Received: 12 June 2017 | Revised: 8 August 2017 | Accepted: 8 August 2017

DOI: 10.1002/dta.2292

WILEY

REVIEW

MDA, MDMA, and other "mescaline-like" substances in the US military's search for a truth drug (1940s to 1960s)

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Abstract

This article describes the context in which 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxymethamphetamine (MDMA) and other mescaline-like compounds were explored as hallucinogens for military and intelligence purposes from the 1940s to the 1960s. Germans first tested mescaline as a "truth drug" in a military context. In the 1940s, the United States military started testing hallucinogenic substances as truth drugs for interrogation and behavior manipulation. After tests carried out using mescaline and other drugs in 1950, some derivatives of mescaline were synthesized by the Army for the exploration of possible "speech-inducing" effects. After insufficient animal testing, the substances were given to patients at the New York State Psychiatric Institute (NYSPI). 3,4-Methylenedioxy-*N*-ethylamphetamine (MDE), a compound almost identical to MDMA, was among the compounds delivered for testing at the NYSPI. During tests with other derivatives (3,4-dimethoxyphenethylamine (DMA), 3,4-methylenedioxyphenethylamine (MDPEA), MDA) in 1952–53, an unwitting patient died in these tests, which was kept secret from the public. Research was interrupted and toxicological animal testing procedures were initiated. The secret animal studies run in 1953/1954 revealed that some of the "mescaline derivatives" tested (e.g. MDA, MDE, DMA, 3,4,5-trimethoxyamphetamine (TMA), MDMA) were considered for further testing in humans. In 1955, the military changed focus to lysergic acid diethylamide (LSD), but some interest in mescaline-like compounds remained for their ability to change mood and habit without interfering with cognition and sensory perception. Based on the known documents, it remains unclear (but probable) whether any of the mescaline derivatives tested were being used operationally.

KEYWORDS

mescaline, methylenedioxymethamphetamine (MDMA, Ecstasy), methylenedioxyamphetamine (MDA), methylenedioxyethylamphtemaine (MDE), MK ULTRA, truth drugs

1 | INTRODUCTION

This article provides an outline of the history about how some "mescaline derivatives" such as 3,4,5-trimethoxyamphetamine (TMA), 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxy-*N*-ethylamphetamine (MDE) and 3,4-methylenedioxymethamphetamine (MDMA) were synthesized and experimented with by the military. These mescaline derivatives were not researched as psychochemicals for mass intoxications in "unconventional warfare" [1] as was lysergic acid diethylamide (LSD). It appears that these compounds were researched to inform the United States (US) military in particular about drug-assisted interrogation and behavior manipulation from the late 1940s. Notably only a few aspects of the research on mescaline derivatives by the US military are present in the literature.[2-5] We present an overview, including some new material.

1.1 | Early "truth drug" research

The beginning of truth drug research can be traced back to the American physician Robert House.[6] House attended childbirth in 1916. The mother in labor was under the influence of scopolamine, a substance given in addition to morphine to assist with pain management and anxiety.[7] During the birth process, House asked the father about the baby scale, a question to which the father did not know the answer. But

surprisingly the mother, while being in a twilight state of consciousness, gave instructions where the scale could be found. House's further experiments revealed that individuals under the influence of scopolamine – "during states of decreased will-power" – generally could not withhold secrets, thus, making scopolamine a powerful "truth serum." [8]

Starting at the beginning of the twentieth century, comprehensive research was conducted in Germany on the hallucinogen 3,4,5-trimethoxyphenethylamine (mescaline).[9] German psychiatrist Kurt Beringer in his seminal monograph on "the mescaline inebriation", stated: "the patient has the inclination to reveal otherwise hidden secrets, to express himself in an unbridled way."[10] In 1931, a report titled *Confessions during mescaline inebriation*, was published by the Italian psychoanalyst Baroni.[11] In 1936, British psychiatrist John Stephen Horsley reported trials with the sedative drug Nembutal (a barbiturate). According to Horsley, through a weakening of cortical functions by the barbiturate, a "psychical disinhibition" was induced, accompanied by decreased cognition, and enhanced suggestibility. Horsley suggested that these effects could be utilized for military use to extract information from unwilling subjects.[12]

1.2 | Research into mescaline and its derivatives in the USA before World War II

In the 1920s, American neurologist Heinrich Klüver and pharmacologist Gordon A. Alles were interested in mescaline. Klüver's research on mescaline focused on the "mechanisms of hallucination."[13,14 (p. 100)] He noted that during the mescaline inebriation that "the ability to organize and to abstract material is lost; the determining tendencies suffer. To concentrate on something for a long while becomes impossible."[13 (p. 100)] During the 1930s, Klüver evaluated the synthetic mescaline derivatives 3,4-dimethoxyamphetamine (DMA), 3,4-dimethoxyphenethylamine (DMPEA), amphetamine and MDA in animals.[14 (p. XIII)] All four substances subsequently became part of military research.

Alles's research focused on the derivatives of adrenaline and amphetamine. He discovered the psychophysiological effects of amphetamine in 1927 while studying derivatives of adrenaline. After accidentally ingesting a higher dose of MDA (126 mg p.o.)[15 (p. 196)] in 1934, he provided the first description of its psychoactive effects.[15 (p. 198)] Afterwards he became interested in mescaline derivatives.[16 (p.241–243)] In 1937, Alles synthesized TMA, another analog of mescaline. He compared its effects to amphetamine in animals and in self-experiments, and found it to have quite different effects (e.g. paranoid thought distortions, restlessness, and anxiety) compared to MDA.[15 (p. 208; p. 238)] From 1937, Alles studied mescaline and some methylenedioxy ring-substituted compounds (including MDA) in mice, rats and humans,[17, 15 (p. 202–203), 16 (p. 245)] partially in collaboration with Klüver.[14 (p. XVI)] Results of these studies were published much later, but without reference to MDA,[17] presumably to prevent publicity for information potentially useful to the military.

1.3 | Nazi research on truth drugs

The first hint at the use of mescaline in interrogation came from an intercepted telecommunication received by British intelligence on July 24, 1942. In this message, a Schutzstaffel (SS)-Führer of Dnjepropetrowsk, a town in Ukraine, requested the delivery of 50 grams mescaline for interrogation purposes from the medical headquarters of the SS in Berlin, because "experiments to date of injecting parachutists with scopolamine were successful. Therefore experiments with mescaline are to be undertaken, since these injections produce an enhanced effect through intoxication".[qouted in ref. 5 (p. 36)]

Since 1943, German military physicians working at the concentration camps Dachau and Auschwitz experimented with barbiturates, morphine derivatives, and mescaline for interrogation purposes.[5,9 (p. 38–39; p. 408)] According to Walter Neff, a prisoner's nurse involved in experiments at Dachau, the goal was "to eliminate the will of the person examined." After "research" on 30 inmates, the leading camp physician Dr Kurt Plötner concluded that "the best results were achieved giving the mescaline mixed with coffee. In single cases, the [prisoners] got furious, in other cases very gay or melancholic ... The examining person in every case succeeded drawing even the most intimate secrets from the [inmates] when the questions were cleverly put."[qouted in ref. 28 (p. 410)] Despite these apparent successes, Plötner concluded, that mescaline was "too unreliable to be a truth drug. Sometimes it worked, sometimes it didn't." [qouted in ref. 5 (p. 40)].

It seems improbable that these experiments were known to the allies during World War II. However, the experiments at Dachau are mentioned in a report of the US Naval Technical Mission, which after the end of the war worked on collecting useful scientific knowledge gained by the Nazis,[18] and triggered the interest of the US military in mescaline and other substances as truth drugs.

1.4 | Research on truth drugs by the US military beginning in the 1940s

It appears that the first trials by the US military to use drugs in interrogation reach back to 1941, when US Army General George V. Strong asked the National Defense Research Council to devise an effective way to use drugs for extracting information from captured German U-boat officers. The Office of Strategic Services (OSS) scientists informed him that trials run in December 1941 had failed.[4 (p. 213)] On October 31, 1942, the US National Research Council of the US Army reported that the Russians and Germans were using truth drugs for interrogation purposes.[5 (p. 36)] In response, the OSS, a predecessor of the Central Intelligence Agency (CIA), set up a Truth Drug Committee in spring of 1943 under Dr Winfred Overholser. In the same year, mescaline was tested in a Philadelphia hospital. Three OSS officers volunteered, but "... the experiment was a dismal failure. None of the three men had given up any information..."[3 (p. 215), 4 (p. 219)] After more experiments (with mescaline, barbiturates, scopolamine), *Cannabis indica* was found promising and used for further tests.[3 (p. 6–7), 5 (p. 42–49)] Although their experiments failed for the most part, the researchers established a number of criteria for their drug of choice:

"1. It must be administered without the subject's knowledge.
2. It must induce a talkative mood and, if possible, a full exposure of the truth, as the subject knew the truth.
3. It must not be habit-forming or physiologically harmful; and

4. It must leave no remembrance or suspicion of any kind."[quoted in ref. 4 (p. 216)]

At a routine scientific staff meeting at Edgewood Arenal in 1946, one physician who had just returned from Germany from interrogations of captured Nazi scientists "remarked that he had been surprised to learn that the Germans [had] conducted what appeared to be elaborate human experiments [on concentration camp prisoners] using hallucinogenic drugs ... including mescaline and various compounds drawn from ergot."[quoted in ref. 4 (p. 70)] Subsequently, in 1947, the US Navy started project CHATTER, a drug testing program, which claimed to be a reaction to the presumed successes of the Soviets' uses of truth drugs and behavior manipulation.[19,20] CHATTER included animal and human studies with scopolamine, mescaline, and LSD. Some results were published in the 1950s.[21]

1.5 | Central intelligence agency (CIA) research on truth drugs

The prominent Hungarian Cardinal Mindszenty, known for his opposition to the Communist regime, was arrested in 1948 and put on trial in 1949. During the trial Mindszenty looked absent-minded, showed "robotic movements" and confessed to crimes he had never committed.[22] The Americans presumed a certain method of "behavior manipulation."[2 (p. 223–224)]

On June 14, 1949, immediately after the trial, the then CIA Deputy Director for Plans, Allen Dulles, put a team of experts together "[to] apply special methods of interrogation for the purpose of evaluation of Russian practices."[quoted in ref. 23 (p. 96)] Through this order, US research on mind control and manipulation increased its intensity.[3 (p. 21)]

Another shock for the US public came in 1950, when US prisoners of war captured in Korea claimed (spiked with communist rhetoric) that the USA had used biological weapons in Korea.[23] CIA officials concluded that certain measures of behavior manipulation had been used on them.[24,25] It became a top priority to know more about techniques used for behavior manipulation and interrogation.[2 (p. 78)]

On April 20, 1950, CIA Director Roscoe Hillenkoetter authorized Project BLUEBIRD, with the following goals:

"a. Discovering means of conditioning personnel to prevent unauthorized extraction of information from them by known means,

b. Investigating the possibility of control of an individual by application of special interrogation techniques,

c. Memory enhancement, and

d. Establishing defensive means for preventing hostile control of agency personnel." [26 (p. 387)]

In November 1950, a BLUEBIRD memorandum stated that experiments should be conducted with "the surreptitious oral application of drugs on unwilling subjects for speech inducement purposes."[quoted in ref. 2 (p. 118)] At a CIA-initiated meeting on July 23, 1951, the intelligence divisions of Army, Navy, Air Force, and the Federal Bureau of Investigations (FBI), came together to explore the possibility of mutual coordination of mind-control research. Except for the FBI, all agreed to cooperate in a joint program.[2 (p. 87)] In August 1952, the Office of Naval Intelligence informed the CIA that the project CHATTER developed a truth drug treatment with the desired characteristics.[3 (p. 35)] In September 1952, under Operation CASTIGATE, drugs were administered to 8 Soviet defectors at Camp King, a US interrogation center located near Frankfurt/Main, Germany. The trials used alternating injections of sodium pentothal, methamphetamine, and tetrahydrocannabinol (THC). However, the trials were unsuccessful and project CHATTER was terminated in 1953.[3 (p. 34–40)]

On April 13, 1953, the CIA authorized Project MK ULTRA, an umbrella project on mind control, which included all BLUEBIRD/ARTICHOKE projects and additional research "... on radiation, electroshock, various fields of psychology, psychiatry, sociology, and anthropology, graphology and paramilitary devices and materials."[2 (p. 131)] According to its principal architect, CIA Director Richard Helms, the main parts of MK ULTRA were designed to "... investigate the development of a chemical material which causes a reversible non-toxic aberrant mental state ... This material could potentially aid in discrediting individuals, eliciting information, and implanting suggestions and other forms of mental control."[quoted in 2 (p. 132)]

1.6 | Henry K. Beecher and the "newer derivatives of mescaline"

Henry K. Beecher studied chemistry and medicine. In 1941, Beecher became Professor of Anesthesia at the Harvard Medical School in Boston. From the mid-1940s he was a consultant for the US Army and the OSS[27] with respect to truth drugs. On February 7, 1947, Beecher received a brochure entitled *German Aviation Medical Research at the Dachau Concentration Camp*,[18] which detailed 30 mescaline experiments on Dachau Concentration camp inmates.[27] On June 15, 1950, Beecher reported to the CIA that he had consulted with colleagues about the "considerable problem here in the use of healthy young volunteers" to test "synthetic agents in the mescaline group,"[quoted in ref. 27 (p. 411)] synthesized by the Army's Chemical Corps at Edgewood Arsenal, Maryland.

On behalf of the Army, in September 1951, Beecher traveled to England, France, and Germany to evaluate the research "on the subject of 'ego-depressant' drugs, usually called truth serums," paying particular attention to mescaline.[quoted in ref. 27 (p. 411)] In a report on his trip, Beecher concluded that "it would be desirable for me to return [to Camp King], perhaps in a year, when we know better the signs and symptoms of the newer derivatives of mescaline..., to interrogate especially high level escapees from Russian interrogation."[quoted in ref. 27 (p. 412)] In another statement in 1952, Beecher claimed that "these agents are being studied by some 200 investigators, probably on both sides of the Iron Curtain. I earnestly hope that the US will not get behind in this field ..."[28 (p.1)]

1.7 | Drug research at the New York State Psychiatric Institute (NYSPI)

Since at least 1950, some psychochemical substances, including derivatives of mescaline (Figure 1 and Table 1), have been synthesized at Edgewood Arsenal. Beginning in 1951, the Army Chemical Center's Special Operations Division (SOD) studied psychochemical agents in humans under controlled laboratory conditions. They were contracted for this purpose by the New York State Psychiatric Institute (NYSPI) because of their extensive experience in hallucinogenic drug testing on humans.[2 (p. 171)]

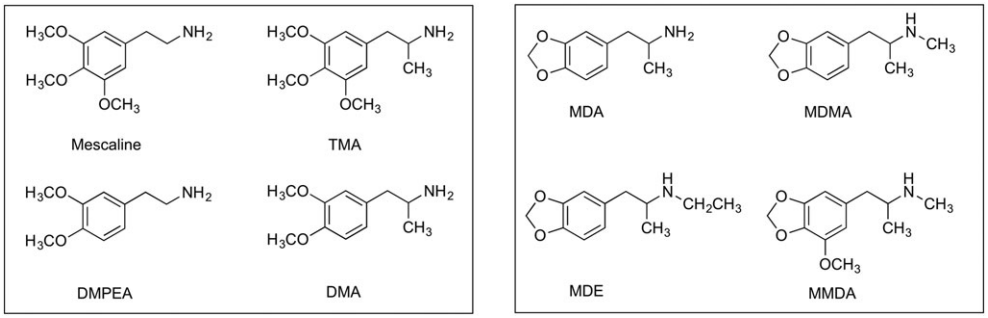

FIGURE 1 Some representative examples of the two groups of substances (phenethylamine and the methylenedioxy compounds) discussed in the text. TMA: 3,4,5-trimethoxyamphetamine; DMA: 3,4-dimethoxyamphetamine; DMPEA: 3,4-dimethoxyphenethylamine; MDA: 3,4-methylenedioxyamphetamine; MDMA: 3,4-methylenedioxy-*N*-methylamphetamine; MDE: 3,4-methylenedioxy-*N*-ethylamphetamine; MMDA: 3-methoxy-4,5-methylenedioxyamphetamine

TABLE 1 List of mescaline analogs tested in the context of military research.

Abbreviation*	EA-code**	Chemical name
MDPEA	EA-1297[a,b]	3,4-Methylenedioxyphenethylamine
MDA	EA 1298 [a,b]	3,4-Methylenedioxyamphetamine
DMPEA	EA-1302[b]	3,4-Dimethoxyphenethylamine
MDE	EA-1304 [a,b]	3,4-Methylenedioxy-*N*-ethylamphetamine
Mescaline	EA-1306[b]	3,4,5-Trimethoxyphenethylamine
DMA	EA-1316 [a]	3,4-Dimethoxyamphetamine
TMA	EA-1319[b]	3,4,5-Trimethoxyamphetamine
DMMA	EA-1322[a]	2,5-Dimethoxy-*N*-methylamphetamine
MDMA	EA-1475[b]	3,4-Methylenedioxy-*N*-methylamphetamine
MDDM	Unknown[b]	3,4-Methylenedioxy-*N*,*N*-dimethylamphetamine
MMDA	Unknown	3-Methoxy-4,5-methylenedioxyamphetamine
LSD	EA-1729	Lysergic acid diethylamide

*Abbreviations used as given in the relevant original literature.

**Code numbers as given by Edgewood Arsenal (EA).

[a]Compounds delivered to the New York State Psychiatric Institute (NYSPI) in November 1952 for tests in humans.[29]

[b]Compounds tested in animal toxicology study at University of Michigan 1953–1954.[30]

Founded in 1896, the NYSPI was one of the most prominent psychiatric research institutions in the USA. In 1946, the NYSPI started to experiment with mescaline.[4 (p. 530)] In 1948, Professor of Psychiatry Paul H. Hoch became director of the NYSPI's Department of Experimental Psychiatry, where the US Military's research took place. According to Army contracts "the [NYSPI] will conduct studies of psychochemical agents on human beings to determine clinical effects on psychological behavior, including controls on normal human subjects necessary to evaluate the more profound changes expected in the behavior of psychiatrically liable subjects."[quoted in ref. 4 (p. 160)] It was expected that "new technical data ... will provide a firmer basis for the utilization of psychochemical agents both for offensive use as sabotage weapons and for protection against them."[quoted in ref. 29 (p. 1)]

The Edgewood Arsenal coding with the consecutive numbers EA-1304 to EA-1322 (Table 1) suggests that most mescaline derivatives were synthesized consecutively during years 1950–1952.[Beecher quoted in ref. 27 (p. 411)] If this were true, then the numbering scheme used for MDMA, LSD, and 3-methoxy-4,5-methylenedioxyamphetamine (MMDA) suggests that these substances might have been synthesized a while later.

In November 1952, the Army Chemical Corps delivered the following substances to the NYSPI for human tests: MDPEA, MDA, MDE, DMA and 2,5-dimethoxy-*N*-methylamphetamine (DMMA) (Table 1).[29 (p. 2)] None of these had been previously tested in humans. Animal testing was grossly deficient. "The five ... compounds were tested only on mice, for less than one month and only to determine the LD (lethal dose) 50."[29 (p.3)] Nevertheless, "within a month of receiving the drugs, NYSPI experimenters began injecting them into patients."[31 quoted in ref. 2 (p. 500)] (Table 2), without their informed consent. It is obvious from available documents, that MDPEA, MDA, and DMA were repeatedly tested on patients at the NYSPI. In at least 2 known cases, researchers tested a low first dose of MDA or DMA (ca. 1 mg/kg intravenous, i.v.). In a next step and without further testing, the patients were injected a 10 times larger dose (10 mg/kg i.v.).[29 quoted in ref. 2 (p. 500), 31]

1.8 | The death of Harold Blauer

The tennis professional Harold Blauer was a patient suffering from depression and from December 1953 attended the NYSPI for psychiatric/psychotherapeutic treatment. This treatment modality was intended to be made more effective by the administration of hallucinogenic drugs. On December 11, 1952, the treatments involved administration of low dose MDA, then DMA, then MDPEA, then DMA and concluded with a very high dose of MDA (Table 2).[29 (p. 3)] Before the fourth injection of DMA, Blauer requested to withdraw because he was experiencing terrible hallucinations from those injections.

TABLE 2 List of consecutive injections given to patient Harold Blauer at the New York State Psychiatric Institute (NYSPI).[29]

12/11/1952	MDA	EA-1298	0.4 mg/kg
12/18/1952	DMA	EA-1316	1.0 mg/kg
12/23/1952	MDPEA	EA-1297	5.0 mg/kg
12/30/1952	DMA	EA-1316	10.0 mg/kg
01/08/1953	MDA	EA-1298	6.47 mg/kg (= 450 mg total dose)

Nevertheless, on December 30, 1952, he received an injection of DMA, which resulted in a strong body tremor.[29 (p. 4)] On January 8, 1953 at 9.53 a.m., Blauer was injected with a fatal dose of 450 mg MDA. Immediately after injection, Blauer developed a state of high arousal, tremor, and sweating, and experienced an epileptic seizure, extensive movements of the limbs and finally coma. "Oxygen was administered, as was glucose, sodium amytal and artificial respiration,"[2 (p. 171)] but approximatively 30 minutes later, Blauer was dead.[32 (p. 136–137)] The death certificate recited that "a chemical compound had activated a previously unknown heart condition, causing a fatal coronary attack."[2 (p. 171)] The official version was that Blauer died from an "unusual reaction" to a medication he received during the treatment at the NYSPI. According to the Inspector General report of 1975, without appropriate knowledge of MDA's toxicity, "dosage levels were set not by research on toxicity, but by guess." [31 quoted in ref. 2 (p. 500)]

On the same day as Blauer, another patient was injected with MDA. She was given 150 mg instead of the planned 450 mg dose of MDA, because her reaction to MDA "... was so violent that the injection was stopped when it was only one-third complete."[29 (p. 2)]

Immediately after Blauer's death, Amedeo Marazzi, Director of the Army's Medical Corps at Edgewood Arsenal, traveled to the NYSPI and instructed Drs Hoch and Cattell. "... not to continue the experiments until certain safety measures were implemented. ... [But because] the results of the experiments obtained thus far were very useful for the Army's purposes, he recommended continuation of the experiments ...".[29 (p. 4)] Therefore. he advised implementing safety measures to continue with experiments. The Army Chemical Corps renewed the contracts with the NYSPI in 1953. The Army administrators were eager to keep the involvement of the Army in these experiments and the Blauer case secret "to protect national security."[2 (p. 173–174)] Marazzi instructed the Medical Examiner to not disclose any details of Blauer's death. All related files were stamped *secret* and transferred to Marazzi's safe at Edgewood Arsenal.[29 (p. 5), 4 (p. 529)] None of the eight NYSPI reports to the Chemical Corps referred to the Blauer fatality.[2 (p. 173)] When pressure from Blauer's family intensified, officials of the US Justice Department responded that secret contracts could not be revealed under any circumstances. The same officials suggested that the NYSPI should falsely state "that mescaline derivatives had been coming into general use for the diagnosis and therapy of mental patients."[quoted in ref. 4 (p. 164)] At last, the trial was avoided by paying an amount of $18,000 to Blauer's relatives.[29 (p. 7)]

In 1975, the Inspector General of the Army led an official examination of Blauer's death. This report is still partially secret, but "... suggests by implication that although Army testing was woefully inadequate, primary blame for Blauer's death must rest with the psychiatric experimenters at NYPSI.[2 (p. 172)] This suggests that Blauer was administered an accidental overdose (possibly caused by the steep dose escalation scheme as mentioned in Table 2). A subsequent evaluation by the judges examining the case concluded, that "if the Chemical Corps had not been negligent in performing its LD-50 tests on mice, then the information ... would have been enough for Dr Hoch to know that the dose of 6.47 mg/kg of EA-1298 that killed Harold Blauer was dangerously high. Therefore, the Chemical Corps' negligence in producing the toxicity tests was a proximate cause of Blauer's death."[29 (p. 11)]

1.9 | Animal toxicology studies at the University of Michigan

Less than a month after Blauer's death, on February 4, 1953, Hoch and Cattell met again with Edgewood's Special Operations Division (SOD) officers at the NYPSI. It was decided to continue the drug experiments, and "to regain safety, the materials used should be tested in animal studies for their toxicity." [31 (p. 7–8) quoted in ref. 2 (p. 500)] In 1953, on behalf of the Army Chemical Warfare Corps, toxicological animal testing of some mescaline derivatives began in secrecy at the University of Michigan. In the 1940s, Dr Maurice H. Seevers, Director of the Department of Pharmacology at Michigan University in Ann Arbor, conducted pharmacokinetic animal studies with cocaine and mescaline.[33-35] He was a consultant to the Army Medical Laboratories in a survey of substances "... of immediate interest: the mescaline series, the lysergic acid diethylamide and the marijuana series." [quoted in ref. 4 (p. 166–167)] It is worth mentioning that Seevers had already intended to do (or did) research on derivatives of mescaline. This is suggested by a publication on mescaline, where he acknowledges "... the furnishing of several synthetic mescaline derivatives" by the Swiss pharmaceutical company Hoffman-La Roche for their experiments.[35 (p. 205)] However, results of tests in mice with 21 derivatives were only mentioned at Marazzis secret 'Psychochemical conferences'.

The Army's toxicological studies at Seevers's Department commenced in 1953 and were completed in 1954. Seven substances, all being structural variations of mescaline, were studied: DMPEA, MDPEA, MDA, alpha-ethyl-MDPEA, DMA, TMA, and MDMA. Behavioral parameters and toxicity were evaluated in 5 animal species (mice, rats, guinea pigs, dog, and monkeys) and compared to mescaline.[30] The seven compounds produced comparable physiological and behavioral effects in the animals, but demonstrated quite different toxicity, with the methylenedioxy compounds (MDPEA, MDA, alpha-ethyl-MDPEA, and MDMA) being the most toxic (Table 3). An important conclusion from these studies was that the dog was a much more reliable animal to detect hallucinogenic effects than rodents or monkeys. Dogs showed a specific behavioral difference under the influence of mescaline-like hallucinogens, which was virtually undetectable in monkeys.[30 (p. 306)]

TABLE 3 The LD_{50} for mescaline and seven of its derivatives in five species of animals (mg/kg bodyweight of the hydrochloride salts , i.p. or i.v.)[30]

Substance	**Mouse** Swiss Webster	**Rat** Sprague Dawley	**Guinea pig**	**Dog** Mongrel dogs	**Monkey** *Macaca mulatta*
Mescaline	212	132	328	54	130
DMPEA	363	146	375	122	220
MDPEA	176	55	245	28	45
MDA	68	27	28	7	6
α-ethyl-MDPEA	82	95	88	16	20
DMA	168	48	195	59	53
TMA	240	149	172	23	31
MDMA	97	49	98	14	22

The data from animal testing were considered interesting, but "... do not permit satisfactory prediction of the pharmacologic actions of these agents in man."[30 (p. 308)] Therefore, the authors hoped that the "... extensive data contained in this report provide a base for further studies in man,"[30 (p. 306)] which suggests that further testing in humans was intended. In relation to structure–activity relationships the authors concluded: "modifications in the mescaline structure which alter pharmacologic activity include: decreased potency following removal of the 5-methoxy group or N-demethylation, and increased potency following alpha-substitution on the side chain or introduction of the 3,4-methylenedioxy group."[30 (p. 299)] All methylenedioxy compounds were more toxic than MDA. The military researchers may have tried to avoid substances that were more toxic than MDA, which had already caused an unpredicted death.

1.10 | Further research on truth drugs in the 1950s by the military and the CIA

In 1952, the CIA's MK ULTRA program on behavior manipulation through drugs focused more on LSD. This substance is active at minute doses (1/10,000 of a gram), colorless, tasteless, and odorless. In view of this, LSD seemed to offer advantages for administration to unwitting subjects or as an aerosol to be sprayed over wide areas or filled into water reservoirs. As Dr Gerald Yonetz of the Army's Edgewood Arsenal stated in 1953: "There was a long, long list of drugs.... but somebody high up the ladder became enthralled with LSD and for a while everything else took a back seat." [quoted in ref. 4 (p. 316)].

The secret work for the Army at the NYSPI continued after the death of Blauer and lasted throughout the 1950s. According to participating researcher Sidney Malitz, one focus was to determine if "a particular personality type might 'break' more rapidly under a drug stress than another type" during military interrogations. [quoted in ref. 36 (p. 63)] It is not clear whether this research included mescaline derivatives, because no documents on the post-1953 research at the NYSPI are known.

During the mid-1950s, Clark and Beecher tested 20 paid volunteers to withhold information from an interviewer while being under the influence of drugs. The experimental subjects were dosed with thiopental, atropine, amphetamine, methamphetamine, sodium amobarbital, alcohol, scopolamine, pentobarbital, morphine, caffeine, and mescaline. The drugs were sometimes administered in such high amounts that the subjects became semi-comatose and deliriant, or became panicked, talkative, and euphoric. Notably, no subject experienced "sufficient ego impairment" to not identify the significance of questions about the suppressed information, and no secret information was revealed.[37]

During the years 1954/1955, a few psychochemical conferences were organized by Marazzi at Edgewood Arsenal, which had, among others, Hoch, Abramson and Seevers as participants. The first conference was opened by Marazzi stating "it is perfectly obvious that the military objective is to produce ... mental incapacitation with ... the drain it places upon the military resources of a great number of people. Obviously, such an objective might be accomplished in large groups or small groups or even in single individuals." [quoted in ref. 4 (p. 166)].

In the mid-1950s, other studies on mescaline and its derivatives were conducted under secret military contracts. Robert G. Heath, Chairman and Professor of the Department of Neurology and Psychiatry at Tulane University and heavily involved with the CIA's research in mind control,[2 (p. 192; p. 336–338)] implanted 6 patients with subcortical electrodes and gave them mescaline and LSD to study their EEGs and behavior. A major finding was identification of a specific subcortical paroxysmal activity caused by LSD and mescaline, which occurred in every patient.[38] This finding provided a foundation for later studies conducted by Californian pharmacologist Gordon A. Alles. Alles had carried out some self-initiated experiments in the mid-1950s with DMA, TMA, MDA, and MMDA in cats to develop a new screening method for hallucinogenic effects in animals. By at least 1960, Alles had become a contractor of the Army's secret research on mescaline derivatives. For this purpose, Alles synthesized four methylenedioxy compounds in his laboratory as outlined by Alles's co-worker Fairchild.[39 (p. 8)] Subsequently, he "... submitted about 10 grams each of the salts of four 3,4-methylenedioxy-amphetamine derivatives to the Directorate of Medical Research, Army Medical Center." His further statement that the "preliminary animal work on toxicity and relative motor activity in man was to be the responsibility of the Directorate of Medical Research" [40 (p. II)] implies that these compounds were intended for human testing. The fact that only two methylenedioxy compounds (MDA and MMDA) [39] were used in Alles's later tests, suggests that other methylenedioxy compounds were not researched further. Besides the well-known MDA, Alles had demonstrated that his newly synthesized methylenedioxy compound MMDA (3-methoxy-4,5-methylenedioxyphenethylamine), was much less less toxic than MDA, MDMA, MDPEA, and alpha-ethyl-MDPEA (cf. Table 3).[40 (p.45)] In his further experiments, cats were implanted with subcortical EEG electrodes. In contrast to amphetamine, all hallucinogenic compounds produced the expected high-amplitude, low-frequency activity with hypersynchronous wave forms in the EEG.[39] This indicates, that "there is a gross correlation between the ability of these compounds to produce hypersynchronous bursting activity in the brain of the cat and their hallucinogenic potency in man."[39 (p.113)] In the Final Report to the Army on these experiments, Alles expressed some disappointment: "It was hoped that another small, closely related series of compounds, whose potency ... in experimental animals has been investigated by us, would also have been evaluated by the Army Chemical Center for their hallucinogenic activity in man. This goal failed of any notable achievement." [40 (p. II)] It is unknown whether the US military did any further research into the derivatives of mescaline later than this. However, researchers at the British Chemical Warfare facility at Porton Down were using Alles's procedures for testing a lot of hallucinogenic phenylalkylamines during the 1970–1974 timeframe.[41]

2 | DISCUSSION

Research on truth drugs commenced in the early 1920s. It was initiated by chance findings rather than being a result of goal-directed research. Substances to be selected first as truth drugs were scopolamine and mescaline. Scopolamine was discarded because it induced a delirium-like state of mind with disorientation, mental confusion, disordered thinking, and clouding of consciousness (plus a very dry mouth, which

hindered speaking).[42 (p. 25–34)] Similiar problems appeared to be relevant for sedating substances like the barbiturates (e.g. sodium amytal), which inhibit cortical activity and suppress ego-control over speech and withholding of information. In comparison to scopolamine, sodium amytal induced a milder clouding of consciousness and disorientation, but still produced extracted information of questionable validity.[37,43]

The research on mescaline and its derivatives took another turn. After experimenting with mescaline in 1943, the OSS "... rejected it because it produced these 'hallucinations' that got in the way, that made things more confusing, in this process of eliciting information."[45 (p. 36)]

After first testing LSD for interrogation in 1952, "reports seemed promising. In one instance LSD was given to an officer who had been instructed not to reveal 'a significant military secret' [but when questioned] he gave all the details of the secret ..." [44 (p. 13)] Therefore, the military researchers thought like "we have got the truth drug."[45 (p. 37)] Since at least 1955, LSD has been used operationally for interrogations.[26 (p. 94)] After their initial euphoria, the researchers realized the same problem the OSS had had with peyote, a mescaline-containing cactus: excessive hallucinations, thought disturbance, and confusion. Especially in the crude contexts in which LSD was adminstered, it produced a lot of "freak-outs," which hindered the process of interrogation. A CIA review on LSD use in interrogation concluded that "medical research has established that information obtained through the use of these drugs is unreliable and invalid."[26 (p. 99)] Therefore, the use of LSD for interrogation was stopped in 1966.

Starting around 1950, the Army synthesized mescaline-like compounds to minimize these "counter-productive" effects of mescaline. They had 4 main goals as stated in a 1955 CIA document:[26]

1. To raise the potency of the compounds for easy delivery by covert means.
2. To alter psychological functioning more specifically, ie, minimizing some of mescaline's effects.
3. To develop drugs with effects "... which can be reasonably well predicted for each individual." [26 (p. 79)]
4. To produce "substances which will produce 'pure' euphoria with no subsequent let-down."[26 (p. 125)]

In comparison to LSD and mescaline, the methylenedioxy compounds were a useful starting point for the development of such drugs. These compounds were virtually devoid of hallucinogenic activity and left subjects with widely intact cognition. Nevertheless, the impact of their bundled effects could make a subject more vulnerable, unstable, and cooperative by lowering anxiety, defensiveness, and self-control. This fitted into the conclusion of a review on *The use of drugs in interrogation* that "... some drugs lower conscious ego control, thereby facilitating recall of repressed material and increasing the difficulty of withholding available information. The ideal drug for an interrogator would be one which not only accomplishes this feat, but does so without interfering with integrative capacities and intellectual functioning."[46 (p. 113)] Research at the NYSPI on "antagonizing" mescaline's and LSD's effects had revealed that a stimulant like methamphetamine (given during the LSD intoxication) improved "reality contact," attenuated "autism" and made the subjects more present ("more here").[47] By implication, this favored research into the borderland between mescaline and amphetamine, which could be seen in the methylenedioxy compounds. Consequently, Alles synthesized and tested new methylenedioxy compounds in the mid-1950s and came up with the less toxic compound MMDA.[39] The fact that the animal studies initiated after the death of Harold Blauer at the NYSPI included four methylenedioxy compounds also suggests a specific interest in this type of compounds.[30] That some mescaline derivatives were tested further in humans is suggested by the continuation of the Army's contracts with the NYPSI, but no documentation exists.

It is unknown whether any of the tested mescaline derivatives ever reached operational use (as did LSD). But it was stated clearly, that the "final testing phase of MK ULTRA substances ... on unwitting subjects is recognized to be an activity of genuine importance in the development of ... MK ULTRA products."[48] According to CIA Deputy Director of Support, Lyman B. Kirkpatrick, the CIA's Technical Services Staff (TSS) had reached "some concrete results" and noted that "six specific products" had been developed for operational use. Three had been applied operationally on 6 occasions with 33 subjects.[4 (p. 470)] The extent of field use (and which substances were used) will probably never become clear, because virtually all files on "operative use of mind manipulation techniques" related to projects ARTICHOKE and MK ULTRA (1951 to 1955 timeframe) were ordered for destruction in 1960[4 (p. 578)] and in 1973 (1953–1964 timeframe).[26 (p. 9)]

However, it remains unclear why the research on the mescaline derivatives ceased. The unpredicted death of Blauer might have been one reason. However, the investigation of mescaline derivatives proceeded, but as it appears, without any further testing in humans. What may have triggered further research in the methylenedioxy compounds was the search for compounds with more predictable and specific effects. A significant contextual reason for leaving the research on mescaline derivatives may have been that LSD, with its specific physical properties, appeared to have indicated a larger potential for military and intelligence purposes. However, it was found early on that reactions to LSD did not have sufficient predictability and that it induced severe anxiety and ego-disintegration, and that it could not be used for interrogation or other operational purposes.[49] This may have favored again the search for drugs with less hallucinatory and disturbing mental effects. Alles's expectation about further testing of mescaline derivatives in humans in the early 1960s points in this direction. Nonetheless, a decreasing interest in the search for drugs potentially useful for interrogation purposes emerged in the early 1960s, presumably reflecting the recognition that all drugs tested had failed as truth drugs. Consequently, "by the early 1960s, ... the CIA finalized an interrogation paradigm based on behavioral methods, not drugs ...". [27 (p. 413)].

ACKNOWLEDGEMENT

We thank Dr Marie Claire Van Hout who kindly assisted with the proofreading of the manuscript.

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How to cite this article: Passie T, Benzenhöfer U. MDA, MDMA, and other "mescaline-like" substances in the US military's search for a truth drug (1940s to 1960s). *Drug Test Anal*. 2017;1–9. https://doi.org/10.1002/dta.2292