple doses of either MDMA or MDA caused marked reduction in both serotonin and 5-HIAA, as well as in the associated enzyme tryptophane hydroxylase (TPH). Single injections elevated striatal dopamine concentrations, although after repeated injections, these values became normal. Striatal tyrosine hydroxylase (TH) was not changed.

Takeda, H., Gazzara, R.A., Howard, S.G. and Cho, A.K. Effects of Methylenedioxymethamphetamine (MDMA) on Dopamine (DA) and Serotonin (5-HT) Efflux in the Rat Neostriatum. Fed. Proc. 45 1059 (#5266) April 13-18, 1986.

Employing electrodes implanted in the neostriatum of anesthesized rats, the MDMA-

induced efflux of dopamine and serotonin was measured. The serotonin efflux was significantly increased by MDMA, and had returned to normal by three hours. The dopamine efflux increased slightly, and then dropped below normal. MDA decreased the dopamine efflux.

Trulson, T.J. and Trulson, M.E. 3,4-Methylenedioxymethamphetamine (MDMA) Suppresses Serotonergic Dorsal Raphe Neuronal Activity in Freely Moving Cats and in Midbrain Slices in vitro. Soc. Neurosci. Abstr. Vol. 13, Part 3, p. 905 (1987) No. 251.7.

A study of the decrease of brain serotonin levels in cats given 0.25-5.0 mg/Kg MDMA is reported. Pretreatment with p-chloroamphetamine greatly attenuated the suppressant action of MDMA, and it is suggested that the action of the two drugs is similar.

Wilson, M.A., Ricaurte, G.A. and Molliver, M.E. The Psychotropic Drug 3,4-Methylenedioxymethamphetamine (MDMA) Destroys Serotonergic Axons in Primate Forebrain: Regional and Laminar Differences in Vulnerability. Soc. Neurosci. Abstr., Vol. 13, Part 3, p. 905 (1987) No. 251.8.

The monkey shows a striking brain loss of serotonin terminals following exposure to MDMA twice daily for 4 days at 5 mg/Kg. The distribution and extent of this damage is reported.

Woolverton, W.L., Virus, R.M., Kamien, J.B., Nencini, P., Johanson, C.E., Seiden, L.S. and Schuster, C.R. Behavioral and Neurotoxic Effects of MDMA and MDA. Amer. Coll. Neuropsychopharm. Abstrts. p. 173 (1985).

In behavioral studies in rats and monkeys trained to distinguish amphetamine from saline, MDMA mimicked amphetamine. With chronic administration, MDMA caused a degeneration of serotonin uptake sites, but no change in affinity of the undamaged sites. These results were similar to, but greater than, those seen with MDA.

Yey, S.Y. and Hsu, F-L. Neurotoxicity of Metabolites of MDA and MDMA (Ecstasy) in the Rat. Soc. Neurosci. Abstr., Vol. 13, Part 3, p. 906 (1987) No. 251.11.

MDA, MDMA, and a number of potential metabolites (4-OH-3-OMe-amphetamine, alpha-methyldopamine, alpha-methylnorepinephrine) were studied in the rat, and the serotonin decreases measured. These metabolites have a lower neurotoxicity than the parent compound.

Yeh, S.Y., Battaglia, G., O'Hearn, E., Molliver, M.E., Kuhar, M.J. and De Souza, E.B. Effects of MDA and MDMA (Ecstasy) on Brain Monoaminergic Systems: In vivo studies.

The chronic treatment of rats with MDMA or MDA (20 mg/Kg, twice daily, for 4 days) produced dramatic decreases in both serotonin and 5-HIAA in various brain locations. Other neurotransmitters and their metabolites were not affected.

(6) TOXICOLOGY

Brown, C.R., McKinney, H., Osterloh, J.D., Shulgin, A.T., Jacob III P. and Olson, K.R. Severe Adverse Reaction to 3,4-Methylenedioxymethamphetamine (MDMA). Vet. Hum. Toxicol., 28 490 (1986).

A 32 year old female presumably ingested a "standard" dose, and became comatose, but survived. Serum level was reported to be 7 micrograms/mL.

Brown, C. and Osterloh, J. Multiple Severe Complications from Recreational Ingestion of MDMA (Ecstasy). J. Amer. Med. Soc. 258 780-781 (1987).

A considerable body of clinical detail and selected laboratory finding is present in an apparent MDMA toxicity situation involving a 32 year old female. Serum levels of 7 micrograms/mL and urine levels of 410 and 816 micrograms/mL were reported (the latter upon admission and on the second day). An immunoenzyme assay for MDMA (using a system designed for amphetamine) reacted with MDMA at 25 micrograms/mL at the amphetamine cut-off point of 300 nanograms/mL. The observed complications were similar to those observed in amphetamine overdoses, and might possibly be due to an idiosyncratic reaction, an allergic reaction, or to malignant hyperthermia.

Davis, W.M. and Borne, R.F. Pharmacologic Investigation of Compounds Related to 3,4-Methylenedioxyamphetamine (MDA). Substance and Alcohol Actions/Misuse, 5 105-110 (1984).

Acute toxicity studies on MDMA and several homologs, in mice, showed LD-50's of about 100 mg/Kg (i.p.) (for MDMA). In aggregate, the lethality was increased several-fold.

Davis, W.M., Hatoum, H.T. and Waters, I.W., Toxicity of MDA (3,4- Methylenedioxyamphetamine) Considered for Relevancy to Hazards of MDMA (Ecstasy) Abuse. Alcohol and Drug Abuse, 7 123-134 (1987).

The toxicological literature is reviewed, and it is suggested that the toxicological data obtained from MDA be extrapolated to MDMA. A comparison of these two drug is presented.

Downing, G.P., McDonough III, E.T. and Bost, R.O. 'Eve' and 'Ecstasy' A Report of Five Deaths Associated with the Use of MDEA and MDMA. J. Amer. Med. Assoc. 257 1615-1617 (1987)

Five deaths occurred in the Dallas area which have involved either MDMA or MDE. One death was stated to be due to MDMA. Two of the others had had preexisting heart conditions, one had asthma, and one was electrocuted, apparently from having climbed and fallen from a power pole. In these latter cases, MDMA was not felt to have been the primary cause of death. It is suggested that a preexisting cardiac disease may predispose an individual to sudden death with MDMA. It was only with the asthma death that there was given a body level (blood) of MDMA, and it was 1.1 micrograms/mL.

Frith, C.H. 28-Day Oral Toxicity of Methylenedioxymeth- amphetamine Hydrochloride (MDMA) in Rats. Project Report, Toxicology Pathology Associates, Little Rock, Arkansas (1986)

A controlled toxicological study on some 100 rats with chronically administered MDMA (dosages up to 100 mg/Kg) showed several behavioral signs (hyperactivity, excitability,

piloerection. exophthalmus, and salivation). Neither gross nor microscopic pathology was evident at necropsy.

Frith, C.H., 28-Day Oral Toxicity of Methylenedioxymeth- amphetamine Hydrochloride (MDMA) in Dogs. Project Report, Toxicology Pathology Associates, Little Rock, Arkansas (1986)

A controlled toxicological study of some 24 dogs with chronically administered MDMA (dosages up to 15 mg/Kg) showed several behavioral signs including circling, depression, dilated pupils, hyperactivity, rapid breathing, and salivation. On necropsy, there were examples of reduced testicular size, including microscopically noted atrophy. Prostatic hyperplasia was present in two high dose males.

Frith, C.H., Chang, L.W., Lattin, D.L., Walls, R.C., Hamm, J. and Doblin, R. Toxicity of Methylene-dioxymethamphetamine (MDMA) in the Dog and the Rat. Fundamental and Applied Tox. 9, 110-119 (1987).

Toxicity studies were performed on dogs and rats and signs are described. No histopathological lesions within the CNS were observed in either species, although unusual clinical observations were recorded.

Goad, P.T. Acute and Subacute Oral Toxicity Study of Methylene- dioxymethamphetamine in Rats. Project Report, Intox Laboratories, Redfield, Arkansas, (1985).

Subacute toxicity studies on rats in graded doses (25 mg/Kg/day in 25 mg increments to 300 mg) were conducted. In acute studies, the LD-50 is given as 325 mg/Kg, some 6x the reported i.p. LD-50. No histological evidence of brain damage was observed.

Hardman, H.F., Haavik, C.O. and Seevers, M.H. Relationship of the Structure of Mescaline and Seven Analogs to Toxicity and Behavior in Five Species of Laboratory Animals. Tox. and Appl. Pharmacology 25 #2 (June) pp. 299-309 (1973).

This report describes several studies supported by the Army Chemical Center during the period 1953-1954, and declassified in 1969. MDMA was one of eight compounds (including also mescaline, DMPEA, MDPEA, MDA, DMA, TMA and alpha-ethyl-MDPEA) studied in five animals (mouse, rat, guinea pig, dog, and monkey).

The toxicology study showed MDMA to be one of the more toxic of the drugs studied, in most animals second only to MDA. The average LD-50's given were 97, 49 and 98 mg/Kg (for the mouse, rat and guinea pig, resp. – following i.p. administration), and 16 and 26 mg/Kg (for the dog and monkey, i.v. administration).

Behavioral studies in dog and monkey were made over the dosage ranges of 5-50 and 10-75 mg/Kg respectively. These levels evoked a broad range of motor activity, autonomic activity and CNS activity in both animals (the dog more than the monkey) but the ranges studied included the lethal dose levels. Interestingly the monkey showed behavior interpreted as hallucinations for MDMA, whereas mescaline (an acknowledged hallucinogenic compound) produced no such behavior at doses more than 2x higher (200 mg/Kg i.v.). Structure-activity relationships are discussed.

Hayner, G.N. and McKinney, H. MDMA The Dark Side of Ecstasy. J. Psychoactive Drugs 18 341-347 (1986).

The emergency treatment of two toxic episodes involving MDMA are described. One case, a 34 year old male, had a complex drug history involving mainly opiates, but the timing

of the crisis suggested that MDMA injection was responsible. The other case, involving a 33 year old female, has been discussed in detail (see Brown et al., above). A listing of the side-effects that may be experienced in cases of MDMA toxicity is also presented.

Reynolds, P.C., Personal Communication, 1986.

A 35-years old male, who claimed to have taken MDMA, Valium, and LSD (and who died shortly after admission) had the following body levels (in micrograms/mL):

	Blood	Urine	Bile	Gastric (total)
MDMA	1.46	13.7	1.98	414 mg.
MDA	.03	(present)		

Neither diazepam nor nordiazepam were found.

Schmidt, C.J., Neurotoxicity of the Psychedelic Amphetamine, Methylenedioxymethamphetamine. J. Pharm. Exptl. Therap. 240 1-7 (1987).

Evidence is presented that MDMA has a complex effect on rat serotonergic neurons, that results in a neurotoxic effect on the nerve terminals. A parallel is drawn to the neurotoxin para-chloroamphetamine.

Schmidt, C.J., Levin, J.A. and Loverberg, W., In Vitro and In Vivo Neurochemical Effects om Methylenedioxymethamphetamine on Striatal Monoaminergic Systems in the Rat Brain, Biochem. Pharmacol. 36 747-755 (1987)

This study compares the effects of MDMA and MDA on the neurotransmitter release in vitro and the (+) isomer is the more effective. The (+) isomer is also the more effective in vivo.

Shulgin, A.T. and Jacob III, P., 1-(3,4-Methylenedioxyphenyl)-3- aminobutane: A Potential Toxicological Problem. J. Toxicol. - Clin. Tox. 19, pp 109-110 (1982).

An alert is written for the toxicological community that through the ambiguity of the term "piperonylacetone" two different chemical precursors for both MDA and MDMA have been publically advertised and made available. Efforts to synthesize MDMA might, through misrepresentation, yield a largely unexplored homolog.

Smilkstein, M.J., Smolinske, S.C., Kulig, K.W. and Rumack, B.H. MAO Inhibitor/MDMA Interaction: Agony after Ecstasy. Vet. Hum. Toxicol. 28 490 (1986).

An abstract of a report of a 50 year old male who injected alleged MDMA while on a fixed regimen of the monoamine oxidase inhibitor phenelzine. He developed severe hypertension, diaphoresis, an altered mental status, and marked hypertonicity. With supportive care he recovered fully in some 6 hours. Caution is expressed in possible interations between MDMA and MAO inhibitors.

Smilkstein, M.J., Smolinske, S.C. and Rumack, B.H. A Case of MAO Inhibitor/MDMA Interaction: Agony after Ecstasy. Clin. Toxicol. 25 149-159 (1987).

This is the actual published paper that appeared as an abstract under similar authorship and similar title above. There are considerable clinical details concerning the emergency room intervention.

Verebey, K., Alrazi, J. and Jaffe, J.H. The Complications of "Ecstasy" (MDMA). J. Am. Med. Assoc. 259 1649-1650 (1988). Osterloh, J. and Brown, C., In Reply. ibid. 259 1650 (1988).

The body levels of MDMA and MDA following a single human trial of 50 mg are given. The peak plasma level seen (105.6 ng/Ml at 2 hrs.) decreased to 5.1 ng/Ml at 24 hrs. MDA occurred in plasma at lower levels, and both compounds appeared in urine. This suggests that the toxic incident reported by Brown and Osterloh may have followed a considerable overdose.

(7) CLINICAL STUDIES

Buffum, J. and Moser, C. MDMA and Human Sexual Function. J. Psychoactive Drugs, 18 355-359 (1986).

A survey of some 300 MDMA users produced a response of 25%. An analysis of the presented data is offered, organized as to types of activity and performance. There was a significant increase in intimacy, and a decrease (especially for males) in performance.

Downing, J. The Psychological and Physiological Effects of MDMA on Normal Volunteers. J. Psychoactive Drugs 18 335-340 (1986).

This is certainly the most complete clinical study on the effects of MDMA on the normal human subject. A total of 21 normal volunteers were administered known amounts of MDMA, orally. The entire group had analyses of blood chemistry, timed and frequent physiological measures, including pulse and blood pressure (for all) and as well as neurological and electrocardiographic tests (for some). The neurological and electrocardiogram evaluations were continued for 24 hours.

Physicologically, all subjects experienced an elevation in blood pressure and pulse rate, with a peaking on the average at about one hour. At the sixth hour, most subjects were at or below their pre-dose levels, and at 24 hours all were within their normal ranges. Eye dilation was seen in all subjects, more than half had jaw clench and an increased jaw reflex, which persisted in one subject at the 24 hour point. Some neurological reflexes were enhanced (deep tendon) or equivocal (plantar reflex), and there were signs of incoordination (finger-nose testing, gait) in some subjects, giving a strong warning against motor vehicle operation. One subject was nauseous, with vomiting, but there were no difficulties with either urination or defecation, and there were neither headaches nor insomnia. Appetite was suppressed in all subjects to varying degrees.

At the psychological level, all subjects reported a heightened sensual awareness, and three reported sexual arousal. It is concluded that MDMA produces remarkably consistent psychological effects that are transient, and is free of clinically apparent major toxicity.

Greer, G. MDMA: A New Psychotropic Compound and its Effects in Humans. Privately published, 333 Rosario Hill, Sante Fe, NM 87501. Copyright 1983. 15 pages.

The most complete study of the effects of MDMA published as of this date, describing the results of administration of MDMA to 29 human subjects (none with serious psychiatric problems) in a therapeutic setting. It is concluded that the best uses of MDMA are: facilitation of communication and intimacy between people involved in emotional relationships; as an adjunct to insight-oriented psychotherapy; and in the treatment of alcohol and drug abuse. He explains why MDMA does not lend itself to over- use, since its most desirable effects diminish with frequency of use.

Greer, G. Recommended Protocol for MDMA Sessions. Privately published. 333 Rosario Hill, Sante Fe, NM 87501. Copyright 1985. 6 pages.

This is a generalized protocol designed to cover the clinical use of MDMA. It reviews the issues of law, of safety, and of efficacy.

Greer, G. Using MDMA in Psychotherapy. Advances, 2 57-57 (1985).

A conference was held at Esalen March 10-15 1985, to discuss the potential of MDMA for therapy, and to evaluate its differences from earlier therapeutic tools such as LSD. A total of 13 subjects, with the supervision of several experienced psychiatrists, participated in an experiment designed to familiarize the potential clinician with the actions of MDMA. Most of the attendees had already known of the drug in a therapeutic context, and their collected comments are presented and discussed.

Greer, G. and Tolbert, R. Subjective Reports of the Effects of MDMA in a Clinical Setting. J. Psychoactive Drugs 18 319-327 (1986).

This article summarizes and gives additional detail on the collection of 29 therapeutic trials discussed earlier. The format of drug administration, a review of both the benefits and the undesirable effects, and an outlining of the changes seen in the patients, is presented. There is a considerable body of retrospective evaluation.

Shulgin, A.T. and Nichols, D.E. Characterization of Three New Psychotomimetics, The Psychopharmacology of Hallucinogens, Eds. R.C. Stillman and R.E. Willette, Pergamon Press, New York. (1978).

The psychopharmacological properties of MDMA are presented, in company with two new compounds, para-DOT (2,5- dimethoxy-4-methylthioamphetamine) and alpha,O-DMS (5-methoxy-alpha-methyltryptamine). It is described as evoking an easily controlled altered state of consciousness with emotional and sensual overtones. It appears to be with little hallucinatory component. This is the first clinical report of the effects of MDMA in man.

Siegel, R.K. MDMA: Nonmedical Use and Intoxication. J. Psychoactive Drugs 18 349-354 (1986).

From a group of 415 acknowledged MDMA users, a sub- group of 44 were chosen for examinations and tests. They were interviewed, physically examined, and tested by several of a large battery of psychological evaluation procedures. From this, patterns of use and the nature of the intoxicating effects were deduced.

The author has concluded that the visual effects of MDMA intoxication were typical of the intoxications from the classical hallucinogens such as mescaline with imagery characteristic of drug-induced hallucinations, as well as those induced by isolation and stress. These are mollified when attention is directed towards external events. There were, nonetheless, no abnormal profiles on the psychological tests. It is felt that the MDMA intoxication is neither uniformly controllable nor uniformly predictable.

Tatar, A. and Naranjo, C. MDMA in der Gruppenpsychotherapie. Symposion "Uber den derzeitigen Stand der Forschung auf dem Gebiet der psychoaktiven Substanzen." Nov. 29 - Dec. 12, 1985, in Hirschhorn/Neckar, Germany.

Two independent reports of clinical utility are presented. Both investigators report MDMA use in group settings. The groups consisted mainly of psychosomatic patients involving problems such as allergies, eczema, sexual dysfunction, troublesome urination, cardiac irregularities, and cancer. There were some positive changes reported, and in some cases there were no improvements. No details are presented.

Wolfson, P.E. Meetings at the Edge with Adam: A Man for All Seasons. J. Psychoactive Drugs 18 329-333 (1986).

An extensive discussion is presented listing the potential virtues and hazards of MDMA use in the psychotherapeutic setting. The roles of drugs currently used, and those of MDMA-like action that might some day be available, are reviewed. A case report of the use of MDMA in a family problem situation is presented in considerable detail.

(8) ANALYSIS

Bailey, K., By, A.W., Legault, D. and Verner, D. Identification of the N-Methylated Analogs of the Hallucinogenic Amphetamines and Some Isomers. J.A.O.A.C., 58 pp 62-69 (1975).

> MDMA and four analogous methamphetamine derivatives (corresponding to 2-, 3-, and 4-methoxyamphetamine (MA) and 3-methoxy-4,5-methylenedioxyamphetamine (MMDA)) were synthesized and spectroscopically characterized. The synthesis was for the corresponding phenylacetone through the Leuckart reaction with N-methylformamide. The reported m.p. (of the hydrochloride salt) is 147-8. The U.V., NMR, IR and mass spectral data are presented. Rf values (five systems) and GC retention times (four systems) are also given.

Eichmeier, L.S. and Caplis, M.E. The Forensic Chemist; An "Analytic Detective", Anal. Chem. 47 pp 841A-844A (1975).

> An analytical anecdote is presented showing the logical procedure used to distinguish MDMA from closely related drugs such as MDA in a seized sample. MDMA was acknowledged to be similar to MDA but, whereas MDA is a controlled substance, MDMA is exempt (sic) from federal control.

Gupta, R.C. and Lundberg, G.D. Application of Gas Chromatography to Street Drug Analysis. Clin. Tox. 11 437-442 (1977).

> A gas chromatography screening procedure is described, in which the retention times of over 100 drugs are compared to methapyriline or codeine. MDMA is amongst them.

Hansson, R.C. Clandestine Laboratories. Production of MDMA 3,4- methylenedioxymethamphetamine. Analog. 9 (November, 10 pages) (1987).

> A compilation of forensic information pertaining to MDMA is presented, including spectra (UV, MS, IR), synthetic approaches, and observations from clandestine laboratory operations (seen in Australia).

Hearn, W.L., Hime, G. and Andollo, W. Recognizing Ecstasy: Adam and Eve, the MDA Derivatives – Analytical Profiles. Abstracts of the CAT/SOFT Meetings, Oct. 29 - Nov. 1, 1986, Reno/Lake Tahoe, Nevada.

> A study is reported comparing MDA, MDMA and MDE in the EMIT immunoanalytical assay system that is designed for amphetamine. Even though they are all of decreased reactivity, there is cross-reactivity and they may be picked up as positives. Using the bottom limit cut-off of 300 nanograms/mL for amphetamine there would be a response from as little as 10-15 micrograms/mL of MDMA. This is a value that might be encountered in the early stages of MDMA use.

Holsten, D.W. and Schieser, D.W. Controls over the Manufacture of MDMA. J. Psychoactive Drugs. 18 371-2 (1986).

> A strong argument is made for attending to the quality of manufacture, and the basic concepts of ethical principles in the exploring of drugs that have not been evaluated against

the usual pharmaceutical standards. Government interference in such studies becomes neccessary, to safeguard the public.

Newmeyer, J.A. Some Considerations on the Prevalence of MDMA Use. J. Psychoactive Drugs 18 361-362 (1986).

An epidemiology survey of MDMA use (as of 1986) from the usual information sources (Drug Abuse Warning Network, DAWN; the Community Epidemiology Work Group, CEWG; police department reports, medical examiner or coroner's office reports) gives little indications that there is a medical problem associated with its use. Epidemiologically, it can not be considered at the present time a problem. It may well be that the material currently enjoys controlled, careful use by a number of cognoscenti (as did LSD in the early 1960's) and perhaps in future years a larger number of less sophisticated individuals will be drawn into its usage, and will find ways to evince adverse reactions, police involvement, and other unpleasant consequences.

Noggle Jr., F.T., DeRuiter, J. and Long, M.J., Spectrophotometric and Liquid Chromatographic Identification of 3,4-Methylenedioxyphenylisopropylamine and its N-Methyl and N-Ethyl Homologs, J. Assoc. Off. Anal. Chem., 69 pp 681-686 (1986).

A synthesis of MDEA (the N-ethyl homolog of MDA) is reported, and the infra-red spectra of the free bases, the hydrochloride salts, and the phenylisothiocyanate adducts are recorded, as is the HPLC retention behavior for both the bases and these derivatives.

Noggle Jr., F.T., DeRuiter, J., McMillian, C.L. and Clark, C.R. Liquid Chromatographic Analysis of some N-Alkyl-3,4-Methylenedioxyamphetamines. J. Liq. Chromatog. 10 2497-2504 (1987).

The HPLC separation characteristics of MDA, MDMA, MDE and MDDM (N,N-dimethyl-MDA) are reported on a reversed phase column.

O'Brian, B.A., Bonicamp, J.M. and Jones, D.W., Differentiation of Amphetamine and its Major Hallucinogen Derivatives using Thinlayer Chromatography, J. Anal. Tox. 6, pp 143-147 (1982).

Two thin-layer chromatographic systems, and several procedures for detection, are described for MDMA and 18 analogs. The retention times and the visualization color changes are compared and described. Detection limits in urine were determined from artificially spiked samples. The reference sample of MDMA was synthesized from MDA by methylation with methyl iodide, and separation from the co- generated dimethyl and trimethylammonium homologs by liquid- liquid extraction and preparative TLC.

Renfroe, C.L. MDMA on the Street: Analysis Anonymous. J. Psychoactive Drugs 18 363-369 (1986).

In the twelve years (up to 1983) that PharmChem conducted its Analysis Anonymous service, they evaluated over 20,000 samples of street drugs. MDMA and MDA had been classified together (some 610 examples) and of these 72 had been alledged to be MDMA. In the years 1984-1985, a cooperating reference laboratory (S.P., Miami, Florida) reported an additional 29 alleged MDMA samples.

Of these 101 samples, over half proved to be, indeed, MDMA, and half of the remaining contained MDMA. This is considered a remarkably high validity rate. The origins, descriptions, and costs are discussed.

Sedgwick, B., Lo, P. and Yee, M. Screening and Confirmation of 3,4-Methylenedioxy-

methamphetamine (MDMA) in Urine: Evaluation of 1000 Specimens. Abstracts of the CAT/SOFT Meetings, Oct. 29 - Nov. 1, 1986, Reno/Lake Tahoe, Nevada.

A sequence of 1000 "at risk" samples were screened for the presence of methamphetamine (MA) and/or MDMA (not distinguishable in the initial analysis). Of 133 presumptive positive tests, none proved to be positive for MDMA.

Shaw, M.A. and Peel, H.W. Thin-layer Chromatography of 3,4- methylenedioxyamphetamine, 3,4-Methylenedioxymethamphetamine and other Phenethylamine Derivatives. J. Chromatog. 104 pp 201-204 (1975).

A broad study is presented on the TLC analyses of many phenethylamines. The compound specifically named in the title, 3,4-methylenedioxymethamphetamine (MDMA), was a misprint that was subsequently corrected to the intended compound, MMDA. MDMA was not a part of this study.

(9) REVIEWS AND COMMENTARIES
(and a sampling of the magazine, newspaper, and radio commentary that was part of the popular scene at the time of illegalization).

Abramson, D.M. Ecstasy: The New Drug Underground. New Age, October, 1985. pp 35-40.

This article addresses the questions that are raised by the conflict of governmental banning of drugs that are of potential value in psychotherapy, and the therapist's determination to continue exploring their use.

Adamson, S. "Through the Gateway of the Heart: Accounts of Experiences with MDMA and other Empathogenic Substances." Four Trees Publications, San Francisco. Foreword by R. Metzner. 1985.

This book is a collection of some fifty personal accounts, largely involving MDMA. Some are from the notes of therapists involving clinical usage, and others are personal accounts from self-exploration.

Adler, J., Getting High on 'Ecstasy', Newsweek, April 15, 1985, p. 96.

This is a short, apparently factual, overview of both the chemical and the "street" use of MDMA. It is generally sympathetic to its medical potential.

Anon: Several reports from the Brain/Mind Bulletin:

(1) MDMA: Compound raises medical and legal issues. Brain/Mind Bulletin, Vol. 10, #8, April 15, 1985.
The title article is presented, and nearly the entire issue is given over to a thorough coverage of the medical and scientific aspects of MDMA.

(2) Psychiatrists, drug-abuse specialists testify in L.A. at first MDMA hearing. Brain/Mind Bulletin, Vol. 10, #12 July 8, 1985.
A news report on the first round of hearings in Los Angeles, concerning the scheduling of MDMA. An overview of the testimony is presented.

(3) Judge proposes more lenient schedule for MDMA. Brain/Mind Bulletin, Vol. 11, #11 June 16, 1986.
Adminstrative Law Judge Francis Young recommended, at the conclusions of the MDMA hearings, that the DEA put the drug into Schedule III, partly to ease research with the compound, and partly due to the absence of demonstrated abuse of the drug.

(4) MDMA: Federal court decides that DEA used improper criteria. Brain/Mind Bulletin, Vol. 13, #2 November, 1987.
A report is given as to the First Court of Appeals in Boston, ruling that the DEA had not sufficiently considered the arguments concerning the current medical use of MDMA.

Anon: DEA Proposal to Ban New Psychedelic Protested. Substance Abuse Report, December, 1984. pp 4-5.

The several letters that were addressed to the DEA in response to its announcement in

the Federal Register to consider the scheduling of MDMA, are here abstracted and commented upon.

Anon: Ecstasy: 21st Century Entheogen. Private Tract, 28 pages.

This is an elaborate thesis that is directed totally to the promotion of the use of MDMA. There is a presumed question and answer section, that is designed for the cautiously curious.

Anon: MDMA. NIDA Capsules. Issued by the Press Office of the National Institute on Drug Abuse, Rockville, Maryland. July 1985.

A two-page precis describing the health problems encountered with MDMA use, its relationship to the neurotransmitters, and the moves being made at the Justice Department to combat "designer drugs" such as MDMA in the future.

Anon: Designer Drugs: A New Concern for the Drug Abuse Community. NIDA Notes, December, 1985, pp. 2-3.

A discussion of "designer drugs" is arranged in four groups: variations on fentanyl, on meperidine, on PCP, and on amphetamione and methamphetamine. MDMA fits this last group. The research directions of NIDA are discussed.

Barbour, J. Cracking Down: What You Must Know About Dangerous Drugs. The Associated Press. 1986.

This is a 63 page illustrated essay, aimed at stopping drug use and abuse by scaring the reader. Unfortunately, the information is not completely accurate. MDMA is spun together with other designer drugs as things that destroy the brain.

Barnes, D.M. New Data Intensifies the Agony over Ecstasy. Science 239 864-866 (1988).

A review and commentary is presented of the Winter Conference on Brain Research, 23-30 January, 1988, in which there was a section on MDMA. A distillation of the comments made, with the feeling that more clinical work is needed to define the value, and that there would not likely be any further clinical work done. There are extensive quotations from some of the authors of recent animal studies on serotonin toxicity.

Barnett, R. DEA: RSVP re MDMA. Editorial from KCBS, July 29, 1985.

With the possibilty of therapeutic value seen in some psychiatric cases, KCBS felt that the action of the DEA (making MDMA illegal) short-circuited the hearings process, and was premature. A request is made to allow research on the effects and potentials of this drug to continue.

Baum, R.M. New Variety of Street Drugs Poses Growing Problem. Chemical and Engineering News, September 9, 1985. pp. 7-16.

A completely professional article discussing the challenges presented to law enforcement officials, legislators and scientists, by the invention of analogues of illegal drugs by underground chemists. MDMA is held out as being quite apart from the fentanyl and meperidine examples, and is analysed at some length.

Beck, J. MDMA: The Popularization and Resulting Implications of a Recently Controlled Psychoactive Substance. Contemporary Drug Problems Spring, 1986. pp 23-63.

A historical analysis is made of the relationship between drug illegalization and social issues. MDMA is used as a specific example, and a considerable body of first hand observations of its use is also presented.

Beck, J. and Morgan, P.A. Designer Drug Confusion: A Focus on MDMA. J. Drug Education 16 267-282 (1986).

This article discusses the competing definitions and issues surrounding the various designer drugs, but is primarily devoted to an examination of MDMA. A rationale is offered as to why interest in MDMA will continue to grow.

Buchanan, J. Ecstasy in the Emergency Department. Clinical Toxicology Update, 7 (#4, July-August) p 1-4 (1985).

A review of the history and the pharmacology of the psychoactive amphetamines is given. The overall recommendation for the emergency room is to expect an overdosed patient to present with signs similar to those with an amphetamine overdose, and to expect to treat primarily signs of anxiety and hypertension. The attending physician can expect the patient to be unaware of the actual toxin he has taken, and careful laboratory work will be needed to identify the chemical in body fluids and drug samples.

Callaway, E. The Biology of Information Processing. J. Psychoactive Drugs 18 315-318 (1986).

A review is presented of the difficulties that are classically part of the communication of information, and the roles of the many psychologists and physicians who have addressed the problem. The study of neurotransmitters, and thus drugs that involve these brain chemicals, is part of the eventual understanding. The role of non-classic "unsleepy drugs" (stimulants) such as MDMA are speculated upon as potential tools in this study.

Climko, R.P., Roehrich, H., Sweeney, D.R. and Al-Razi, J. Ecstasy: A Review of MDMA and MDA. Int'l Journal of Psychiatry in Medicine. 16 359-372 (1986-87).

A review of the pharmacology and toxicity of MDA is presented, with some additional data for MDMA. A balanced presentation with 75 references.

Cohen, S. They Call It Ecstasy. Drug Abuse & Alcoholism Newsletter, Vista Hill Foundation. 14 # 6. September, 1985.

A basically negative overview of the prospects of MDMA in therapy. There is wistful note with the "we've been through all this before" feeling. LSD had hope, LSD failed, and this too shall fail.

Deluca, N. Closed Doors/Closed Minds. KCBS Editorial. July 10, 1986.

An opinion is expressed, that the easy answer to MDMA given by the federal government, illigalization by placement into Schedule I, was the wrong answer. It appears that MDMA warrants a closer look by therapists, and the DEA should not simply lock the drug away where it cannot be investigated.

Doblin, R. Murmurs in the Heart of the Beast: MDMA and the DEA, HHS, NIDA, NIMH, ADAMHA, FBI and the WHO. Privately printed. August 8, 1984.

This is a collection of many of the letters exchanged between between the DEA and the FDA, that led to the decision to place MDMA in the listings of scheduled drugs. Also included are the DAWN (medical emergency) reports, and letters written in response to the proposed scheduling.

Doblin, R. The Media Does MDMA. Privately printed, August 5, 1985 - July 2, 1987.

This is a collection of articles, newspaper accounts, writings from many sources, that touch upon MDMA. It is arranged in a collage.

Doblin, R., A Proposal for Orphan Pharmaceuticals, Inc. A Division of Neurobiological Technologies, Inc. August 4, 1987.

A review of the history of MDMA and the arguments for its legitimate commercial consideration are presented. The NTI Board of Directors did not accept this proposal.

Dowling, C.G. The Trouble with Ecstasy. Life Magazine, August, 1985. pp. 88-94.

A pictorial article timed to coincide with the first of the hearings concerning the eventual fate of MDMA, and with the effective placement of it under emergency legal control.

Ehrlich, B. Understanding Ecstasy: The MDM Story. Privately Printed Book Manuscript. About 70 pages. 1986.

This is a partial draft of a book, privately printed and circulated, covering the history and para-medical use of MDMA.

Ehrnstein, L.B., Reflections on Drug Enforcement and Drug Use. Psychedelic Monographs and Essays, 2 17-24 (1987).

This is an instructive and favorable review of the history and the possible usefulness of MDMA. There are suggestions offered as to how the inexperienced subject might approach MDMA for personal development.

Gallagher, W. The Looming Menace of Designer Drugs. Discover 7 #8 (August, 1986). p. 24.

A long and gloomy article on the growing problems of uncontrolled analogues of heroin. There is a heavy emphasis on the medical professional's use and involvement in drug abuse. A one page side-box gives a view of MDMA, with balance between therapeutic potential and the risks of using unevaluated and unapproved new drugs.

Gertz, K.R. "HugDrug" Alert: The Agony of Ecstasy. Harper's Bazaar, November 1985. p. 48.

A popular article is offered, with a balanced discussion of the case for, and the case against, the use of MDMA.

Glennon, R. A. Discriminative Stimulus Properties of Phenylisopropylamine Derivatives. Drug and Alcohol Dependence 17 119- 134 (1986).

A broad review of many substituted phenylisopropyl- amines and their responses in discriminative studies in animals trained to discriminate amphetamine (or, separately, DOM) from saline. MDMA produced no DOM-appropriate response (DOM is an hallucinogen) but did cross react with amphetamine (a stimulant).

Gold, M.S. Ecstasy, Etc. Alcoholism and Addiction Sept-Oct. 1985. p. 11.

Criticism of the popular use of untested drugs such as MDMA is presented. It is argued that all new "wonder euphorogenics" should be considered extremely dangerous until proven safe and effective for a specific condition by the FDA and the medical research community.

Grinspoon, L. and Bakalar, J.B. What is MDMA? Harvard Medical School Mental Health Letter 2 #2 (August, 1985). p. 8.

A quite brief presentation of the cogent facts that define MDMA.

Grinspoon, L. and Bakalar, J.B. A Potential Psychotherapeutic Drug? The Psychiatric Times, January, 1986. pp 4-5, 18.

A review of the development of the use of drugs in psychotherapy, and a discussion of the role that a drug like MDMA might play in this medical area.

Grinspoon, L. and Bakalar, J.B. Can Drugs be Used to Enhance the Psychotherapeutic Process? Amer. J. Psychotherap. 40 393-404 (1986).

There is evidence that the psychotherapeutic process can be enhanced by the use of drugs that invite self- disclosure and self-exploration. Such drugs might help to fortify the therapeutic alliance and in other ways. One drug that may prove promising for this purpose is the psychedelic amphetamine MDMA.

Hagerty, C. "Designer Drug" Enforcement Act Seeks to Attack Problem at Source. American Pharmacy NS25 #10 October, 1985 PP. 10-11.

An extensive argument is presented for the passage of the "Designer Drug" Enforcement Act, to effectively attack the sources of new drugs.

Harris, L. S. The Stimulants and Hallucinogens under Consideration: A Brief Overview of their Chemistry and Pharmacology. Drug and Alcohol Dependence, 17 107-118 1986.

A literature review is made of a number of drugs that are under consideration for international control. MDMA is briefly mentioned, and described as being in man more of a stimulant than a hallucinogen.

Hershkovits, D. Esctasy: The Truth About MDMA. High Times November, 1985. p. 33.

An interview was held with Richard Seymour, author of the book MDMA. Many good and reasonable questions, directly and accurately answered.

Hollister, L.E. Clinical Aspects of Use of Phenylalkylamine and Indolealkylamine Hallucinogens. Psychopharmacology Bulletin 22 977-979 (1986).

A generally negative evaluation of the use of hallucinogens (such as MDA, MDMA, LSD)

based largely on the potential of neurotoxicity and the absence of clinical verification of value. Most of the value must be gleaned from studies of twenty years ago, and the absence of recent research is ascribed to unusually high toxicity or to the lack of interest. The legal difficulties are not addressed.

Jones, R. Why the Thought Police Banned Ecstasy. Simply Living, 2 #10. p. 91-95.

A review of the United States controversy concerning MDMA as seen through Australian eyes. Implications of considerable use there in Australia.

Kirsch, M.M. "Designer Drugs" CompCare Publications, Minneapolis. 1986.

This book is organized into chapters that treat each of some half-dozen drugs that have been created or modified so as to circumvent explicit legal restrictions, or have recently emerged into popularity. One chapter, entitled "Ecstasy", spins together the popular lore concerning MDMA with quotations from various writers and lecturers and several anonymous users.

Klein, J., The New Drug They Call 'Ecstasy', New York (magazine), May 20, 1985, pp 38-43.

This is a popular article that brings together quotations that express the broad range of attitudes held by both the proponents and the opponents of the current clinical employment of MDMA. Some historical background is presented, as well as an articulate description of the effect the drug produces.

Leavy, J. Ecstasy: The Lure and the Peril. The Washington Post June 1, 1985. Zagoria, S. More "Peril" than "Lure." ibid. July 3, 1985,

A well researched and careful article reviewing all aspects of the MDMA palavar. The reply by Mr. Zagoria expressed the thought that Ms. Leavy's presentation was too enticing, with lure outweighing peril.

Leverant, R. MDMA Reconsidered. J. Psychoactive Drugs 18 373- 379 (1986).

A summations of thoughts and impressions gathered at the Oakland, California Conference on MDMA (May, 1986). The theme presented is the need of open-mindedness in the area of personal and well as clinical freedom of research, and MDMA was used as a focal point.

McConnell,H. MDMA. The Journal, The Addiction Research Foundation, Toronto. July 1, 1986 pp. 11-12.

A thorough review of the Oakland, California MDMA conference is presented, in considerable detail and with excellent balance.

Nasmyth, P. The Agony and the Ecstasy. The Face, October, 1986 p. 52.

A popularized article from England on the properties and the uses of MDMA. It strongly suggests that the drug is already deeply instilled in British culture.

Nichols, D.E., MDMA Represents a New Type of Pharmacologic Agent and Cannot be Considered to be either a Hallucinogenic Agent or an Amphetamine-type Stimulant.

This is an unpublished essay submitted both to the DEA and to the WHO group, through the offices of Richard Cotton. It presents a point by point analysis from both in vitro and in vivo studies of the pharmacological properties of MDMA and its isomers, with MDA (a structurally related hallucinogenic compound) and other amphetamines. He concludes that its actions represent a new classification of pharmacology, and clinical research with it in psychotherapy would argue against placing it in Schedule I.

Nichols, D.E. Differences Between the Mechanism of Action of MDMA, MBDB, and the Classic Hallucinogens. Identification of a New Therapeutic Class: Entactogens. J. Psychoactive Drugs 18 305-313 (1986).

This article presents a review of the extensive neurological and pharmacological evidence that supports the stand that MDMA and MBDB should be classified neither as hallucinogens (psychedelic drugs) nor as simple stimulants. An argument is made for a novel classification, entactogens.

O'Rourke, P.J. Tune In. Turn On. Go To The Office Late on Monday. Rolling Stone, December 19, 1985 p. 109.

The MDMA popularity craze is presented in a humorous retrospective of the drug attitudes of the 1960's.

Peroutka, S.J. Incidence of Recreational Use of 3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy") on an Undergraduate Campus. New England J. Med. 3171542-1543 (1987).

A random, and anonymous, poll of undergraduates at Stanford University (California) showed that some 39% of all students were experienced with MDMA (mean number of uses was 5.4, and dosage range was 60-250 mg). To date, he finds no evidence to suggest that MDMA is neurotoxic in humans.

Riedlinger, J.E. The Scheduling of MDMA: A Pharmacist's Perspective. J. Psychoactive Drugs 17 167-171 (1985).

A critical viewpoint of the scheduling procedures employed with MDMA. This paper is adapted from the original letter of protest sent to the DEA, and from the written testimony presented at the hearings.

Rippchen, R. MDMA Die Neue Sympathiedroge. Der Grüne Zweig 103 Medieneexperimente D-6941 Löhrbach, West Germany 1986.

A book of some 47 pages, giving an immense body of information on MDMA (in German) including translations of articles by Greer. Also included is information on other drugs such as MDE and 2C-B.

Roberts, M. Drug Abuse. MDMA: "Madness, not Ecstasy" Crosstalk section, Psychology Today. June, 1986.

An update of an earlier article (Psychology Today, May, 1985) which emphasizes the neurological findings, and the concept of unregulated drug synthesis. Congressional action prohibiting the manufacture and distribution of similar drugs is urged.

Roberts, T.B., The MDMA Question. Section on Social Concerns. AHP Perspective. May, 1986. p. 12.

This is a soul-searching review asking the questions as to where we must acknowledge the line between the need of drug use in therapy, and the need of drug use in society. Provisions must be made, of course, for both.

Schulman, R. The Losing War Against "Designer Drugs." Business Week, June 24, 1985 pp. 101-104.

An overview of the MDMA controversy. A preview is presented, of the pharmaceutical industry's response (OK to ban it, but not with the haste that might have a chilling effect on the development of new pharmaceuticals) and local law enforcement enthusiasm (Florida has granted the State Attorney General the power to place a drug on the Controlled Drug List in as little as 24 hours).

Seymour, R.B. "MDMA" Haight-Ashbury Publications, San Francisco. 1986

This is a volume devoted entirely to the single drug MDMA. Nine chapters discuss its origins, facts that apply to it, its bright side and dark side, in a carefully balanced presentation. It was made available for the Oakland, California symposium, MDMA: A Multidisciplinary Conference, May 17-18, 1986.

Seymour, R.B. Ecstasy on Trial. High Times, November, 1986. p. 33.

A retrospective review article of the controversies stirred up by the publicity that followed the government hearings and the illegalization of MDMA.

Seymour, R.B., Wesson, D.R. and Smith, D.E. Editor's Introduction. J. Psychoactive Drugs. 18 287 (1986).

An introduction is made to an entire issue of the Journal, dedicated to the several papers presented at a two- day conference on the topic of MDMA. This was held May 17- 18, 1986, at the Health Education Center of the Merritt Peralta Medical Center, in Oakland California.

Shafer, J., MDMA: Psychedelic Drug Faces Regulation. Psychology Today May, 1985. pp. 68-69.

This is a short overview presenting the clinical and legal views of a number of psychiatrists, administrators and researchers.

Shulgin, A.T. Twenty Years on an Ever-changing Quest, Psychedelic Reflections, Eds. L. Grinspoon and J.B. Bakalar, Human Science Press, New York (1983). pp. 205-212.

This is an essay on the philosophy of research associated with psychedelic drugs. MDMA is described briefly, with some of its history, pharmacology, and therapeutic potential.

Shulgin, A.T. What is MDMA? PharmChem Newsletter 14 #3 3-11 (1985).

A hypothetical interview is presented, distilling the questions fielded from many reporters, and the substance of the answers given to these questions.

Shulgin, A.T. The Background and Chemistry of MDMA. J. Psychoactive Drugs 18 291-304 (1986).

This review gathers together the physical properties of MDMA, and the published information as to toxicity and pharmacology, as of the date of the Oakland, CA conference (May, 1986).

Siegel, R.K. Chemical Ecstasies. Omni, August 1985. p. 29.

This short essay advises caution in the immediate acceptance of drugs that are entheusiastically promoted but which have not been thoroughly researched.

Smith, D.E. and Seymour, R.B. Abuse Folio: MDMA. High Times, May, 1986. p. 30.

This is one of a continuing series of drug information sheets, one being published in each issue of High Times. There is a neutral, factual presentation of the nature and use, and of the hazards and liabilities associated with the drug MDMA.

Smith, D.E., Wesson, D.R. and Buffum, J. MDMA: "Ecstasy" as an Adjunct to Psychotherapy and a Street Drug of Abuse. California Society for the Treatment of Alcoholism and Other Drug Dependencies News 12 (September) 1985 pp 1-3. A letter to the Editors in response: Holsten, D.W. and Schieser, D.W. Controls over the Manufacture of MDMA. The original authors' reply: ibid. 12 (December) 1985 pp 14-15.

A brief review of the therapeutic virtues and abuse risks that are associated with MDMA, and the chilling effect that illegalization of drugs has on medical resarch. They were reminded in rebuttal (Holsten and Schieser) that the exploratory use of new drugs outside of the controls that apply to the pharmaceutical industry carry real risks as to safety and quality of product.

Straus, H. From Crack to Ecstasy; Basement Chemists can Duplicate almost any Over-the-border Drug. American Health, June, 1987 pp. 50-54.

A brief review of the concept of special formulations or syntheses of drugs for the extra-medical market. MDMA is brought in as a minor example.

Toufexis, A. A Crackdown on Ecstasy. Time Magazine. June 10, 1985. P. 64.

A news report on the placing of MDMA into emergency Schedule I status. The complement to Newsweek's positive article.

Turkington, C. Brain Damage Found with Designer Drugs. Amer. Psychological Assn. Monitor March, 1986.

A negative review of the neurotransmitter research. This is probably the source of the oft-quoted "fact" that these drugs are the first demonstration of a neurotransmitter being modified to a neurotoxin.

Wolfson, P.E., Letter to Richard Cotton, Dewey, Ballantine, Bushby, Palmer & Wood, Washington, D.C.

A report is made of the effective use of MDMA in conjunction with psychotherapy, in the treatment of both depressed and schizophrenic patients. The apparent anti- manic and anti-paranoia action of MDMA allowed the opening of discourse and allowed intervention with more conventional therapy. It is suggested that there is a promising potential for its use in certain psychotic situations, and a telling argument is made against its legal classification in Schedules I or II.

Woolverton, W.L., A Review of the Effects of Repeated Administration of Selected Phenethylamines. Drug and Alcohol Dependence 17 143-150 (1986)

A review from the literature of the chronic toxicological findings regarding a number of compounds that are being proposed for international control. One reference to MDMA is cited, the Fed. Proc. note (Virus, et al. 45 1066 (1986) which has been published (see Commins, et al., 1987, section 6 above).

QUOTATIONS FROM REVIEWS IN WHICH MDMA HAS BEEN NOTED:

Burger, A. "Drugs and People" University Press of Virginia, Charlottesville, 1986. p. 65. This quotation, from the chapter on neurohormones, will be the sole example given of the irresponsible misinformation that can be published by experts in the field.

[in reference to designer drugs] "Others are synthetic compounds tried out by addicts in the hope that they might give them a new mental high. The most dangerous of these materials are 3-methylfentanyl and MDMA, a relative of methamphetamine. Both produce dangerous damage to the general health of the users and cause heroin-like addiction at unbelievably low doses."

Glennon, R.A., Rosecrans, J.A. and Young, R., Drug-induced Discrimination: A Description of the Paradigm and a Review of its Specific Application to the Study of Hallucinogenic Agents. Medical Research Reviews 3 289-340 (1983).

"Racemic – MDA produces (conditioned response) effects similar to those of DOM, however, administration of its N- methyl derivative, racemic MDMA, to the DOM-trained animals, resulted in disruption of behavior."

Nichols, D.E. and Glennon, R.A., Medicinal Chemistry and Structure-Activity Relationships of Hallucinogens, in Hallucinogens: Neurochemical, Behavioral, and Clinical Perspectives Ed. B.L. Jacobs, Raven Press, New York. (1984)

"N-Alkylation of the phenethylamines abolishes or greatly attenuates biological activity. Two noteworthy exceptions are the (N-methyl and N-ethyl) 3,4-methylenedioxy substituted compounds. These retain potency nearly comparable to the parent MDA, but present a different qualitative picture. Their duration of action is reduced to about 1-1/2 to 2 hours and they produce only minor disruption of normal sensory processing. They apparently amplify empathy and would seem to be ideal candidates as adjuncts to psychotherapy."

Shulgin, A.T., Psychotomimetic Drugs: Structure-Activity Relationships. Handbook of Psychopharmacology Volume 11; Stimulants, Eds. L.L.Iversen, S.D. Iversen and S.H. Snyder, Plenum Press, New York. p. 292. (1978)

"MDMA has a higher threshold level than does MDA but otherwise it is very similar in potency. Within the effective dose range (100-150 mg orally) the effects are first noted very quickly, usually within one-half hour following administration. With most subjects the plateau of effects is reported to occur within another one-half hour to one hour. The intoxication symptoms are largely dissipated in an additional two hours, except for a mild residual sympathomimetic stimulation, which can persist for several additional hours. There are few physical indicators of intoxication, and psychological sequelae are virtually nonexistant. Qualitatively, the drug appears to evoke an easily controlled altered state of consciousness with emotional and sensual overtones very reminiscent of low levels of MDA."

Shulgin, A.T., Hallucinogens. Burger's Medicinal Chemistry, 4th Edition, Part III, Ed. M.E. Wolff, Wiley and Son, New York. p 1120. (1981)

> "This affective interaction (a state of sensory amplification and enhancement without appreciable sympathomimetic stimulation, an easy communication between subject and observer) is even more clearly evident in the N- methyl homolog of MDA (i.e., MDMA) which is substantially free of perceptual distortion at effective dosages (75-150 mg)."

Shulgin, A.T., Chemistry of Psychotomimetics, Psychotropic Agents Part III, Alcohol and Psychotomimetics; Psychotropic Effects of Central Acting Drugs, Eds. F. Hoffmeister and G. Stille, Springer-Verlag, Berlin. p 14. (1982)

> "Several of these substituted amphetamine analogs have been studied as their N-methyl homologues (in analogy with the relationship between amphetamine and methamphetamine). Although most show a striking drop in potency, MDMA (the N- methyl homologue of MDA) retains full activity."

Stafford, P., Psychedelics Encyclopedia, Revised Edition, J.P. Tarcher, Inc., Los Angeles, CA p 289. (1983)

> "Synthesis of MDMA, active in the doses of the 75-100 mg range and shorter and milder in its effects than MDA, was not reported in the scientific literature until 1960. It has since been established that MDMA was one of the "Experimental Agents" tested at Edgewood Chemical Warfare Service, where it was labeled EA-1475. (MDA was labeled EA- 1299)."

Weil, A. and Rosen, W., Chocolate to Morphine: Understanding Mind-active Drugs, Houghton Mifflin Company, Boston, 1983. p 108

> "A newer drug, MDM (methylenedioxymethylamphetamine, also known as MDMA, Adam, and "XTC"), gives the same general effect (as MDA) but lasts four to six hours instead of ten to twelve. Because of the shorter duration of action, it seems gentler on the body with less day-after fatigue."

(10) LEGAL HISTORY
(This section is organized chronologically)

1970

Sreenivasan, V.R. Problems in Identification of Methylenedioxy and Methoxy Amphetamines. J. Crim. Law 63 304-312 (1972).

In a study of the spectral properties of several substituted amphetamine analogs, the properties of an unknown sample seized from an apparent drug abuser were recorded. The evidence indicated that this material was MDMA. As this report was initially presented to a group of crime laboratory chemists in August, 1970, this is probably the earliest documentation of illicit usage of MDMA.

1972

Gaston, T.R. and Rasmussen, G.T. Identification of 3,4- Methylenedioxymethamphetamine. Microgram 5 pp. 60-63 (1972).

Several exhibits were encountered in the Chicago area, which were identified as MDMA as the hydrochloride salt. Chromatographic and spectrographic properties are presented.

1982

Anonymous. Request for Information, Microgram 15, p 126 (1982).

The Drug Control Section of the DEA (Drug Enforcement Administration) has solicited information concerning the abuse potential of both MDMA and MDE. The request covered the abuse potential, the illicit trafficking and the clandestine syntheses, since 1977.

1984

Randolph, W.F., International Drug Scheduling; Convention on Psychotropic Substances; Stimulant and/or Hallucinogenic Drugs. Federal Register 49 #140 July 19, 1984. Pp 29273-29274.

A request has been made from the Food and Drug Administration for information and comments concerning the abuse potential, actual abuse, medical usefulness and trafficking of 28 stimulants and/or hallucinogenic drugs, including MDMA. International restrictions are being considered by World Health Organization.

Mullen, F.M., Schedules of Controlled Substances Proposed Placement of 3,4-Methylenedioxymethamphetamine into Schedule I. Federal Register 49 #146 July 27, 1984. pp 30210-30211.

A request has been made for comments, objections, or requests for hearings concerning the proposal by the Drug Enforcement Administration (DEA) for the placement of MDMA into Schedule I of the Controlled Substances Act.

Cotton, R. Letter from Dewey, Ballantine, Bushby, Palmer & Wood, 1775 Pennsylvania Avenue, N.W., Washington, D.C. 20006 to F. M. Mullen, Jr., DEA. September 12, 1984.

This is a formal request for a hearing concerning the listing of MDMA as a Schedule I drug. The retaining parties are Professor Thomas B. Roberts, Ph.D., George Greer, M.D., Professor Lester Grinspoon, M.D. and Professor James Bakalar.

Mullen, F.M., Schedules of Controlled Substances. Proposed Placement of 3,4-Methylenedioxymethamphetamine into Schedule . Hearing. Federal Register 49 #252 December 31, 1984. pp. 50732-50733.

This is a notice of an initial hearing in the matter of the placement of MDMA into Schedule I of the Controlled Substances Act. This is to be held on February 1, 1985 and is intended to identify parties, issues and positions, and to determine procedures and set dates and locations for further proceedings.

1985

Young, F.L. Memorandum and Order. Docket No. 84-48. February 8, 1985.

A formal Memorandum and Order is addressed to the Drug Enforcement Administration, laying out the ground rules for the hearings to be held in the matter of the scheduling of MDMA.

Anon : Request for Information, Microgram, 18 25 (1985).

A brief review is presented of the requests for hearings regarding the scheduling of MDMA. A request is made for any information that might be found concerning illicit trafficking, clandestine synthesis, and medical emergencies or deaths associated with the use of MDMA. All such information is to be sent to the Drug Control Section of the DEA.

Young, F.L. Opinion and Recommended Decision on Preliminary Issue. Docket No. 84-48. June 1, 1985

The question of where to schedule a drug such as MDMA is considered. The Schedules have only one place for drugs without currently accepted medical use, Schedule I. But a second requirement that must be met is that the drug have a high abuse potential. There is no place for a drug without currently accepted medical use and less-than-high abuse potential.

The first opinion is that such a drug cannot be placed in any schedule. And if that is not acceptable to the administrator, then into Schedule III, IV or V, depending upon the magnitude of the less-than-high abuse potential.

Lawn, J.C. Schedules of Controlled Sunstances; Temporary Placement of 3,4-Methylenedioxymethamphetamine (MDMA) into Schedule I. Federal Register 50 # 105, Friday, May 31, 1985. pp. 23118-23120.

The DEA invoked the Emergency Scheduling Act powers, to place MDMA into Schedule I on a temporary basis, effective July 1, 1985. This move is valid for a year, and can be extended for six months. This occurred just before the first hearing was to take place, to determine the appropriate schedule for MDMA.

[The chronology of the hearings was as follows:]

June 10, 1985 Los Angeles, California
July 10,11, 1985 Kansas City, Missouri
October 8,9,10,11, Nov. 1, 1985 Washington, D.C.
February 14, 1986 (submitting briefs, findings, conclusions, and oral arguments) Washington, D.C.

1986

Anon: Verordnung des BAG über die Betäubungsmittel und andere Stoffe und Präparate. March 17, 1986.

Effective April 22, 1986, MDMA has been entered into the Controlled Law structure of the Narcotics Laws of Switzerland.

Young, F.L. Opinion and Recommended Ruling, Findings of Fact, Conclusions of Law and Decision of Administrative Law Judge. Docket 84-48. May 22, 1986.

This 70 page decision was handed down as a product of the three hearings held as outlined above. A careful analysis is given of the phrase "currently accepted medical use" and of the phrase "accepted safety for use." The final recommendation was that MDMA be placed in Schedule III.

Stone, S.E. and Johnson, C.A. Government's Exceptions to the Opinion and Recommended Ruling, Findings of Fact, Conclusions of Law and Decision of the Administrative Law Judge. Docket No. 84-48. June 13, 1986.

The attorneys for the DEA reply to the decision of Judge Young with a 37 page document, including statements that he had given little if any weight to the testimony and document proferred by the DEA, and had systematically disregarded the evidence and arguments presented by the government. Their statement was a rejection of the suggestion of the Administrative Law judge, in that they maintained that MDMA is properly placed in Schedule I of the SCA because it has no currently accepted medical use, it lacks accepted safety for use under medical supervision, and it has a high potential for abuse.

Lawn, J.C. Schedules of Controlled Substances; Extension of Temporary Control of 3,4-Methylenedioxymethamphetamine (MDMA) in Schedule I. Federal Register 51 # 116 June 17, 1986. pp. 21911-21912.

The provision that allows MDMA to be placed in Schedule I on an emergency basis (due to expire on July 1, 1986) has been extended for a period of 6 months or until some final action is taken, whichever comes first. The effective date is July 1, 1986.

Anon: Zweite Verordnung zur Änderung betäubungsmittelrechtlicher Vorschriften. July 23, 1986.

Effective July 28, 1986, MDMA was added to the equivalent of Schedule I status, in the German Drug Law. This was in the same act that added cathenone, DMA, and DOET.

Lawn, J.C. Order. Docket 84-48 August 11, 1986.

In reply to a motion by the respondents (Grinspoon, Greer et al. to strike portions of the DEA exceptions that might allege bias on the part of the Administrative Law Judge, and to request an opportunity for oral presentation to the Administrator. The bias was apologized for, and struck. The opportunity for oral presentation was not allowed.

Kane, J. Memorandum and Opinion. Case No. 86-CR-153. In the United States District Court for the District of Colorado. Pees and McNeill, Defendents. October 1, 1986.

The is an early decision dismissing a prosecution charge for unlawful acts involving MDMA, on the basis that MDMA had been placed into Schedule I using the Emergency Scheduling Act, and the authority to invoke this Act was invested in the Attorney General, and the Attorney General had never subdelegated that authority to the DEA. This transfer had not occurred at the time of the charges being brought against the defendents, and the charges were dismissed.

Lawn, J.C. Schedules of Controlled Substances; Scheduling of 3,4-Methylenedioxymethamphetamine (MDMA) into Schedule I of the Controlled Substances Act. Federal Register 51 # 198. October 14, 1986. pp. 36552-36560.

A complete review of the scheduling process history of MDMA, including the receipt of Administrative Law Judge Young's recommendations and a 92 point rebuttle of it, is presented. There is an equating of standards and ethical considerations concerning human research, with legal constraints. It is maintained that the original stands taken, that there is no currently accepted medical use, and there is a high abuse potential, were both correct, and this then is the final placement of MDMA into Schedule I, on a permanent basis. The effective date is November 13, 1986.

1987

Coffin, Torruella, and Pettin. United States Court of Appeals for the First Circuit. Lester Grinspoon, Petitioner, v. Drug Enforcement Administration, Respondent. September 18, 1987.

This is the opinion handed down in answer to the appeal made by Grinspoon (Petitioner) to the action of the DEA (Respondent) in placing MDMA in a permanent classification of a Schedule I drug. Most points were found for the DEA, but one specific claim of the petitioner, that MDMA has a currently accepted use in the United States, was accepted. The finding of the court was that the FDA approval was not the sole criterion for determining the acceptability of a drug for medical use. An order was issued to vacate MDMA from Schedule I.

1988

Lawn, J.C. Schedules of Controlled Substances; Deletion of 3,4- Methylenedioxymethamphetamine (MDMA) From Schedule I of the Controlled Substamces Act. Federal Register 53 2225 (1988) January 27, 1988.

Notice is posted in the Federal Register that MDMA has been vacated from Schedule One of the Controlled Substances Act and now falls under the purview of the Analogue Drug Act. It is no longer a Scheduled Drug. This ruling was effective December 22, 1987, and will be effective until such time as the Administrator reconsidered the record in the scheduling procedures, and issues another final ruling.

Lawn, J.C. Schedules of Controlled Substances; Scheduling of 3,4-Methylenedioxymethamphetamine (MDMA) into Schedule I of the Controlled Substances Act; Remand. Federal Register 53 5156 (1988) February 22, 1988.

Notice is posted in the Federal Register that MDMA has been placed again into Schedule

I. The DEA has accepted the Appelate Court's instruction to develop a standard for the term "accepted medical use," and they have done so. The conclusion is that MDMA is properly assigned to Schedule I, and as there have already been hearings, there is no need for any further delay. Effective date, March 23, 1988.

Meyers, M.A. In the United States District Court for the Southern District of Texas, Houston Division, The United Sates of America v. A.E. Quarles, CR. No. H-88-83. Memorandum in Support of Motion to Dismiss. March 25, 1988.

This memorandum (13 pages and attached literature) is an instructive vehicle addressing the applicability of the Analogue laws to MDMA, and the possible unconstitutional vagueness of the Act itself.

Hug, Boochever and Wiggins, Ninth Circuit Court of Appeals, California. United States, Plaintiff-Appellee v. W.W. Emerson, Defendant-Appellant.

An appeal was made, and was allowed, by three defendents, that the use of the Emergency Scheduling Act by the DEA for the placement of MDMA into Schedule I was improper, in that this power was invested specifically in the Attorney General, and that he had failed to subdelegate this authority to the DEA for its use.

Harbin, H. MDMA. Narcotics, Forfeiture, and Money-Laundering Update, U.S. Department of Justice, Criminal Division. Winter, 1988. pp. 14-19.

A brief legal history of MDMA is presented, detailing its changing status from emergency schedule, to permanent schedule, to non-schedule, to schedule again, a case against its occasional status in-between as an analogue substance. In U.S. v. Spain (10th Circuit, 1987, 825 F.2d 1426), the MDMA conviction was undermined both by the absence of sub- delegation of emergency scheduling powers by the Attorney General to the DEA, and by the failure of the DEA to publish a formal scheduling order 30 days after the publication of its "notice-order", as required by statute. This latter failure was successful in overturning the conviction in the U.S. v. Caudel (5th Circuit, 1987, 828 F.2d 1111)

These reversals were based on the temporary scheduling status of MDMA. The vacating of the permanent scheduling Grinspoon v. DEA (1st Circuit 1987, 828 F.2d 881), coupled with these successful appeals of the temporary scheduling action, will certainly serve to allow further challenge to be made to any and all legal action that took place prior to the final and unchallenged placement of MDMA in Schedule I on March 23, 1988.