DIRECT TESTIMONY OF HAROLD F. HARDMAN, M.D., Ph.D.

I, Harold F. Hardman make the following statement:

I am a pharmacologist employed as Professor and Chairman of the Department of Pharmacology and Toxicology at the Medical College of Wisconsin. I received my doctorate in pharmacology from the University of Michigan in 1954, and my M.D. from the University of Michigan in 1958. I have served in my present capacity at the Medical College of Wisconsin since 1962. A copy of my curriculum vitae is attached as Exhibit 1.

While a medical student at the University of Michigan I conducted a study to determine the toxicity and pharmacological effects of mescaline and 7 analogs in 5 species of animals. The study was part of a contract funded by the Army Chemical Center, Edgewood Arsenal. The results of the study were declassified in 1969 and subsequently published in Toxicology and Applied Pharmacology 25, 299-309 (1973).

The compounds studied included mescaline, 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxyamphetamine (MDMA) and other substituted phenethylamines. Substances were provided by the Army Chemical Center at Edgewood Arsenal. The toxicity of the compounds were determined in mice, rats and
guinea pigs after single intraperitoneal injections of the hydrochloride salts in saline and in dogs and monkeys after single intravenous injections of the hydrochloride salts. LD-50's, the amount of a substance which proves lethal in 50% of each species, were calculated on the basis of mortality within 24 hours of drug administration. A molar toxicity ratio (LD-50 in millimoles per kilogram of mescaline / LD-50 in millimoles per kilogram of the analog) was used for comparison of toxicities. MDA was the most toxic substance in all 5 species. MDMA was the second most toxic compound in the rat, dog and monkey and the third most toxic compound in the mouse and guinea pig. MDMA was up to 6 times more toxic than mescaline and between 1.3 and 3 times less toxic than MDA. Death was preceded by the same series of physiological events after administration of lethal doses of mescaline, MDA and MDMA.

The effects of the subject compounds relating to the central nervous system, motor and autonomic functions were observed in the dog and monkey. The effects observed included ataxia, clonic and tonic convulsions, muscular rigidity, muscle tremor, mydriasis, piloerection, salivation, vascular flushing, emesis, apprehension/fright, bizarre body attitudes, apparent hallucinations, dyspnea and hypernea. These effects are part of the classical pharmacological response of the dog to intravenous mescaline.

The classical pharmacologic response to intravenous mescaline in the dog is characterized by an immediate hind limb weakness accompanied by a fluttering motion of the hind leg so
that the dog is forced to assume a sitting position. Salivation, gagging, emesis and defecation are frequent sequelae to the initial motor effects. The dog may then appear negativistic and assume bizarre body attitudes with the head and neck arched toward the floor and the front legs spread widely apart. During this period, which may last for several hours, the dog shows minimal reaction to loud noises or noxious stimuli. Subsequently, the dog appears to be weak and sleepy; however, when forcefully aroused he exhibits a pronounced hind limb ataxia. With adequate doses the initial motor effect on the hind limb consisting of overt tremors is followed by tonic and clonic convulsions. The convulsive episodes are preceded and followed by barking, yelping and apparent hallucinations. The dog usually exhibits marked mydriasis and runs wildly about the room bumping into walls and furniture. The dog also appears to be apprehensive, frightened and disoriented; barking or snarling at inanimate objects is noted frequently. With the exception of vascular flushing, all the above effects were observed after administration of both MDA and MDMA.

I have reviewed the document entitled, "Schedule I Control Recommendations Under the CSA for 3,4-methylenedioxymethamphetamine (MDMA)" and the reference literature relating to the animal pharmacology of MDMA. MDA and MDMA both produce increased motor activity in mice as well as analgesic effects in several procedures in mice. MDA and MDMA exhibit similar qualitative central nervous system effects in animals which differ in the dose at which the effects appear.

Structure-activity relationships in phenethylamine compounds
indicate that adding a N-methyl group retains central nervous system activity. Further, the toxicity studies which I conducted indicated that adding a methylenedioxy substituent on the phenyl ring results in increased toxicity. Thus from these considerations it is likely that MDMA would produce central nervous system effects similar to those of MDA.

In conclusion, although there is insufficient data available to completely characterize MDMA pharmacologically, the available information does indicate that MDMA is a centrally active stimulant compound, somewhat less toxic than MDA but more toxic than mescaline. Because of general pharmacological similarities between MDA and MDMA in animals, I would expect them both to be associated with the same types of toxic and pharmacological effects at equipotent doses in humans.

I declare under penalty of perjury that the foregoing statement is true and correct.

Executed on April 18, 1985.

Harold F. Hardman, M.D., Ph.D.
EXHIBIT 1
CURRICULUM VITAE

1. HAROLD F. HARDMAN, M.D., Ph.D.
   Professor and Chairman
   Department of Pharmacology and Toxicology
   Medical College of Wisconsin
   8701 Watertown Plank Road
   Milwaukee, Wisconsin 53226

2. SOCIAL SECURITY NUMBER:
   143-20-2731

3. HOME ADDRESS:
   1120 Indianwood Drive
   Brookfield, Wisconsin 53005

4. HOME TELEPHONE: OFFICE TELEPHONE:
   (414) 782-9193 (414) 257-8267

5. BIRTH DATE, LOCATION:
   August 2, 1927
   East Orange, New Jersey

6. MARITAL STATUS:
   Married: Wife: Jean
   Children: David, Timothy, John and Susan

7. NEXT OF KIN:
   Dr. David Hardman (son)
   13 Burnwood Place
   Chapel Hill, NC 27514
   (919) 544-4817

8. CITIZENSHIP:
   U.S.A.

9. EDUCATION AND TRAINING:
   B.S., Pharmacy, 1949
   Rutgers University
   Newark, New Jersey

   M.S., Pharmacology, 1951
   University of Illinois
   Chicago, Illinois
9. EDUCATION (Cont'd.):

   Ph.D., Pharmacology, 1954
   University of Michigan
   Ann Arbor, Michigan

   M.D., 1958
   University of Michigan
   Ann Arbor, Michigan

10. MILITARY SERVICE:

    Army of the United States
    Sgt., 1st Cavalry Division, 8th Regiment

11. PROFESSIONAL LICENSURE:

    None

12. BOARD CERTIFICATION:

    None

13. FACULTY APPOINTMENTS:

    Instructor (part time) of Pharmacology,
    University of Michigan, Ann Arbor, Michigan
    1954-1958

    Assistant Professor of Pharmacology,
    University of Michigan, Ann Arbor, Michigan
    1958-1960

    Associate Professor of Pharmacology,
    Marquette University School of Medicine
    1960-1961

    Professor and Chairman of Pharmacology
    Medical College of Wisconsin, Milwaukee, Wisconsin
    1962-

14. HOSPITAL STAFF APPOINTMENTS:

    None

15. OTHER APPOINTMENTS:

    Rockefeller Foundation Visiting Professor, January -
    June 1965, University del Valle, Cali, Columbia, South
    America
16. PROFESSIONAL SOCIETY MEMBERSHIPS AND AWARDS:

American Foundation for Pharmaceutical Education
Scholarship, 1945-1953
Rho Chi, National Honorary Pharmaceutical Society
Galens, Honorary Medical Society, University of Michigan
Alpha Omega Alpha, Honorary Medical Society
John and Mary Markle Scholar, 1958-1963
Alpha Kappa Kappa Award for excellence in preclinical instruction, Marquette University School of Medicine, 1962, 1967
Sigma Xi
Outstanding Educator of America Award, 1973
Who's Who in America, 38th Edition
American Society for Pharmacology and Experimental Therapeutics
Program Committee, 1973-1976 (Chairman)
Member, Committee on Education and Professional Affairs, 1973-1976
Councilor, 1976-1979
President-Elect, 1981-1982
President, 1982-1983
Association for Medical School Pharmacology
Secretary, 1970-1972
President, 1978-1980
American Chemical Society, Division of Medicinal Chemistry
American Association for the Advancement of Science
American Federation for Clinical Research
Wisconsin Heart Association
Research Grant Review Committee
American Heart Association
Medical Society of Milwaukee County
Member Ad Hoc Committee on Alcoholism and Drug Abuse, 1971
Milwaukee Academy of Medicine (1962-present)
Program Committee, 1963-1969
Council, 1971-
Vice President, 1970-1972
President Elect, 1973
President, 1974
International Society on Oxygen Transport to Tissue
Wisconsin Heart Club
Federation of American Societies for Experimental Biology (FASEB)
President-Elect, 1982-1983
President, 1983-1984

17. OTHER PROFESSIONAL ACTIVITIES AND COMMUNITY ACTIVITIES:

Journal of Medicinal and Pharmaceutical Chemistry
Editorial Board, 1962-1967
Wisconsin Medical Journal
Contributing Editor "Comments on Treatment", 1962-1968
Journal of Pharmacology and Experimental Therapeutics
Cardiovascular Field Editor, 1964-1965
Editorial Board, 1976-
Research Communications in Substance Abuse
Editorial Board, 1980-
Joint Food and Drug Administration/National Institute of Mental Health Drug Abuse Advisory Committee, 1971-1974
National Institute on Drug Abuse
Ad Hoc Member Biomedical Review Panel, 1975-
17. OTHER PROFESSIONAL ACTIVITIES AND COMMUNITY ACTIVITIES (Cont'd.):

National Institute of General Medical Sciences
Ad Hoc Member, Pharm Study Section, 1977-
Pharmaceutical Manufacturers Association Foundation, Inc.
Member, Basic Pharmacology Advisor Committee, 1975-1981
Journal of Cardiovascular Pharmacology
Editorial Board, 1977-

18. MEDICAL COLLEGE COMMITTEES AND ADMINISTRATIVE APPOINTMENTS:

Administrative Appointments:
1962-present Chairman, Department of Pharmacology
1962-present Executive Committee of the Faculty
1968-1970 Associate Dean for Basic Science Affairs

Search Committees:
1964-1965 Biochemistry Chairman
1974-1975 Psychiatry Chairman
1976-1977 President of Medical College of Wisconsin

Medical School Committees:
1962-1977 Curriculum Committee
1962-1966 Marquette University Board of Graduate Studies
1963-1967 Marquette University Committee on Growth and Development
1963-1967 Committee on Relocation of Basic Sciences
1964-1967 Marquette University Committee on Conditions of Faculty Service
1967-1969 Chairman, Basic Science Building Committee
1973-present Basic Science Chairmen Committee
1976-1977 Ad Hoc Hearing Committee for Dismissal of a Tenured Faculty Member
1977 Ad Hoc Subcommittee to Evaluate 7 Year Up or Out Ruling on Faculty
1978-present Graduate Studies Council
1978-present Ad Hoc Committee on Policies for Promotion, Tenure and Extended Contracts
1979-1980 Intramural Review Committee, Department of Medicine
1981- Intramural Review Committee of Central Academic Administration
1980-1982 Member of the Board of Directors, Medical College of Wisconsin

19. HOSPITAL COMMITTEES:

None

20. GRANTS OR CONTRACTS:

National Institutes of Health, No. DA 00124, May 1972 - April 1975
 Principal Investigator
Title: Hypotensive and Hypothermic Response to Marihuana
$140,945
20. GRANTS OR CONTRACTS (Cont'd.):

National Institutes of Health, No. DA 00124, May 1975 - April 1978
Principal Investigator
Title: Hypotensive and Hypothermic Response to Marihuana
$169,216.

Principal Investigator
Title: Hypotensive and Hypothermic Response to Marihuana
$328,114.

National Institutes of Health, No. DA 00124, July 1981 - June 1984
Principal Investigator
Title: Hypotensive and Hypothermic Response to Marihuana
$296,882.

National Heart, Lung and Blood Institute, No. HL 08311, September 1964 - August 1967
Principal Investigator
Title: Effects of Drugs upon Myocardial Hypoxia
$84,504.

National Heart, Lung and Blood Institute, No. HL 08311, September 1967 - August 1972
Principal Investigator
Title: Effects of Drugs upon Myocardial Hypoxia
$102,220.

National Heart, Lung and Blood Institute, No. HL 08311, September 1972 - August 1975
Principal Investigator
Title: Effects of Drugs upon Myocardial Hypoxia
$115,967.

National Heart, Lung and Blood Institute, No. HL 08311, June 1976 - May 1979
Principal Investigator
Title: Effects of Drugs upon Myocardial Hypoxia
$120,596.

National Heart, Lung and Blood Institute, No. HL 08311, June 1978 - May 1982
Principal Investigator
Title: Effects of Drugs upon Myocardial Hypoxia
$178,015.

Travenol, Inc., June 1975 - conclusion
Principal Investigator
Title: To Determine the Validity that DPG Levels are of Significant Value in Post Coronary Transplant Cardiac Function
$20,000.
20. GRANTS OR CONTRACTS (Cont'd.):

Searle Laboratories, February 1976 - conclusion
Principal Investigator
Title: Hemodynamic Studies
$18,255

Parke-Davis, May 1977 - conclusion
Principal Investigator
Title: Studies on Bevantolol, a New Beta Blocking Agent
$9,625.

Bristol-Myers Company, February 1979 - conclusion
Principal Investigator
Title: Studies on Sotalol
$20,460.

Wisconsin Heart Association, July 1974 - June 1975
Principal Investigator
Title: Measurement of Regional Coronary Blood Flow
$9,000.

Wisconsin Heart Association, July 1975 - June 1976
Principal Investigator
Title: Analysis of Myocardial Hypoxia
$9,550.

Wisconsin Heart Association, July 1976 - June 1977
Principal Investigator
Title: Antagonism of Myocardial Hypoxia
$9,550.

Training Grant, National Institutes of Health, 5T1 GM 370,
1962 - 1972
Principal Investigator
$720,521

21. PUBLICATIONS:

See Attached Publications.

22. ABSTRACTS:

See Attached Abstracts.

23. PRESENTATIONS (National, Regional, Local Meetings):

Symposia

(1) American Society for Pharmacology and Experimental
Therapeutics, August 1976
The Effect of Antianginal Drugs upon Oxygen
Supply and Oxygen Demand in the Myocardium.
Davis, California
23. PRESENTATIONS (National, Regional, Local Meetings) (Cont'd.):

(2) American Heart Association, November 1975
Effect of Propranolol and Nitroglycerin on Hemoglobin Oxygen Affinity.
Anaheim, California

(3) Western Pharmacology Society, January 1979
Colorado Springs, Colorado

(4) Oshkosh Symposium, June 1975
"MCW Research Profile"
Oshkosh, Wisconsin

Presentations:

(1) Federation of American Societies for Experimental Biology

(2) American Society for Pharmacology and Experimental Therapeutics

(3) American Heart Association
1975

24. PARTICIPATION IN WORKSHOPS, CONSULTATIONS, STUDY SECTIONS, SURVEY TEAMS:


(4) PMAF (Pharmaceutical Manufacturers Association Foundation). Study Section Member 1975 - 1978, Study Section Member 1978 - 1981


25. TEACHING:

Advisor of the following students:

Richard C. Dage, Ph.D.
Walter D. Meester, Ph.D.
Sandra S. Smith, M.S.
25. TEACHING:

Advisor of the following students:

Richard C. Dage, Ph.D.
Walter D. Meester, Ph.D.
Sandra S. Smith, M.S.
Richard C. Dage, Ph.D.
Raynaldo Sandoval, M.D., M.S.
Jose S. Serrano-Molina, M.D., Ph.D.
David C. Warltier, Ph.D.

Committee member of the following students:

William Douglas Brooker, Ph.D.
Pitambar Somani, M.D., Ph.D.
Shakil Mohammed, M.D., Ph.D.
Paulo de Miranda, Ph.D.
Lewis H. Stocks, Ph.D.
Donald O. Allen, Ph.D.
John J. Lech, Ph.D.
Nicola Zampaglione, Ph.D.
Michael A. Commarato, Ph.D.
Clinton N. Corder, Ph.D.
Peter Savarie, Ph.D.
Hector J. Gomez, M.D., Ph.D.
Philip J. Kadowitz, Ph.D.
Romeo T. Bachand, Jr., Ph.D.
Richard D Heilman, Ph.D.
Antonio Guerra, M.D., Ph.D.
Karl F. Ober, M.D., M.S.
Mahendr S. Kochar, M.D., M.S.
Gary J. Jesmok, Ph.D.
William T. Schmeling, Ph.D.
Stanley R. Jolly, Ph.D.
James D. Buck, M.S.
Cecilia J. Hillard, Ph.D.
Publications

1. Hardman, H.F.:
   Khellin as a coronary vasodilator (M. Sc. degree thesis).
   University of Illinois, Chicago Professional College, June 1951.

2. Hardman, H.F., Yard, A.C. and Chenoweth, M.B.:
   The effect of the ethylenediamine component of aminophylline on the
   duration of reversal of cardiac failure.

3. Hardman, H.F.:
   An analysis of the cardiovascular activities of selected purine
   derivatives with special reference to the constituent parts of aminophylline.

4. Hardman, H.F., Moore, J.I. and Lum, B.K.B.:
   A method for analyzing the effect of pH and the ionization of drugs
   upon cardiac tissue with special reference to pentobarbital.

5. Hardman, H.F., Baird, W.M., Suits, D.B. and Lum, B.K.B.:
   Analysis of the common carotid occlusion pressor reflex in the anesthe-
   sized dog.

6. Waddell, W.J. and Hardman, H.F.:
   The intracellular pH of the isolated perfused turtle heart.

7. Lucchesi, B.R. and Hardman, H.F.:
   The influence of dichloroisoproterenol (DCI) and related compounds
   upon ouabain and acetylstrophanthidin induced cardiac arrhythmias.

8. Baird, W.M. and Hardman, H.F.:
   An analysis of the effect of pH, procaine cation, nonionized procaine
   and procaine ethylchloride cation upon cardiac conduction time, stimu-
   lation threshold, amplitude of contraction and the relationship of
   these parameters to antiarrhythmic activity.

9. Hardman, H.F.:
   Molecular form of theophylline responsible for positive inotropic
   activity.

10. Hardman, H.F.:
    Tribute to a retiring editor.
11. Hardman, H.F.:
Vasodilator drugs.

12. Hardman, H.F.:
Perspective in our chemical environment.

13. Hardman, H.F.:
Pharmacology "A Justification".

14. Hardman, H.F.:
Chemotherapy of herpes simplex virus and vaccinia virus.

15. Hardman, H.F.:
New concepts in the therapy of angina pectoris.

16. Hoffman, N.E., Barboriak, J.J. and Hardman H.F.:
A sensitive gas chromatographic method for determination of lactic acid.

17. Hardman, H.F. and Reynolds, R.C.:
An effect of pH upon epinephrine inotropic receptors in the turtle heart.

18. Meester, W.D., Hardman, H.F. and Barboriak, J.J.:
Evaluation of various adrenergic blocking agents in isolated rabbit and turtle hearts.

19. Hardman, H.F. and Bukhamana, P.:
Cardiac seasonal variation: a qualitative change in pharmacological response to ethylenediamine.

20. Barboriak, J.J. and Hardman, H.F.:
The effect of pH on glycogenolysis in turtle hearts.

21. Smith, S., Barboriak, J.J. and Hardman, H.F.:
Utilization of glucose in the anaerobically perfused turtle heart.

22. Mohammed, S., Hardman, H.F. and Yard, A.C.:
Mechanism of vasodilator response to pheniprazine.
23. Meester, W.D. and Hardman, H.F.:
   Blockade of the positive inotropic actions of epinephrine and theophylline by acetylcholine.

24. Dage, R.C. and Hardman, H.F.:
   Histamine responses and seasonal variation in isolated perfused turtle ventricles.

   Nutritional circulation in the heart. I. Effect of change in heart rate on myocardial oxygen consumption and nutritional circulation with constant total coronary blood flow.

   Nutritional circulation in the heart. II. A reappraisal of the effect of nitroglycerin on myocardial hemodynamics, oxygen consumption and nutritional blood flow in the isolated supported heart preparation.

27. Somani, P., Laddu, A.R. and Hardman, H.F.:
   Nutritional circulation in the heart. III. Effect of isoproterenol and beta adrenergic blockade on myocardial hemodynamics and 86rubidium uptake in the isolated supported heart preparation.

   Nutritional circulation in the heart. Effect of isoproterenol and beta-adrenergic blocking drugs.

29. Dage, R.C. and Hardman, H.F.:
   Histamine induced changes in tension and contractile force in the turtle ventricle.

30. Hardman, H.F., Domino, E.F. and Seevers, M.H.:
   General pharmacological actions of some synthetic tetrahydrocannabinol derivatives.

31. Domino, E.F., Hardman, H.F. and Seevers, M.H.:
   Central nervous system actions of some synthetic tetrahydrocannabinol derivatives.

32. Hardman, H.F., Domino, E.F. and Seevers, M.H.:
   Structure activity relationships of Δ3-tetrahydrocannabinols.
33. Lahiri, P.K., Barboriak, J.J. and Hardman, H.F.: 
Metabolism of free fatty acids in the perfused turtle heart. 

34. Reynolds, R.C. and Hardman, H.F.: 
The effect of pH changes and ionization on the action of epinephrine 
upon the isolated rabbit ileum. 

35. Serrano, J.S., Hardman, H.F. and Barboriak, J.J.: 
pH limits of contractility in isolated turtle heart. 

36. Haavik, C.O. and Hardman, H.F.: 
The effect of tetrahydrocannabinols on body temperature. 
The Pharmacology of Thermoregulation Symposium. Fifth Int. Congress 
on Pharmacology, San Francisco, 1972. pp. 410-416 (Karger, Basel, 
1973).

37. 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. 

38. Laddu, A.R., Somani, P. and Hardman, H.F.: 
Effect of beta receptor blockade upon myocardial hemodynamics and 
nutritional circulation in the heart. 
Myocardial Metabolism: Recent Advances in Studies on the Cardiac 

39. Laddu, A.R., Somani, P. and Hardman, H.F.: 
Nutritional circulation in the heart. IV. Effect of calcium chloride 
and potassium chloride on myocardial hemodynamics and clearance of 
86Rubidium. 

40. Haavik, C.O. and Hardman, H.F.: 
Evaluation of the hypothermic action of tetrahydrocannabinols in 
mice and squirrel monkeys. 

41. Haavik, C.O. and Hardman, H.F.: 
Hypothermic action of Δ⁹-tetrahydrocannabinol, 11-hydroxy-Δ⁹-tetra-
hydrocannabinol and 11-hydroxy-Δ⁶-tetrahydrocannabinol in mice. 

42. Haavik, C.O., Collins, F.G. and Hardman, H.F.: 
Studies on the mechanism of hypothermic action of tetrahydrocannabinols. 
In Temperature Regulation and Drug Action, eds. P. Lomax, E. Schonbaum, 
J. Jacob, pp. 293-309, Proc. Symposium, Paris, 1974 (Karger, Basel, 
1975).


65. Jesmok, G.J., Buck, J., Warltier, D.C. and Hardman, H.F.:
Beneficial actions of bevantolol on subendocardial blood flow and
contractile function in ischemic myocardium.

66. Buck, J.D., Gross, G.J., Warltier, D.C. and Hardman, H.F.:
Beta blockade on subendocardial blood flow and contractile function
in ischemic myocardium.

67. Warltier, D.C., Hardman, H.F. and Gross, G.J.:
Transmural perfusion gradients distal to various degrees of coronary
artery stenosis during resting flow or at maximal vasodilation.

68. Warltier, D.C., Gross, G.J., Jesmok, G.J., Brooks, H.L. and Hardman,
H.F.:
Protection of ischemic myocardium: Comparison of effects of proprano-
lol, bevantolol and N-dimethyl propranolol on infarct size following
coronary artery occlusion in anesthetized dogs.
Cardiol. 65: 133-146, 1980.

Comparative effects of FR 7534, a new calcium antagonist, nitroglycerin
and dipyridamole on regional myocardial blood flow and contractile
function during partial coronary artery occlusion in the dog.

70. Warltier, D.C., Gross, G.J. and Hardman, H.F.:
Subepicardial steal and reduction of myocardial oxygen consumption
by adenosine.

71. Haavik, C.O. and Hardman, H.F.:
An investigation of the hypothermic action of Δ⁹-tetrahydrocannabinol
by use of pharmacological blocking agents.

The effect of Δ⁹-tetrahydrocannabinol on oxygen consumption, body
temperature and heat loss.

Relaxation of potassium-depolarized canine, bovine and porcine large
coronary arteries by nitroglycerin, chromonar and two dihydropyridine
calcium antagonists.

Comparison of two dihydropyridine calcium antagonists on regional
myocardial blood flow in acute myocardial ischemia.


