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A REVIEW OF THE BIOMEDICAL EFFECTS OF MARIHUANA ON MAN IN THE MILITARY ENVIRONMENT

DECEMBER 1970

Prepared for

LIFE SCIENCES DIVISION, ARMY RESEARCH OFFICE
OFFICE OF THE CHIEF OF RESEARCH AND DEVELOPMENT
DEPARTMENT OF THE ARMY
WASHINGTON, D.C. 20310

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FOREWORD

This is a technical report prepared for the Life Sciences Division, Army Research Office, Office of the Chief of Research and Development, Department of the Army, by the staff of the Life Sciences Research Office, Federation of American Societies for Experimental Biology, in accordance with the provisions of U.S. Army Contract No. DA-HC19-71-C-0006. A feasibility study on the biomedical effects of marihuana was initiated on May 20, 1970. This study is one of a series in the biomedical sciences undertaken by the staff to provide scientific assessment of a subject based upon a comprehensive critical literature review and the views of knowledgeable scientists actively engaged in research in the field. The report develops a factual basis for subsequent discussions by research administrators. A judicious attempt has been made to incorporate balanced points of view of this controversial subject. We acknowledge the assistance of the ad hoc review group participants and the investigators who have examined the report. The authors accept the responsibility for the contents of the report.

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SUMMARY

This review documents in detail the current state of knowledge of the effects of marihuana on man. The study examines the relationships between marihuana use and performance of the man in a military environment and identifies opportunities for future research by the Army in this field.

The scope of the study includes the botany and phytochemistry of Cannabis sativa, isolation, characterization, and synthesis of the plant constituents, the pharmacology of these compounds, and the need for quantitative estimation of the tetrahydrocannabinols and their derivatives in biological samples. Special attention is directed to the effects of smoking marihuana, the composition of marihuana cigarette smoke, and the resulting somatic, subjective, perceptual, and cognitive changes that may influence the performance of the smoker.

This review includes a description of behavioral tests used to measure marihuana effects, the influence of an individual's expectations, and effects of environmental setting on human subjects. The anecdotal literature on marihuana is being replaced by reports of controlled laboratory studies; however, investigations that measure performance in real-life situations are required to answer crucial military questions on marihuana effects. Information on the chemistry, pharmacology, and behavioral effects of marihuana that is necessary for these future studies is being developed at the present time.

The report identifies and assesses the research opportunities that are related to the requirements of the Army. It is suggested that the unique research experience and facilities of the Army in assessing the performance abilities of men exposed to incapacitating agents may be utilized to answer the pressing questions concerning marihuana smoking and its influence on the performance of the man in the military environment. The suggestions for future research are given in Section IV (See Page 69).

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I. THE PROBLEM

The social problem of drug abuse exists throughout the world and thus penetrates military life at home and abroad and includes the use of the controversial drug marihuana.* The literature on marihuana does not meet modern standards of scientific investigations. Most reports are biased, ambiguous, anecdotal, and yield little valid information. The need for factual data provided the stimulus for this technical review of the subject undertaken for the Life Sciences Division, Army Research Office, Office of the Chief of Research and Development, Department of the Army. The extensive investigations by the civilian scientific community in recent years were to be documented in a report and any relationship between marihuana use and the performance capability of the man in the military environment was to be examined. Where needs for research by the Army were identified, specific suggestions for future investigations were to be made.

The legal or punitive aspects of marihuana use, education, rehabilitation, and factors that may lead to marihuana use were excluded from this review. These aspects of drug abuse within the military have been addressed by the Department of Defense Drug Abuse Committee** and its Task Group on Drug Abuse Policy.***

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* In this report the word "marihuana" with anglicized spelling is used interchangeably with Cannabis. The term "drug" is not used in the legal pharmacologic sense or as a narcotic but rather a pharmacologically active material without implying therapeutic properties.

** Department of Defense Directive Number 1300.11, Illegal or Improper Use of Drugs by Members of the Department of Defense, October 23, 1970, 11 p.

*** Mack, W.P., Chairman, Report of the Task Group Convened to Recommend Appropriate Revisions to DoD Policy on Drug Abuse, July 24, 1970, 58 p.

The Task Force on Narcotics and Drug Abuse of the President's Commission on Law Enforcement and Administration of Justice (1), recently reviewed the Federal law controlling marihuana and the current legal status of Cannabis. The extent of use of marihuana in the United States and legal sanctions were considered and the Task Force made tentative recommendations for future research. Many of these recommendations have been embodied in the recently enacted drug abuse legislation known as the Comprehensive Drug Abuse Prevention and Control Act of 1970 (H.R. 18583).

In March, 1967, the National Institute of Mental Health (NIMH) was charged with the development of a marihuana program that includes studies of the composition of marihuana, its pharmacology, and its toxicological, psychological, and sociological effects. Cannabinoids are being isolated, identified, synthesized and made available for research studies. The program is concerned with acute and chronic toxicity studies in several animal species, as well as the biochemical and clinical pharmacologic aspects of marihuana use. The major thrusts of the NIMH marihuana program have recently been described (2).*

This Life Sciences Research Office report provides a scientific basis for evaluating the problem of marihuana usage in the Army without considering the legal aspects. The primary concern is the ability of the soldier to meet the performance requirements placed upon him as these may be modified by marihuana use. The health of the soldier is the responsibility of The Surgeon General of the Army and traditionally Army medical research programs have as their goal the protection of the man against the hazards of a hostile environment. Performance decrements may be caused by the extreme physical and mental demands of military requirements, by therapeutic drugs, e.g., antimalarials, or socially acceptable drugs such as alcohol and tobacco (3, 4). With the prevalence of marihuana smoking in our society and among

---

* On September 25, 1970 the National Institute of Mental Health, Department of Health, Education, and Welfare submitted a preliminary report on the health consequences of marihuana usage to the United States Congress in compliance with Title V of P.L. 9-296 (Marihuana and Health Reporting Act).

military personnel, it is important to assess any impact of this drug on the performance of the man in a military environment.

By international convention the World Health Organization Expert Committee on Addiction-Producing Drugs has established the following criteria for drug dependence of Cannabis (marihuana) type:

> "Drug dependence of the Cannabis type is a state arising from chronic or periodic administration of Cannabis or Cannabis substances (natural or synthetic). Its characteristics are: (a) moderate to strong psychic dependence on account of the desired subjective effects; (b) absence of physical dependence, so that there is no characteristic abstinence syndrome when the drug is discontinued; (c) little tendency to increase the dose and no evidence of tolerance" (5).

Individual variations preclude absolute statements, but almost all investigators agree that marihuana smokers do not develop dependence of the morphine type. Generally, marihuana users are able to stop the habit without experiencing abstinence symptoms even after long and continuous use. Thus, the use of marihuana should be viewed in a different context. Therefore, the problem becomes one of reviewing the subjective, perceptual, cognitive, and somatic changes produced by marihuana use, and how these changes affect behavior and performance. Objective tests are required to answer these fundamental questions. The principal concerns of this study were to review the evidence developed by research in this field that may be logically extrapolated to the military environment.

II. SCOPE OF THE STUDY

The basic objectives of this study are: to review and document in detail the current state of knowledge of the effects of marihuana on man; to identify gaps in existing knowledge on the effects of marihuana on man specifically related to the military environment; and to identify any need for research by the Army in this field.

This study includes a consideration of the botany of Cannabis because it is recognized that active constituents vary within plant parts, with conditions of growth and genetic characteristics of the plant. The general chemical nature of the biologically active plant constituents has been known for several years. Modern developments in chemistry have only recently made it possible to isolate, identify, and synthesize the specific and varied plant constituents.

The pharmacology of marihuana is reviewed as it relates to: the effects of the plant when ingested orally or smoked; factors of absorption, distribution, metabolism, and excretion of active ingredients; long-term studies on experimental animals; and the actions on the central nervous system of man and animals. The behavioral features of marihuana smoking are considered and compared with tobacco smoking as well as the composition of marihuana smoke, and dose-effect response relationships. The criteria for satisfactory research studies on marihuana cigarette smoking are reviewed.

Somatic effects of marihuana use are considered as these may relate to the performance of the man. Primary attention has been directed to the studies on the subjective and perceptual effects of marihuana and the test methods used to evaluate behavioral effects in man. Included are such factors as time judgement, clarity of perception, and sensory stimuli as these influence the operation of military equipment, vehicles, specialized materiel, and the use of hazardous devices and weapons. The relationships to command responsibility and vigilance are additional aspects of military demands on the soldier that may be influenced by marihuana use. The possible long-term effects of chronic marihuana use may constitute another problem of military significance, and research will be necessary to determine the character of these effects. The military has a unique capability for research on the behavioral effects of incapacitating

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agents, an area closely related to the scope of this study.

Historically the implications, both for the individual and for society, attributed to marihuana use have been made primarily by conjecture and speculation with little reference to facts based on scientific methods. Recent developments in psychopharmacology and studies of psychoactive drugs have stimulated investigations on the action of many chemical substances that alter human behavior. This work, related to therapeutic use of these agents in psychiatric diseases, has encouraged collaborative efforts to develop new methods to assess behavior changes induced by drugs. As a result psychopharmacological techniques are available for the careful study of the pharmacology and possible chemical basis of the behavioral aspects of marihuana use. Thus, the anecdotal literature on marihuana is being replaced by scientific reports in the field of psychopharmacology. These investigations have been reviewed in detail because they provide the most useful contemporary information within the scope of this study.

This report was prepared from the discussions of the ad hoc study group, interviews with consultants, and a comprehensive literature survey. Bibliographic surveys and pertinent literature analyses are cited in the introduction of the bibliography, Section V.

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III. REVIEW DISCUSSIONS

A. BOTANY

Cannabis sativa L. is one of the earliest non-food plants domesticated by civilized man. The plant has been cultivated over the centuries for the fiber (hemp) in its stem, the oil in the seed, and the biologically active constituents of the shoots and flowers. Cannabis is still an economically useful plant in some regions of the world, and is currently considered a valuable experimental plant for genetic and physiologic studies. Despite the long association of Cannabis with man, knowledge of its botany is still imperfect and incomplete. Morphological studies of the past several decades have established the unique nature of the plant, but critical ecological and phytochemical investigations have been undertaken only recently.

1. Origin

Vavilov (6) concluded, and most investigators agree, that C. sativa is indigenous to the Central Asian plains north of the Himalayan Mountains. However, the wide morphological variability exhibited by cultigens has prompted speculation that Cannabis might be indigenous to other areas of Central Asia and Europe (7). The study of Vavilov (6) is generally recognized as the most definitive investigation into the origin of Cannabis. Chopra and Chopra (8) have recorded the distribution of Cannabis throughout India. Recently, Haney and Bazzaz (9) analyzed the establishment, spread, and distribution of cultivated and escaped cultigens in Illinois. These investigators found that Cannabis is not present in the southeastern and northeastern sections of the state where most clay soils are low in nitrogen. They suggested that Cannabis can be cultivated in most regions of the United States on alluvial and other soils low in clay. Reinvestigation of the geographical distribution of Cannabis in regions where it is thought to be indigenous by these ecological techniques would provide additional useful data about this plant.

2. Distribution

Originally cultivated for hemp fiber, Cannabis was grown in China before 2800 B. C. The plant was introduced into Europe about 1500 B. C. by the Scythians and into the Americas three thousand years later by the Spanish explorers and English colonists (7, 10). The impetus for domestication throughout the world appears to have been cultivation for the fiber although its biologically active properties were known. The cultivated types constantly escape and man continues to select wild plants for stronger hemp fiber, for higher oil content, or for greater drug potency--depending on his needs. Selection and cultivation of wild plants has been carried on in India and elsewhere for centuries where the biologically active constituents are used in religious ceremonies. These ethnobotanical aspects of Cannabis have been reviewed in detail by Bouquet (11), Boyce (7), and Schultes (10).

At the present time Cannabis is disseminated and cultivated throughout India, Southeast Asia, Europe, and the Americas. In the United States, Cannabis was grown extensively as a crop plant for fiber until late in the 19th Century (12). The anticipated need for hemp fiber during World War II led to renewed interest in Cannabis cultivation. Currently, Cannabis exists as an escaped cultigen throughout the central United States where it had been grown previously as a fiber crop. Man is primarily responsible for its distribution beyond this area. Cannabis has spread rapidly throughout the midwestern United States along the major rivers. There is a correlation of Cannabis distribution with alluvial stream deposits in areas of the plain states where intermittent flooding occurs (9). This situation is not unique as the plant spreads spontaneously throughout the tropical and temperate zones wherever Cannabis has been grown as a fiber or oil seed crop (10). Cannabis is probably the most widely disseminated plant known to contain biologically active constituents.

3. Taxonomy

The classification of *C. sativa* has been reviewed by Schultes (10). Considerable confusion as to taxonomic affinities

and speciation occurs in the early botanical literature. It is generally agreed that there is but a single species, C. sativa, which exhibits variation because of genetic plasticity and influence of environmental conditions. These facts explain the many synonyms for C. sativa found in the literature (10).

4. Description of the Plant

Cannabis is an herbaceous annual that grows readily in both fertile and barren soils. Under cultivation for hemp, or in fertile sites, plants may reach 15-20 feet in height. When grown in rows or dense stands, branching is reduced, but in the wild, if uncrowded, extensive branching occurs. The morphological characteristics of the foliage are distinct and make Cannabis readily identifiable. The foliage is plamately compound with 5-11 dark green leaflets radiating from the petiole. The leaflets are narrow, lanceolate, regularly dentate, and long, often up to 10 inches in length.

Cannabis is diecious, producing male (staminate) and female (pistillate) flowers on separate plants. Monecious plants occur infrequently; normally, in nature the proportion of staminate to pistillate plants is approximately equal. Recently, Haney and Bazzaz (9) have reported that a reduced number of male plants are present in roadside collections from midwestern United States. The male plants are taller and shorter lived, usually dying after pollen is shed. The female plants are wind pollinated and survive until killed by frost or the seed are fully mature.

Staminate and pistillate plants are indistinguishable until the flower buds are well developed. Male flowers are produced in great abundance on the younger parts of the plant. Male flower clusters generally are characterized by sparse foliage when compared to pistillate flower clusters. The male flowers are borne in leaf axils as loosely arranged clusters (axillary panicles). The female flowers are larger, more densely packed clusters (axillary catkins). The fruit (achene) contains a single seed with a hard exterior coat. The fruit is ellipsoid, grey to brown, and approximately 2 - 3.5 mm in diameter. Complete detailed descriptions of the vegetative and floral anatomy have been reported (13). Bouquet (11) and Stearn (14) have published excellent descriptions of the gross morphology and botanical characteristics of C. sativa.

5. Cultivation

Soil fertility, climate, and photoperiod affect plant growth and floral initiation, and such factors as altitude, rainfall, and temperature markedly affect plant growth and production of the cannabinoid constituents. The influence of photoperiod on floral initiation and sex expression have been studied in connection with selection of superior hemp producing cultigens (11, 12, 15). The effects of temperature, soil moisture nutrient level, and cultivation practices on the growth of cultigens that yield high levels of the biologically active cannabinoids are known empirically, but are not critically documented except for one recent publication (15). The older literature lacks experimental data on cannabinoid constituents and conjectural inferences from studies on hemp cultigens have been widely publicized in the popular press.

6. Biologically Active Constituents

The unique plant constituents are called the cannabinoids. These substances are not known to be present in any other plant species. The biogenesis of the cannabinoids has been reviewed recently by Mechoulam (16). It is generally held that the content of active cannabinoids is highest in the resinous exudate of the unfertilized pistillate flowers. There are few data to support this conclusion. Recent studies of the phytochemical characteristics of several Cannabis cultigens suggest that Δ^9- and Δ^8-THC (See Page 20) are distributed throughout the male and female plants (15, 17). Valle et al. (18) have shown equivalent pharmacologic effects in extracts from both male and female plants. Fetterman et al. (17) have reported that the cannabinol, cannabidiol, Δ^9- and Δ^8-THC content of both male and female flowering tops are similar. In addition, gas chromatographic analyses of several cultigens of both hemp and marihuana smoking type Cannabis reveal that the cannabidiol content is high and the Δ^9- and Δ^8-THC content are low in hemp cultigens. The reverse appears to be evident in plants grown for marihuana smoking (17, 19).

Recent studies under the auspices of the NIMH marihuana program (2) and by Krejci (15) have shown that trace amounts of the THCs are present in the seed. These results suggest that cannabinoids are naturally occurring metabolic constituents not directly

produced by photosynthesis. Sequential analyses of cultigens grown in Mississippi from Mexican seed indicate that the cannabinoid content of the seedling and maturing plant foliage rises slowly, reaching a plateau by mid-season. Initiation of flowering triggers an increased synthesis or accumulation in the apical vegetative and floral parts. The highest concentration of Δ^9-THC is found in the bracts associated with the pistillate flowers (17).

These recent investigations await confirmation and extension to a wider diversity of cultigens. The genetic plasticity, environmental variability, and human manipulation of Cannabis add further dimensions of complexity to definitive study of the biologically active cannabinoids. Schultes (10) and others (9) have concluded that an urgent need still exists for intensive botanical study of Cannabis, with emphasis on taxonomic affinities, ecological distribution, and biogenesis of pharmacologically active constituents.

B. CHEMISTRY

1. Chemical Characterization of Plant Constituents

It is now recognized that the reported variations in natural cannabinoids and other elements in Cannabis are related not only to genetic influences but also to environmental factors. Waxes, resins, fixed and volatile oils, sugars and fatty acids have been isolated from Cannabis but the "cannabinols" are pharmacologically the most significant constituents of the plant.

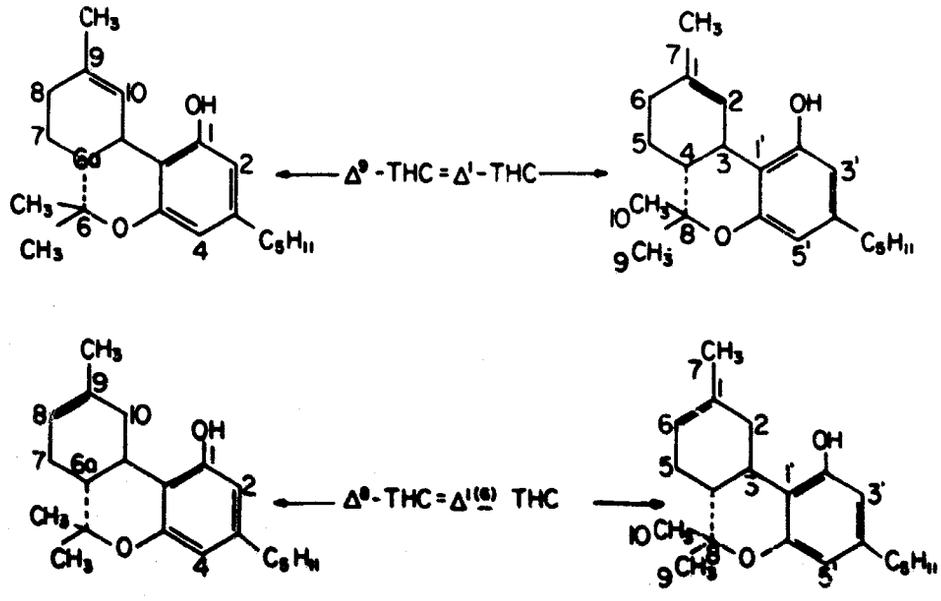
The chemistry of the cannabinoids has been reviewed (16, 20, 21, 22). The early workers identified "tetrahydrocannabinol" as the active constituent(s) of the plant and synthesized numerous derivatives for animal investigations and a few human studies. Unfortunately, between 1930 and 1960 mixtures of isomeric compounds, extracts of the plant, and synthetic materials were all reported in the literature as "tetrahydrocannabinol." For this reason the reports prior to the identification of the correct structure of the THCs must be regarded as misleading. Bryan et al. (23) have recently prepared a bibliography (for the period 1964 through 1969) of research studies on the chemistry of Cannabis and the cannabinoids.

It appears that the major biologically active constituent of Cannabis is (-)Δ^9-trans-tetrahydrocannabinol (Δ^9-THC)*, although the (-)Δ^8-isomer is also active in producing the characteristic biological effects. Currently, most research is focused on these compounds (Figure 1). Only the optically active levorotatory forms of Δ^9- and Δ^8-THC are found in Cannabis. The total Δ^9- and Δ^8-THC content of Cannabis preparations is variable; however, if the Δ^8- form is present it is usually found in very low amounts (24).

---

* The abbreviation THC refers only to tetrahydrocannabinol and implies the presence of a double bond. The location of this double bond is specifically designated by the Δ-prefix, e.g., Δ^9-THC is Δ^9-trans-tetrahydrocannabinol (See Figure 1).

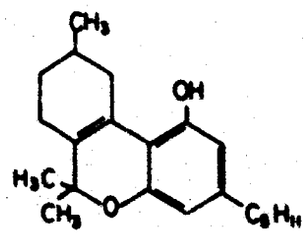
FIGURE 1



Formal pyran-type numbering

Monoterpenoid numbering

This illustrates the two numbering systems for the tetrahydrocannabinols. The formal pyran-type numbering has been used in this report.



Synthetic $\Delta^{8a,10a}$-tetrahydrocannabinol

This is the material synthesized in 1940 (26). It has not been found as a natural product.

A large number of related chemical compounds, e.g., cannabidiol, cannabinol, THC and their acids, have been isolated from Cannabis or resinous mixtures and extracts of the plant (23). However, it is difficult to be positive that any specific compound is a natural product and not an artifact formed during curing, extraction, or isolation.

Prior to the availability of pure Δ^9- and Δ^8-THC as reference standards, investigators used the total THC content of a product as a guide to potency. The total THC content is an unreliable index of the biological potency of a preparation. The pure compounds facilitate standardization of dosage forms for comparative studies and are available through the NIMH marihuana program (2).

The isomeric THCs are oily liquids, insoluble in water, labile to air exposure and temperature changes. The Δ^9-THC is readily isomerized under acidic conditions to Δ^8-THC, and oxidation converts both compounds to relatively inactive cannabinol. Water-insolubility of the cannabinols poses a special problem for the investigator studying their pharmacologic effects in animals or man. Attempts have been made to solubilize Δ^9-THC employing ethanol, polyethylene glycol, dimethyl sulfoxide, Triton X-100, and the Tweens. There is a need for water-soluble derivatives of Δ^9-THC such as the diethylaminobutyric ester (ADL 1137) reported in preliminary tests to have a pharmacologic profile similar to Δ^9-THC (25).

The evidence for the psychoactive properties of Δ^9- and Δ^8-THC is impressive and presumptionally it may be concluded that these are the only active constituents and Δ^9-THC is the compound of primary importance in man (27). Nevertheless, the chemical identity of the numerous plant constituents remains obscure, particularly some unidentified alkaloids, and they should be isolated, identified, and tested. For example, the pharmacologic actions of plant mixtures may differ from the effects of the individual compounds tested singly. It is important to consider these factors in the future systematic investigation of the purified constituents of the plant. Furthermore, inactive compounds may be converted *in vivo* to active compounds by enzyme action or by the presence of chemically unrelated substances in Cannabis preparation. This underscores the need for studies in animals and man.

Many synthetic cannabinol derivatives have been made and investigated pharmacologically in animals and man (16, 26, 28, 29, 30). Some of these compounds produce behavioral effects in man that resemble the effects of natural Δ^9- and Δ^8-THC (28). Mechoulam (16) has reviewed the structure-activity relationships among these compounds. The extensive investigations on synthetic cannabinoid derivatives conducted by the Department of the Army at Edgewood Arsenal have been reported recently (29, 30). These were synthetic derivatives and not the natural substances believed to cause the behavioral effects produced by smoking or ingesting Cannabis or its extracts. These substances are excluded from this report because it is restricted to the pharmacology and behavioral studies of the natural cannabinoids with emphasis on the THCs.

2. Isolation, Identification, and Synthesis of Cannabinoids

There are no direct, rapid methods for the separation and identification of the active THCs and other cannabinoid constituents of marihuana resin. Most of the natural cannabinoids boil within the same temperature range, and separation of the constituents of the active "red oil" (31) by fractional distillation is difficult unless a constituent is present in a comparatively high concentration (21). The structural characteristics of pure compounds have been determined by the use of mass and nuclear magnetic resonance spectrometry, but the separation of the pure cannabinoids requires modern chromatographic techniques, preceded by extraction of the nearly insoluble resin with petroleum ether and other appropriate solvents or separatory procedure (16). Based on sophisticated chromatographic techniques, Gaoni and Mechoulam (32) isolated Δ^9-THC, and shortly thereafter, Hively et al. (33) reported the isolation of a second active constituent Δ^8-THC, generally present in a lower concentration than Δ^9-THC.

Lerner and Zeffert (34) describe a gas chromatographic procedure which makes possible separation and identification of the Δ^9- and Δ^8-isomers of THC from hashish and marihuana. They analyzed a mixture of leaves, stems, and seeds of 14 samples of marihuana, presumed to be of Mexican origin, and on the average found them to contain 1.2 per cent of THC by weight, of which 0.4 per cent was the Δ^8-isomer. A freshly prepared red oil from hashish was found to contain 31 per cent THC of which 3 per cent was the Δ^8-isomer whereas a four-year old sample of red oil con-

tained only 0.8 per cent THC of which 60 per cent was the Δ^8-isomer. The tendency of the percentage of the Δ^8-isomer to increase with the increase or apparent increase in age of the sample, appeared to confirm the observation that Δ^9-THC isomerizes to Δ^8-THC at room temperatures (33) if the change in isomer ratios does not result primarily from the preferential oxidation of Δ^9-THC. Whether Δ^8-THC increases under these circumstances, in absolute terms, is still questionable (35). The chemical characterization of marihuana smoke is under study to identify the breakdown products to determine the nature of the conversion or isomerization of cannabinols and cannabinoids (See Section C6).

To evaluate the changes in the constituents of Cannabis produced by smoking, Miras et al. (36) compared the sublimate obtained from an Ethyl MK VII smoking machine and an extract of the natural product, by column and thin-layer chromatography. They found that cannabidiol which was present in the natural product was missing in the sublimate from the smoke while THC was unchanged. The chemical products in a sublimate, designated as "smoke" but produced by heating a dried extract of hashish at 600° under nitrogen, do not appear to be comparable to the smoke of a marihuana cigarette (37).

(a) Differential Detection of C. sativa

Fetterman et al. (17), using a modification of the Lerner method (34), analyzed manicured samples of nine strains of Cannabis grown for research purposes in Mississippi. On the basis of differences in cannabinoid content these strains were divided into two chemical phenotypes, drug type and hemp type. Although the methods of chromatography have enhanced chemical research on marihuana, the problems of methodology, techniques, and procedure have not yet been resolved.

Simple, rapid chemical tests for the identification of marihuana based on the color reactions with the plant material have been developed. The best known are the Beam reaction (with alcoholic KOH), and the Duquenois (vanillin, acetaldehyde), and Ghamrawy (p-dimethylaminobenzaldehyde) tests (38), none of which is specific for the plant or the active constituents. It has been suggested that the combined Beam and Duquenois tests may be more specific for marihuana. The standard procedure of the Bureau of Narcotics and Dangerous Drugs for the identification

of C. sativa combines a modification of the Duquenois chemical test (39) with a botanical identification of the characteristic cystolith hairs. Although cystoliths of various types are found in many dicotyledonous plants, none of 82 species, which had hairs similar to those of Cannabis, showed a positive Duquenois-Levine reaction (40).

Recently, several simplified thin-layer chromatographic methods have been developed to identify marihuana, particularly the active constituents. One such chromatographic method described by Caddy and Fish (41) used a silver impregnated silica gel. As modified by Turk et al. (42), this technique identifies natural cannabinol, THC, cannabidiol, and "synthetic THC" by color reactions, and is sensitive to concentrations of 0.05 mg.

(b) Isolation and Characterization of Δ^9- and Δ^8-THC Metabolites

The lack of a rapid test for the identification of marihauna users, coupled with the lack of a characteristic identifiable metabolic product of marihuana in man, has made detection difficult. Appropriate analytical methodology has developed slowly partly because reference compounds for thin-layer or gas-liquid chromatography have not been available. This has made it necessary to rely principally on sophisticated chromatographic techniques, mass and nuclear magnetic resonance spectrometry, or on the use of radioactive compounds for detecting and identifying the metabolites of marihuana. The problem is further complicated by the fact that when present in the body fluids, the active constituents are in extremely low concentrations.

By treating a purified extract of Cannabis with tritiated water of high specific activity (5c/ml) Agurell et al. (43) obtained a preparation of 97 per cent pure Δ^9-THC-^{3}H with a specific activity of 41 μc/mg, the remaining 3 per cent of the activity was present in cannabinol. Rats injected intravenously with Δ^9-THC-^{3}H and cannabinols-^{3}H (1.3 to 3.0 mg/kg) eliminated less than 50 per cent of the administered drug during the first week. They found that about 80 per cent of the drug was eliminated in the feces in metabolized form, and the remainder as metabolites in the urine. Although 2 to 6 per cent of the injected activity appeared

in the urine during the first 24-hour period, less than 0.006 per cent cent of the Δ^9-THC, if any, was excreted unchanged. Metabolites of Cannabis liberated by treatment with β-glucuronidase were found (44) in urine of subjects ingesting 750 mg of Cannabis resin. However, Agurell et al. (43) failed to find any glucuronide-bound Δ^9-THC. More recently, Bullock et al. (45) have reported a method in which the Δ^9-THC and other cannabinoids are converted to highly fluorescent dirivatives by condensation with malic acid, permitting detection of 0.6μg total Δ^9-THC added to a 2 ml blood plasma sample.

Burstein et al. (46) injected rabbits with tritiated Δ^8-THC and found several water-soluble substances containing tritium in the urine which they assumed to be conjugates or metabolites of the THC. Mass spectral data for the diacetate derivative of a metabolite suggested an 11-hydroxy THC although they could not exclude the possibility of the aliphatic hydroxyl being located at the C-7 position (See Figure 1). While studying the distribution of ^3H labeled Δ^8-THC in the organs of the rat, Foltz et al. (47) using thin-layer chromatography (TLC) observed several metabolites in liver homogenates from injected rats. Subsequently, with ^{14}C labeled THC they found approximately 13 per cent of the radioactivity in the liver 30 minutes following injection, and of the labeled material, 65 per cent corresponded to the major metabolite. This metabolite had the same R_f value in TLC systems as the metabolite formed in in vitro by the incubation of Δ^8-THC with fortified rat liver microsomes, and identified by means of mass and nuclear magnetic resonance spectrometry as 11-hydroxy-trans-Δ^8-THC. Finally, they synthesized their metabolite from trans-Δ^8-THC and found it to be identical with 11-hydroxy THC.

In a somewhat similar study, Nilsson et al. (48) found at least three major metabolites of Δ^9-THC excreted in the urine of rabbits. Using an essentially similar in vitro system, they incubated [^{14}C]Δ^9-THC with the supernatant from a homogenate of rabbit livers. Following various extraction and TLC procedures, one fraction isolated from the incubated mixture showed 40 per cent of the added [^{14}C] Δ^9-THC had been converted to more polar compounds. A phenolic compound containing 95 per cent of the total radioactivity on the TLC plate was isolated from this fraction. Further TLC procedures finally yielded 20 mg of a semi-crystalline compound of 95 per cent purity identified by its mass and nuclear magnetic resonance spectra as 11-hydroxy THC.

This metabolite, which is described as pharmacologically active in mice, was eventually converted to cannabinol by the same dehydration procedure used by Burstein et al. (46) to convert the metabolite to the inactive cannabinol. By incubating synthetic Δ^9-THC with rat liver homogenates, Wall et al. (49) succeeded in isolating and identifying two separate metabolites produced by the rat liver microsomes. Preliminary behavioral and neuropharmacological screening, presumably in mice, showed one of the metabolites to be as active as and equipotent to Δ^9-THC, while the other metabolite proved to be entirely inactive.

The availability of ^3H and ^{14}C- labeled Δ^9- and Δ^8-THC has assisted in determining the metabolic fate of these two active constituents in marihuana users. Thus the intravenous injection of 0.5 mg [^{14}C]Δ^9-THC into three normal volunteers demonstrated a number of important facts about the metabolism of this compound (50). Metabolites (principally 11-hydroxy-Δ^9-THC) were excreted in the urine one day after administration of Δ^9-THC and about one-half of the radioactivity was recovered in the feces collected for 8 days. Δ^9-THC persisted in plasma for more than three days, and after an initial rapid decline the rate of disappearance was slow with a half-life of approximately 56 hours. Metabolites appeared in the plasma within 10 minutes after injection of Δ^9-THC and persisted along with the precursor compound. It is presumed the Δ^9-THC and the metabolites are stored in lipoids, or other tissues such as the lungs, and this may account for the prolonged excretion of these compounds over the eight-day observation period.

C. PHARMACOLOGY

1. Pharmacologic Classification of Cannabis

Although frequently cited as authoritative references, the classical pharmacologic texts are of little value as sources of information on the pharmacologic actions of Cannabis or its derivatives. As pointed out, the older literature is misleading because pure compounds were not available as reference materials. Consequently, the reports of pharmacologic effects of crude extracts and "synthetic" derivatives in animals and human subjects are unreliable.

Certain generalizations concerning the pharmacology of Cannabis can be drawn from its effects on man and several animal species. The chief site of action obviously is the central nervous system and more significantly the sensorium. A number of somatic effects have been recorded following marihuana use but these are usually mild and the acute toxicity of the drug for man is extremely low. In animals, intravenous doses of marihuana extracts or the active constituents may produce death. However, the insolubility of these materials makes assessment of their toxicity difficult. Intraperitoneal doses are relatively less toxic to animals.

The pharmacologic effects of Cannabis and its various extracts and active constituents appear to be unique and perhaps one result of current research will be characterization of the drug on the basis of its mechanism of action. It has been classified by some writers as a "sedative-hypnotic" but the terms are not properly descriptive because other drugs that do not elicit the effects of Cannabis are traditionally categorized as sedatives or hypnotics. It may not be possible to equate the behavioral effects of marihuana to other drugs although many studies have attempted such a comparison. For example, the sleepy state produced by marihuana obviously resembles the hypnotic effects of numerous central nervous system depressants. The alterations in time sense and cognitive changes produced consistently by marihuana, are experienced only by individuals more deeply sedated by other drugs. Individuals so depressed are quite unable to perform the memory and performance tasks the marihuana user can usually do with some level of achievement.

Dosage is a factor in drug comparisons and depending on the dose a considerable overlap can occur between the dose-effects of marihuana and the dose-effects of other central nervous system drugs. Specifically, most comparisons have been between marihuana and hallucinogenic agents, alcohol, barbiturates, and nitrous oxide. In appropriate doses, these drugs may elicit some of the behavioral effects of Cannabis. Pharmacologically the central nervous system depressants, alcohol, the barbiturates, and anesthetics produce an increasing degree of sedation leading to unconsciousness and death by respiratory paralysis. There is no counterpart of these latter actions produced in man by the natural constituents of Cannabis.

The effects of marihuana have been compared with the actions of alcohol in moderate doses (51, 52, 53, 54). It is true that many of the pharmacologic responses to doses of alcohol equivalent to blood levels of from 50 to 100 mg per 100 ml blood, including the euphoria, uninhibited behavior, and sensory perceptions resemble those elicited by marihuana. The excitement state of induction of anesthesia by the general inhalation anesthetics, e.g., 20-25 per cent nitrous oxide or 3-5 per cent ether in the inspired air, might be compared with the effects of marihuana. However, the differences are more striking than the similarities between these drugs. Pharmacologic similarities between two drugs do not mean that their mechanisms of action are the same even if cross-tolerance exists between the two agents.

Most workers agree that the psychotomimetic or hallucinogenic agents, e.g., LSD, mescaline or psilocybin, produce behavioral changes in the subject that can resemble some of those elicited by Δ^9-THC but which differ in other respects (55, 56). The mechanisms of action of these substances are unknown and future research may clarify these issues. In the meantime, a proper pharmacologic understanding of the unique nature of the marihuana "high" (See Page 47) may resolve much of the present legal, societal, and scientific controversy about this substance.

2. Effects in Animals

In the early studies on the pharmacologic effects of Cannabis extracts animal tests were used to assay the potency of these preparations. A variety of animals was studied, dogs for effects on motor coordination, and rabbits for corneal anesthesia (57). Some in vitro tests on isolated organs with various extracts of Cannabis in comparison with alcohol, morphine, cocaine, and atropine have revealed no unique pharmacologic effects of Cannabis (58). Modern psychopharmacology includes the use of elaborate animal behavioral systems to study the effects of pure Δ^9-THC and related cannabinoids (See Page 39).

3. Absorption, Distribution, Metabolism, and Excretion

To account for the prompt effects of marihuana, presumably the active components of the plant are absorbed rapidly either from the gut or the alveoli of the lungs, and distributed to the effector sites of the central nervous system. Very little is known of this process and blood analyses of subjects or animals under the influence of marihuana have not provided useful data (43). Tissue distribution studies have not been reported in detail but the spinal cord and brain contained very little radioactivity following administration of tritiated Δ^9-THC (16). Successful analysis of these compounds and their metabolites may require extremely sensitive methods if the estimates of an active dose of 2 to 3 nanograms Δ^9-THC/kg are correct (59) (See Page 25).

Presumably, when ingested the cannabinols are largely absorbed from the gastrointestinal tract. Biliary secretion in the rat is for the most part in the form of conjugates, and accounts for the elimination via the feces (16, 47, 60). After intravenous injection of tritium labeled Δ^9-THC emulsified in sesame oil by lecithin and ultrasound, the rat excretes the compound very slowly. Approximately one-half remains in the body for one week and about 80 per cent is excreted in metabolized form in the feces, the remainder as metabolites in the urine. Essentially no unchanged Δ^9-THC was found in the urine. Metabolism and urinary excretion have been reported to be different in the rabbit with polar metabolites excreted chiefly in the urine following administration of Δ^9-THC (about 35 per cent within 24 hours) (16).

The slow elimination of the drug from the body of animals and man is in contrast to the short duration of the pharmacologic effects. Presumably, the drug remains in the body in an inactive form or it may be bound to tissue proteins, because there is evidence that Δ^9-THC combines with plasma proteins (59). The non-polar nature of Δ^9-THC has been cited as the reason this compound may be stored in fat or other tissues (50). It is excreted as polar metabolites in the urine and feces of man.

Metabolites of THC in the blood, tissue or urine of human subjects are beginning to be identified. It is difficult to speculate at this time about in vivo formation of an active metabolite. The concept of an active metabolite is an old one and it has stimulated much work in the field of psychopharmacology. Unfortunately, relatively few active metabolites of psychoactive drugs have been found that appear to play a significant role in exerting a pharmacologic effect in man. The rapid onset of the "high" after smoking marihuana argues against an active metabolite as the only pharmacologically active constituent.

4. Action on Central Nervous System

The electroencephalograms (EEG) of subjects taken after smoking marihuana cigarettes or following parenteral injection of THC have not shown major significant changes. Intravenous injection of 8 mg/kg of Δ^9-THC in rabbits caused restlessness, increased motor activity, and a strong beta rhythm in the electrocorticogram with a lowering of the cortical arousal response threshold (61). These effects were essentially opposite to those produced by morphine in these same animals. Although these two drugs were shown to exhibit analgesic properties in rabbits, apparently their mechanisms of action on the brain are different.

In carefully conducted studies on young male freshman medical students, marihuana smoking in amounts sufficient to produce the usual "high" in experienced subjects, caused only mild or minimal cerebral electrical and neurological changes (62). EEG recordings subjected to detailed analyses to provide mean values and standard errors as well as differences in the power density spectrum curves revealed a minor shift toward the slower alpha frequencies. This kind of decrease in the frequency of alpha rhythm was also observed in an earlier report on marihuana

smoking (63, 64). These changes are not considered very significant and such measures of electrical brain potentials do not reflect the enhanced sensory awareness or the ferment of pleasant confusion within the central nervous system of the marihuana smoker.

Preliminary studies of rapid-eye-movement (REM) sleep revealed only minimal suppression of REM after oral doses of THC. This result resembles the effects produced by some sedative-hypnotic drugs. Additional investigations of REM sleep under the influence of marihuana are necessary.

5. Animal Pathology Studies

Relatively few gross or microscopic pathologic studies have been made in animals after acute or long-term administration of Cannabis extracts or the pure active components of the plant. Complete histologic tissue studies and biochemical determinations should be conducted to determine the toxicity of these compounds. Information of this character is necessary to meet the U. S. Food and Drug Administration regulations prior to testing these compounds in man.

Morphologic changes in the central nervous system are not likely to be found following behavior modifying doses of marihuana because the evidence suggests that all psychopharmacologic agents exert their actions through some biochemical mechanisms which do not distort cell architecture. The early reports of "brain damage" caused by acute marihuana use have never been substantiated. A clear distinction must be made between the pathologic effects of marihuana smoking in the healthy young adult and the aged individual who has smoked or eaten marihuana for many years. The definitive answer can not be given until histopathologic evidence is accumulated from post-mortem examination of young marihuana smokers following accidental death and old chronic users. In this respect the problem of determining the toxicologic effects of marihuana use resembles the problem of assessing the effects of acute and chronic alcohol consumption in contemporary society.

6. Modes of Use

(a) Oral

The active components of the numerous preparations of marihuana, hashish, and related forms of Cannabis used as an intoxicant by man, are absorbed more slowly from the gastrointestinal tract than from smoke. European, Asiatic, and African cultures sometimes employ the drug as a drink or as a constituent of a sweetened cake. In North and South America smoking the dried leaves and natural plant parts is the most common form of administration. The effects of crude extracts of the plant ingested orally cannot be equated with smoking the dried leaves and stems because the rate and degree of absorption, and hence the onset and duration of action, are related to the route of administration. More rapid and complete biotransformation of active constituents may take place in the liver following oral administration of marihuana. Any behavioral study of the effects of marihuana must take into consideration the influence of the route of administration.

(b) Smoking

Because smoking is the most common mode of use of marihuana in our culture, considerable attention has been given to the dosage aspects of this route of administration. Inhalation of volatile compounds as gases, aerosols, or smokes provides intimate contact with the alveolar membranes of the lungs and a prompt absorption into the pulmonary circulation. Administration of drugs by inhalation approaches intravenous therapy in rapidity of action, and the dosage may be roughly equivalent. The pharmacologic effects of tobacco and a number of therapeutic agents are achieved quickly by this easy route of administration.

Marihuana cigarettes differ from tobacco cigarettes in that they are handmade, and thinner to conserve the smoking mixture. The smoker rolls his own cigarette using two papers so as not to lose any marihuana or puncture the paper; thus the cigarette draws poorly and burns more slowly. Depending on the cost, the paper may range from crude brown paper to a finely crafted paper with a special degree of porosity to permit more

air to enter the smoke stream to cool the smoke. After the cigarette is made it is wetted with saliva to slow the burning process, and lighted in a unique way; because the cigarette is unevenly packed, it is necessary to ignite the end evenly to insure slow, complete burning.

(1) Method of Smoking

The technique of smoking marihuana is not the same as smoking tobacco and is highly individualistic. The goal is to utilize and consume the marihuana to the maximum. All the smoke is to be inhaled deeply into the lungs, whereas in tobacco smoking much is simply lost into the air in the so-called side-stream smoke. Again, unlike tobacco smoking, aroma, bouquet, and related esthetic aspects of smoking are not deemed significant. The deep inhalation of the smoke carries the active aerosol into the finer recesses of the bronchi and alveoli. The pharynx and the fauces may be irritated by the nature of the smoking technique and the smoke, and the experienced smoker learns to inhibit the cough reflex and to prevent laryngospasm.

In the smoking process air is inhaled simultaneously along with the smoke by holding the cigarette in the lips and allowing the proper amount of cooler ambient air to admix with the smoke. This technique is useful because it apparently causes an additional condensation of the aerosolized particles in the smoke to coalesce and adhere to the mucous membranes of the mouth, throat and bronchi. The tidal volume and the functional residual lung capacity of the smoker may influence the final dose of the drug.

Having inhaled the smoke the inhalation is maintained and voluntary, forced apnea is produced until it appears impossible to hold the breath longer. Even then, a brief additional inspiration is forced to keep the smoke in the lungs moments longer. Experienced smokers have learned to use the Valsalva maneuver to increase absorption from the lungs. Obviously, all this becomes a highly refined, learned experience for the smoker. The degree of penetration of the alveolar network by the smoke must be great and the solubility of the active components in the smoke in the blood must be high to account for the prompt effects of marihuana smoking.

A single cigarette may be passed from one smoker to another, usually while the inspiration is maintained, in order to utilize efficiently all the products of combustion of a single cigarette. In this manner, three to four people may consume one cigarette. By the time the cigarette has been sequentially smoked and returned to the original smoker, he in turn has exhaled and is prepared for another deep "drag." Depending on the potency of the marihuana, the dose distribution among three to four smokers of a single low-potency cigarette smoked in this manner is not likely to produce a "high." On the other hand, one cigarette of very potent marihuana is reputed to produce the desired effects for as many as five smokers---presumably very experienced, and using the most efficient smoking techniques.

The habitué recognizes the distillation of active resins into the butt of the marihuana cigarette---referred to as a "roach." These are much shorter than tobacco cigarette butts and may be only ¼ inch long. A roach can be smoked by one of several ingenious methods that consume the entire cigarette and the smoke is inhaled so that essentially none of the active ingredients is wasted.

Pipe smoking of marihuana is even more individualistic than cigarette smoking and numerous styles of pipes and techniques are employed. Thus the pipe smoker, if smoking alone, will extinguish the burning marihuana between inhalations while he holds the smoke in his lungs. Each puff requires him to re-ignite the pipe. The smoking process is changed, but the smoker has the same goal as the cigarette smoker---to achieve the maximum dose effect from the least amount of burned drug.

(2) Dose-Effect Response to Smoking

Some observations suggest two qualitatively different effects of marihuana---one produced by smoking, and another resulting from oral ingestion. The former may be modified by the oxidation of volatile constituents in the smoke and the latter by degradation in the body of the subject when the substance is eaten (65). On the other hand, Isbell et al. (27, 55) did not find qualitative differences between smoked and orally administered Δ^9-THC.

The relations between the constituents of marihuana and interconversions under the high temperature of smoking have been studied but are not fully elucidated. It is recognized that THC is more potent when smoked than when ingested orally. In general, smoking produces effects within a few minutes and the desired effects last for an hour or more, depending on dose. The experienced smoker may control his initial dosage according to the effect desired. Oral dosage of equivalent amounts of marihuana preparations will not elicit pharmacologic effects for 30 to 60 minutes; however, the actions last much longer.

(3) Analyses of Marihuana Smoke

The devices and techniques developed for the study of the constituents of tobacco smoke have been applied to analyses of marihuana smoke. Relatively few reports have appeared but some significant information is available. Pyrolysis of Cannabis has been studied in order to ascertain the basic elements of marihuana smoke (See Page 24).

Tobacco cigarette smoke has been analyzed by several methods (66). The complex mixture of gases and particulate matter composing the smoke of a cigarette is difficult to trap and analyze. Chemical reactions taking place in smoking are influenced by numerous variables, e.g., the cigarette paper, rate of puffing and the amount of air drawn through the lighted cigarette. These factors are complicated in the case of the marihuana cigarette smoker, because as noted previously, the cigarettes are made on an individual basis and the technique of smoking is a personal matter.

Manno et al. (67) prepared a 10 mg Δ^9-THC cigarette by mixing 250 mg of test marihuana with 250 mg of placebo (extracted) marihuana. The cigarettes were made by hand, sealed under nitrogen and stored at 0°F until used. By analysis of the smoke and insuring the complete smoking of the butt, they calculated that approximately 50 per cent of the Δ^9-THC originally present in the cigarette was delivered unchanged in the smoke. The remainder of the THCs originally present was converted to cannabinol or cannabidiol as detected by gas chromatograms. They separated the Δ^9- and Δ^8-THC isomers and did not find any increase in the Δ^8-isomer in the smoke. They concluded that approximately 5 mg of Δ^9-THC was ultimately delivered to the smoker---an administered dose of 50 to 75 μg/kg.

In an attempt to determine the nature of some of the major constituents of marihuana smoke, other workers have prepared a model 1-gram cigarette containing 12 per cent moisture, with 14-second paper, 68 mm long, composed of cut, manicured 1.4 per cent THC content marihuana leaves of 8 to 25 mesh size. A smoking machine consumed the cigarette in a series of 35 ml puffs of 2-second duration every 60 seconds. The gas phase, by convention, is all the gaseous material that passes through a standard Cambridge fiberglass filter pad that collects particles 0.3 μ or larger. These are essentially the standard procedures and conditions recommended for analysis of tobacco cigarettes by the U.S. Federal Trade Commission (68). The total combustion products of tobacco cigarette smoke from both sidestream and mainstream smoke have been determined by this procedure (69).

In one series of preliminary analyses approximately equal amounts of Δ^9-THC were recovered in the sidestream and mainstream smoke. The sidestream smoke is defined as the cigarette smoke produced during static burning---the subject receives only the mainstream smoke when puffing. Measured as non-gaseous total particulate matter (the material collected on the Cambridge filter), about 21 per cent of the total Δ^9-THC in the cigarette was found in the sidestream and about 21 per cent was in the mainstream smoke. Approximately 52 per cent of the Δ^9-THC remained in the 20 mm butt indicative of the accumulation of active compounds in the unsmoked butt.

It was a significant conclusion of this study that very little Δ^9-THC was pyrolyzed during smoking. In this model cigarette, 95 per cent of the total Δ^9-THC was accounted for in the smoke and the butt; the remaining 5 per cent was considered to have been pyrolyzed. There is some evidence that Δ^9-THC may be converted to the equally active Δ^8-THC by heat and perhaps interconversion of other cannabinoids takes place during the process of smoking (33). This subject requires additional study (See Page 24). The validity of the technical aspects of this study seems assured because radioactive labeled compounds in tobacco cigarettes were recovered without appreciable loss by these techniques. The analyses for Δ^9-THC and total THC content were made by gas chromatography.

Several significant points have emerged from the study of the composition of marihuana cigarette smoke. Presumably, in experimental situations the irritating qualities of the smoke, the experience of the smoker and indeed, the enthusiasm of the subject for the experiment will influence the quantity of inhaled smoke and hence the dose available for absorption. Depending on these variables, the smoker may inhale from 15 to 100 ml per inhalation. Thus, the tidal volume of each subject should be measured along with his usual inhalation volume when smoking. In addition, unlike tobacco smokers, marihuana smokers hold the inspiration until relatively little visible smoke is exhaled. Experiments have been conducted on these aspects of marihuana smoking and it is generally agreed that tidal volume and inhalation time should be recorded by the experimenter.

In general, quantitatively it appears that in experienced smokers Δ^9-THC is from three to four times more potent when smoked than when taken orally (27). This work should be repeated and extended. The most satisfactory manner to determine the degree of absorption of Δ^9-THC from cigarette smoking at the present time is to use the ^{14}C-labeled compound in the cigarette. Following standardized procedures as noted, it may be possible to measure the blood and urine levels of radioactive compounds and estimate the half-life of the drug. Such a study would give a better estimate of the absorption, distribution, and excretion of the active compounds from smoking than is available at the present time.

Difficulty in preparing a satisfactory "placebo" cigarette to be used in double-blind experiments with marihuana cigarettes has plagued investigators (51, 70). Experienced marihuana smokers are usually, although not always, able to identify the marihuana cigarette after a few inhalations (52). Observers also are able to detect the characteristic odor of marihuana. Manno et al. (67) reported that solvent extracted marihuana was entirely satisfactory as a placebo in their single blind experiments with subjects who smoked a placebo or a Δ^9-THC treated cigarette. Cigarettes prepared according to their method did not differ in taste, burning character, smell, or appearance from the test marihuana cigarette. A wide variety of other plant substances has been tried, e.g., oregano, tansy, catnip, and tobacco laced with other herbs. Most investigators report these placebo substitutes as unsatisfactory.

D. MEASUREMENT AND EVALUATION OF CANNABIS EFFECTS

1. Animal Behavioral Tests

Gross behavior of animals as recorded by trained observers is perhaps the most useful means to detect subtle drug-induced behavioral changes (71, 72). Simultaneous measurement of the multiple effects of a drug, the physiologic state of the animal, and numerous environmental factors require an astute diagnostician. Variability of individual animals in response to drugs is great and outweighs the precision of experimental apparatus to record events. The former is beyond the investigator's control and resembles the clinical situation where the personality and attitude of the subject are important in determining the effects of marihuana or other psychoactive drugs.

Marihuana extract has been reported to decrease fighting behavior in mice and rats in doses that do not reduce total activity of the animals (73, 74). However, in similar studies starved rats injected with marihuana extract exhibited an increase in aggressive behavior though chronic starvation or repeated injections the marihuana extract alone did not produce this aggressive behavior (75). One report states that maze performance of Wistar rats was improved by injecting marihuana extract (76). This effect may have been caused by enhanced motivation resulting from increased appetite. Maze systems might be useful in testing memory responses of animals as modified by Cannabis administration.

Ataxia produced in the dog has been used for many years to bioassay the potency of crude marihuana extracts (57, 77). Postural behavior, estimated by the animal's ability to maintain the upright position, leg and body movements associated with standing or walking and changing body positions are rated by an experienced observer. In spite of the subjective nature of the test, Loewe (57) was successful in estimating the potency of marihuana products with an "accuracy of 10-15 per cent." The dog ataxia test is not used because more satisfactory tests are available.

Relatively few informative studies have employed the classical behavioral tests, e.g., operant schedules of aversive or reward type, to uncover the psychopharmacologic actions of Cannabis

or its constituents. Presumably, all the behavioral techniques used with some success in the discovery of new psychoactive drugs or understanding the mechanisms of action of psychotropic agents, can be applied to this question (71).

Boyd et al. (78) compared the effects of synthetic THCs with pentobarbital, chlorpromazine, and d-amphetamine over a range of doses, on the patterns of operant behavior generated in rats by several schedules. Drug effects varied greatly with the type of schedule used and the parameters of the test situation, and it was difficult to interpret "depression of behavior" or "stimulation of behavior." The THCs depressed all measures of behavior except time judgement. These compounds appeared to increase the ability of rats to judge elapsed time accurately. These observations are difficult to correlate with the recognized pharmacologic actions of marihuana.

Schedule-controlled behavior was studied in pigeons using key-pecking rates with a multiple fixed-ratio 30 response, fixed interval 5-minute schedule of food presentation(79). The effects of Δ^9-THC, 1', 2'-dimethylheptyl THC, and n-hexyl THC were measured two hours after intramuscular injections. The drugs injected once a week for seven weeks all caused a marked decrease in rate of responding under both schedules, and tolerance developed with cross-tolerance among drugs.

In comparable studies there was observed a similar tolerance to repeated injections of Δ^9- or Δ^8-THC (80). Pigeons trained to key peck under a multiple fixed-ratio, fixed interval schedule for food, did not key peck for at least 4 hours after injection of Δ^9-THC. Normal rate of pecking gradually returned after 5 to 8 daily injections. Subsequent large increases in dosage did not cause a decrease in pecking rate when administration was only three times per week. These tolerant birds were also tolerant to Δ^8-THC, whereas nontolerant birds did not key peck for more than 24 hours after the same dose of Δ^8-THC.

Scheckel et al. (81) studied the behavioral effects of Δ^9- and Δ^8-THC in rhesus and squirrel monkeys with operant conditioning techniques. Continuous avoidance behavior was stimulated by both compounds, but high doses of Δ^9-THC also caused depression after the stimulant phase. Complex behavior involving memory and visual discrimination in rhesus monkeys was markedly

disrupted by these agents. In general, these substances caused stimulation, depression, apparent hallucinations, and the loss of ability or motivation to perform complex tasks. It is of interest that these workers report that the d, l-racemates of Δ^9- and Δ^8-THC have essentially the same activities as the synthetic levorotatory isomers.

The long-term behavioral effects of oral doses of Δ^9-THC in the chimpanzee are under study (82). A behavioral baseline for each test has been established using a multiple schedule; differential reinforcement of low rate, fixed-ratio, and a time-out from positive reinforcement schedule. The peak time for drug effects, duration of drug action and prolonged effects can be detected in this manner in these animals. These experiments demonstrated that a marihuana extract distillate administered orally in doses equivalent to 0.2 to 4.0 mg/kg of Δ^9-THC produced both stimulant and depressant effects on reinforcement schedule-controlled operant behavior in the chimpanzee. In similar studies a statistically significant facilitation of differential reinforcement of low-rate responding was obtained with an oral dose as low as 0.4 mg/kg of Δ^9-THC. It was concluded that the minimum effective dose of Δ^9-THC for the chimpanzee is comparable to the effective oral dose for man.

These studies on the chimpanzee will be useful in determining if tolerance, cumulative toxicity, or abstinence syndromes develop upon abrupt withdrawal of the drug after a period of prolonged administration. In addition, the opportunity for tissue pathology studies exists at the termination of the experiment. Studies in these higher primates may be most rewarding and informative.

It is difficult to appraise these various animal behavior reports in terms of the behavioral actions of marihuana on man. There remains a need for more satisfactory behavioral tests in animals to screen the isolated derivatives of Cannabis as they become available for laboratory studies.

2. Behavioral Tests on Man

Modern studies emphasize quantitative measures to determine somatic, perceptual, and psychic changes, and the resultant behavior and performance of the marihuana user. The

precise determination of drug-induced behavior changes is beset with enornous difficulties. These derive from three variables: (a) the validity or reliability of the techniques and methodology used for assaying subjective or behavioral effects, (b) the personality and the "set" of the subjects, and (c) the environment or "setting" in which the measurements are made.

In addition to the classical clinical tools for determining physiological effects, investigators have used a wide variety of psychological methods to measure perceptual, subjective, and behavioral changes. The first major attempt to quantitate the physiological and psychological effects of marihuana, employed a number of well-established tests and procedures (83). In these early studies, Morrow (83) measured performance with tests available at the time such as the Miles Ataxiameter for measuring static equilibrium, and a Whipple Steadiness Tester for hand steadiness, adapted for testing motor activity as a function of tapping speed. The Galton whistle was used to test auditory acuity. This latter study may be compared to the modern, sophisticated approach by Caldwell et al. (84) who fitted their subjects with a pair of stereo headphones that received an input from an audio oscillator in series with a step attenuator. The subjects received, through one ear, a signal tone of constant duration (0.5 sec.) and frequency (1.000 Hz) progressively attenuated and decreased to establish an absolute tone threshold of the individual.

Morrow (83) measured changes in space and time perception by having subjects estimate the length of 3, 5, and 8 inch lines, and also by estimating 30-second, 60-second, and 5-minute intervals, and the time to complete a simple task. Fundamentally, these latter two methods measure time perception. The subject can provide either an estimate of a given time interval or he can give his estimate of the time elapsed to perform a given task. The subjects in Morrow's study were able to estimate short intervals of elapsed time quite accurately; they enormously overestimated the time they required to perform a two-minute task. Thus the nature of the test often causes a bias in the results or masks the actual effects produced by the drug.

Halpern (83) tested intellectual functioning using Form Boards, a Geometric Forms Cancellation Task, and the Pyle's Digit Symbol Test. To test the effects of marihuana on memory

subjects were required to calculate digit sequences forwards and backwards, while their ability of recall was evaluated by having them identify various objects following a 3-second examination, or to reproduce designs observed during a 10-second interval. The emotional reactions and general personality structure of the subjects was explored by means of the Rorschach Test, by having them perform simple tasks for which they supplied their own estimates for completion times, and by assigning them frustrating tasks in the form of insoluble maze problems. The Wechsler Free Association Test, based on words with assumed emotional impact, was used to measure attitudes of guilt, anxiety, and fear. The Binet Lines Test, which purportedly tested the susceptibility of the subject to suggestion, failed to establish any consistent relation between dosage and effect. It is of interest to note that Abramson et al. (85) reported that early in their experiments they observed certain subjects gave positive results only when a placebo was administered. The placebo reactor is now well recognized in psychological drug testing.

In the first demonstration of hashish-like activity of pure Δ^9-THC and in a subsequent comparative study of the effects of Δ^9-THC and LSD-25, Isbell et al. (27, 55) measured somatic changes (rectal temperature, pulse rate, blood pressure, knee-jerk threshold, pupillary diameter) by the usual clinical procedures. They determined subjective effects with measures of personality and mood typically regarded as important determinants of drug effects by means of a 63-item questionnaire. Thirty of the questionnaire items constituted 10 from the "general drug," "marihuana," and "LSD" scales of the Addiction Research Inventory while the remaining 33 questions dealt with alterations in mood, distortion and sensory perceptions, alterations in body image, illusions, delusions, and hallucinations, and were designated as the "psychotomimetic scale" (86).

It is obviously important to define the subjective changes induced by marihuana, nevertheless, the subjective responses still must be related to behavior and more specifically related to performance under operational conditions.

To measure somatic, perceptual, and psychic reactions, Hollister et al. (28) used a Symptom-Sign Questionnaire previously designed for studies with psychotomimetic drugs, as well as

tape recordings of brief conversations to evaluate subjective clinical symptoms resulting from the oral administration of Δ^9-THC. The self-reporting Clyde Mood Scale was used to measure factors listed as friendly, aggressive, clear-thinking, sleepy, unhappy, and dizziness. The distinctive patterns of intellectual impairment were estimated by two forms of the Repetitive Psychometric Measures which the authors have found to be sensitive to the effects produced by psychotomimetic drugs, the Number Facility Test, and the Flexibility of Closure Test. Muscle strength was measured with a finger ergograph by having the middle finger of the right hand act against a fatiguing load for one minute.

To study temporal disintegration produced by the oral administration of Δ^9-THC associated with impaired immediate memory and disorganized speech and thinking, Melges et al. (87) used a Goal Directed Serial Alternation Task which required the subject to hold in his mind, and simultaneously coordinate, rather simple arithmetic manipulations and information relevant to a short-term goal.

After doses of marihuana extracts that produced effects ranging from barely perceptible subjective changes to a mild high, Clark and Nakashima (88) used a battery of tests to measure performance changes. These included hand and foot reaction time to simple and complex visual signals, ability to learn a digit code, estimates of depth perception by positioning white rods at 16 feet, visual flicker fusion tests, auditory frequency discrimination, duration of afterimage induced by the Archimedes Spiral, visual motor coordination measured by a pursuit motor apparatus, and a mirror pattern tracing task. These tests either proved insensitive to the effects of the drug or produced markedly variable results.

Weil et al. (70) used a comprehensive battery of tests in measuring the effects of smoked marihuana on naive and chronic users. A self-rating Bipolar Mood Scale was used to evaluate subjective effects, a Continuous Performance Test in which subjects identified critical letters on a screen served to measure sustained attention, while a Digit Symbol Substitution Test provided a test of cognitive function. In addition to a Rotor Pursuit Test measuring muscular coordination and attentiveness, subjects recorded verbal samples which were used to judge their ability to estimate time intervals. Difficulties are inherent in laboratory

studies designed to evaluate changes in behavior and performance produced by marihuana, and the authors attempted to provide a neutral setting and controlled conditions of dosage and testing. However, inadequate consideration may have been given to the potency of marihuana, the experience of the subjects with marihuana, and smoking techniques (89). In a subsequent study, Weil and Zinberg (90) used recorded verbal samples, mutilated by the Cloze method, to measure the effects of marihuana on immediate memory and speech. These studies are of considerable interest because they revealed subtle speech and memory effects of marihuana.

In a study comparing the effects of marihuana and alcohol on driving performance, Crancer et al. (51) used a modified driving simulator test to approximate field conditions. They monitored the reaction times of "intoxicated" marihuana smokers who were presented a programmed series of emergency driving situations on a large screen. The potency of the marihuana used in this study was not established. Even though realistic models are an improvement for measuring performance, the importance of set and setting and other considerations make these laboratory data unlike performance on equipment in the field.

The chief psychological measure in a recent study by Waskow et al. (91) was the Subjective Drug Effects Questionnaire designed to detect thinking, feeling, perceptual effects, and somatic changes that may occur following psychotropic drugs and at the same time minimize the effects of experimenter suggestion. In addition to many of the tests and measurements that have been described, Jones and Stone (52) used a Rod and Frame Test. In a darkened room, a luminescent rod and tilted frame is presented to a dark-adapted subject who is instructed to move the rod to a vertical position. The task is designed to measure ability to attend to relevant internal cues and to exclude irrelevant external cues. The scores reflect the independence or field dependence of the subject. In a somewhat related study, largely on theoretical considerations linked to the common subjective changes induced by marihuana, Dinnerstein (92) suggested that marihuana induces a perceptual-cognitive style of field dependence.

Manno et al. (53, 67) in their studies on the effects of marihuana and marihuana-alcohol combinations have used the pursuit meter and the delayed auditory feedback (DAF) as measures of motor and mental performance. The pursuit meter consists of

a dual beam oscilloscope with one beam pre-programmed and the second beam attached to a steering device. The subject's task is to superimpose one beam on the other during ten sweeps of the pattern. The DAF is arranged so that the subject's voice plays back in his ear through headphones 0.28 seconds after he speaks. These authors employed a battery of nine different verbal tasks with the DAF.

In this short summary of typical testing procedures used in evaluating the psychic and physical effects of marihuana, the principal objective has been to present a cross-section of the variety of methods utilized by investigators in their attempts to quantitate the responses to marihuana use. Whether or not the results of laboratory testing procedures of performance can provide the proper criteria for predicting performance, with ordinary or sophisticated military equipment in military field operations, is an unresolved problem.

E. EFFECTS OF CANNABIS ON MAN

The first comprehensive behavioral study on the effects of hashish was undertaken by Moreau in 1845 who described most of the sensory effects from experimental human studies (93). Habitue's of Cannabis have written volumes of colorful descriptions of the sensory intensification they have experienced while under the influence of the drug. Attempts to describe more accurately the behavioral effects have been made periodically beginning with the Indian Hemp Drugs Commission Report of 1894. A summary of this work has been published recently (94). The Commission Report noted that there did not appear to be a relationship between the use of "hemp drugs" and insanity, but it did outline many of the subjective and perceptual effects in chronic users. Cannabis smoking by "non-habituated" individuals in an addiction clinic in 1936 produced a series of experiences that have been recorded only recently (95). The symptoms were essentially those reported by marihuana smokers in the United States and were dose related. The LaGuardia Report of 1944 noted the characteristic mental state of well-being, relaxation, and unawareness of surroundings, followed by drowsiness produced by marihuana smoking (83).

1. Description of the "High"

The subjective and perceptual effects in the euphoric state, or "high," produced by smoking marihuana is illustrated by the following description:

> "A marijuana high usually lasts two or three hours, during which a wide range of effects may occur, varying both in intensity and quality. The usual, most noticeable effect is intensification of sensation and increased clarity of perception. Visually, colors are brighter, scenes have more depth, patterns are more evident, and figure-ground relations both more distinct and more easily reversible. Other sense modalities do not have the variety of visual stimuli, but all seem to be intensified. Sounds become more distinct, with the user aware of sounds he otherwise

might not have noticed. Music, recorded and live, is heard with increased fidelity and dimension, as though there were less distance between the source and the listener. Taste and smell are also enhanced under marijuana. The spice rack is a treasure of sensation, and food develops a rich variety of tastes.

"Skin receptors are also effected (sic). Heat, cold, and pressure receptors become more sensitive. Pain produces paradoxical effects. If attention is not on the area of pain, there is a reduced sensitivity to the hurt. But awareness of pain from a lesion, such as a burn or cut, will often persist for a longer period than usual, even allowing for the changed perception of time under marijuana.

"Awareness of proprioceptive responses is enhanced. The person using marijuana may become aware of usually automatic, non-conscious, muscle tensions, small movements, feedback and control processes, and feelings of physical comfort and discomfort. These can be perceived with great clarity and distinctness" (96).

2. Somatic Effects

Several clinical, physiological, and biochemical measures have been made following smoking marihuana or THC-treated cigarettes. Tachycardia appears to be a most consistent change. However, in addition to the classical clinical measures, sophisticated neurophysiological and biochemical studies should be made for they may reveal subtle central nervous system effects that have eluded earlier investigations. The following effects have been studied:

(a) Pulse

The resting radial pulse rate usually increases about 10 per cent with the onset of the first reported subjective effects of smoking marihuana. As the intensity of the drug effect increases, the pulse rate accelerates and larger doses produce correspondingly

greater tachycardia (53, 95). The increase in the pulse rate parallels the intensity of the subjective effects (27).

(b) Conjunctival Blood Vessel Dilation

A conjunctival vascular congestion is one of the most constant recognizable signs following marihuana smoking (27, 53, 95, 96). The degree of vascular dilation is related to the dose of the drug. There does not appear to be any satisfactory explanation for this selective vascular effect that causes the smoker's reddened eyes. The vascular dilation outlasts the tachycardia but does not last for days (53). In India the injection of the transverse ciliary vessels is considered an important sign of ganja use and has been reported present for years after the drug was withheld (8).

(c) Skin Temperature

Accurate measurements of the skin of the fingers and toes have consistently shown a decrease in skin temperature.

(d) Salivary Flow

A dry mouth and throat is generally reported by the marihuana smoker. This does not appear to be entirely related to the irritating nature of marihuana smoke or the technique of smoking. A decrease in salivary flow has been recorded in some carefully conducted studies and appears to be a pharmacologic effect of the drug. The influence of Δ^9-THC should be determined for a number of physiologic functions controlled by the autonomic nervous system.

(e) Blood Pressure

Changes in systolic or diastolic blood pressure are not consistent following use of marihuana. Reports vary, some workers report an increase in systolic pressure (94), others a decrease or no change (27).

(f) Blood Sugar Levels

The increased appetite frequently described by the marihuana smoker has been suggested as related to a fall in the blood sugar level. Numerous reports have noted no significant changes in the blood sugar levels of subjects after smoking marihuana of known potency and at times when they experienced the major somatic and subjective effects (27, 53, 95). Hunger and thirst may result from the actions of the drug on the hypothalamus and may not be related to biochemical metabolic changes *per se*.

(g) Pupil Size

Contrary to some reports, the pupil diameter is not changed by a dose of marihuana that produces behavioral effects (95, 96). The tests have not included refined measures or pupillometry and these should be conducted. Photographic measurements of pupil diameter after Δ^9-THC or marihuana extracts have not revealed significant changes (27, 28, 84). However, there does not seem to be a significant or characteristic pupil response in man.

(h) Achilles Tendon Reflex

The patellar and Achilles deep tendon reflexes are not modified in the marihuana smoker while under the influence of the drug (27, 83, 94).

(i) Diuretic Effect

Oral doses of a Cannabis extract have been reported to be effective as a diuretic with increased sodium and bicarbonate loss in young healthy subjects (8, 64).

(j) Gastrointestinal Symptoms

Nausea is commonly reported by subjects receiving large doses of the active components of Cannabis either orally or

by smoking. The prior experience of the individual may determine the occurrence of nausea, vasomotor imbalance as reflected in pale skin color, and sensations of cold extremities, or vomiting. Knowledgeable subjects usually titrate their dose to avoid these symptoms and undesirable overdosage effects (27, 83, 95).

3. Subjective and Perceptual Changes

In the field of psychopharmacology the assessment of the behavioral effects of the therapeutically useful psychotropic agents in man requires the use of a large number of psychologic tests. These drugs are used in the psychoneuroses and the psychoses to modify abnormal human behavior and it is necessary to evaluate the effectiveness of drug therapy by measuring the subjective and perceptual changes in the mentally ill patient. Very considerable skill has been developed by the clinical psychopharmacologist, the clinical psychologist, and the psychiatrist in rating behavioral change of patients under drug therapy. These same techniques and skills can be utilized in detecting and evaluating behavior changes, both subjective and perceptual, in otherwise normal individuals under the influence of Cannabis. Most of the experimental studies on the behavioral effects of marihuana smoking on man have been conducted by workers from the field of psychopharmacology.

(a) Factors Modifying Behavioral Effects of Drugs

Obviously the physiological makeup of the individual influences drug responses. In addition, psychological factors modify the effects of drugs, e.g., personality, intelligence, attitude, mood, and expectations of the user. These parameters are commonly included in the "set." Furthermore, the environmental "setting," e.g., group interaction versus solitary contemplation, or a mentally demanding milieu versus a relaxed situation, play important roles in determining the behavioral effects of drugs (97).

Individual differences in response to marihuana have been noted (27). Most studies have compared groups of subjects, e.g., naive versus chronic smokers; however, it is important to study the patterns of subjective and perceptual effects in individual subjects. In addition, dose-effect responses in the same person over time may change even though doses of the drug are the same.

It is especially difficult to control the expectations a volunteer subject brings to experimental studies of marihuana effects. Behavioral drug effects are influenced very significantly by the symbolic nature of drug use as well as the social situation. For these reasons the extrapolation of laboratory studies to real life environments is difficult. However, subjective effects in the laboratory were very similar to those reported by questionnaires submitted by marihuana smokers (98).

Illustrative of the type of problem that confronts the investigator in this field is the need to have informed subjects. Some studies have been made with marihuana using former narcotic addicts who were exceedingly knowledgeable of the characteristic subjective and perceptual effects of the drug. However, the interpretation of the results of even very carefully controlled behavioral tasks in these subjects may be called into question if these data are applied to "normal" subjects in the general population. Because environment can be manipulated, most studies have been made on young, experienced marihuana users in a controlled laboratory setting.

Prior marihuana use by the subject modifies the subjective effects produced in a laboratory test or in the social use of the drug. Reports do not define "use," "repeated use," or "chronic use" of the drug and it is essentially impossible to ascertain what is meant by these words. The lay press and psychiatric reports employ these terms to describe prior marihuana use by subjects participating in laboratory studies. Nevertheless, until biochemical measures or neurophysiological tests are available it will not be possible to establish a control base for behavioral studies of marihuana in man. A major emphasis for research in this field should be on objective measures of drug metabolism, analytical biochemical tests, and neurophysiological or neuropharmacological measures of drug actions. This information will undergird the behavioral studies that may be undertaken to provide a proper recognition and comprehension of relevant altered states of consciousness associated with the drug experience.

Behavioral studies must have valid controls. There is a need for an adequate "standard-dose" cigarette for marihuana smoking studies. The rather unique smoking techniques combined with the unusual nature of marihuana smoke itself makes it very difficult for the research investigator to employ an "active" placebo in experimental studies. A true placebo cigarette would be one that looks, tastes, and smells like a marihuana cigarette but is pharmacologically inactive. Such a placebo cigarette to be used in conjunction with a "standard-dose" marihuana cigarette would be extremely useful to research workers.

(b) Experimental Studies

The ideation or feelings of a person resulting from use of a drug, i.e., the subjective response, are perceptible only to the person himself. Despite the variation of dosage and use by many types of individuals, there is a general agreement about the major subjective effects of marihuana, especially marihuana smoking. These have been described in various ways, but the outstanding features are a sense of elation and euphoria with a feeling of relaxation and tranquility; presumably this accounts in part, but not totally, for the attractiveness of marihuana. There follows a dream-like state with a feeling of depersonalization that may be associated with an intensified sensory input, especially stimuli arising from the immediate environment. Intensification of perception of the sexual experience is frequently cited by habitués as a reason for marihuana smoking.

This altered state of consciousness produced by behavioral drugs has been compared to the rapture of the mystic or the transcendental state familiar in Eastern cultures. Uncontrolled mirth and difficulty in maintaining the attention span or rapid cognition, are often symptoms of the subjective effects of marihuana. These symptoms are intermixed with pleasurable perceptual changes and somatic effects, and were described most elegantly for hashish by early authors in the 18th and 19th centuries.

Careful physiological and psychological studies on former narcotic addicts after daily smoking unlimited amounts of marihuana support the general concept that the effects of the drug are characteristically those of gaiety and euphoria. However, the need to increase the amount of smoking over the 39-day study was observed if the subject wished to recapture the initial desirable effects (63).

The subtle discrimination of sensory impressions that relates to awareness of one's surroundings or objects is modified by marihuana smoking. As a result, time is lengthened and space is broadened; seconds may seem minutes and distances to near objects appear remote. It is understandable why mental attention or cognitive skills may be reduced in a subject experiencing such perceptual variations from the norm. The evaluation of these effects poses a challenge for the investigator.

Commands requiring perceptual functions, such as communications in military field operations, may be misinterpreted and erroneously carried out as a result of these distortions of time and space. Objective tests have been developed to measure these changes in an individual under the influence of drugs (See Page 41). Sensory modalities such as visual and auditory thresholds have been evaluated but have not proved to be significantly changed (99). These perceptual studies have not differentiated between sensory input and the subject's own evaluation of that sensory input. The evidence indicates the stimulus is received on the same quantitative level as the normal subject, however, the marihuana user interprets the stimulus differently. Frequently, these two phenomena have been clustered without isolating sensory input from the subject's own evaluation of his sensory input and performance. This may explain in part why workers have not found significant EEG changes after marihuana smoking even after investigating evoked responses to auditory or visual stimuli. Apparently, stimulus reception is not modified, but the integration of information within the brain is changed by this drug in a most novel manner.

(1) Oral Doses

The subjective and perceptual effects on 10 healthy naive, 20 to 30 year old male and female subjects have been described following single oral doses of Cannabis extract (64). There was no estimation of the THC content of the extract but under controlled hospital conditions the subjects described a curious disturbance of consciousness, a disorder of time perception, difficulty in immediate recall that was manifest as thought disorder, and a sense of euphoria.

High doses (341-946 μg/kg) of Δ^9-THC produced sedation, following long-lasting euphoria with dreamlike periods (28). The peak drug effects were reached within 30 to 60 minutes after oral doses of the drug administered in a hydroalcoholic diluent. The subjects were also studied following doses of Synhexyl (a semi-synthetic THC-like compound) and the behavioral data were compared with those obtained in a previous study following administration of LSD in hallucinogenic doses. Tentatively, both Δ^9-THC and Synhexyl were classified as psychotomimetics and as sedatives by these workers. The characteristic sympathomimetic effects of LSD, such as pupil dilation and an increased deep tendon reflex,

were absent following Δ^9-THC or Synhexyl. The differences in subjective and perceptual responses measured in this study under controlled laboratory conditions have established basic guidelines for subsequent investigations of the effects of marihuana on man.

Marihuana extract with a median oral dose equivalent of 32 mg THC, was compared with a median oral dose of 57 gm ethanol in 12 normal subjects executing a battery of performance tests and completing a self-rating mood scale (100). These two drugs were most alike in their effects with the exception of the alteration in time perception produced by marihuana.

Melges et al. (87) demonstrated that Δ^9-THC is capable of impairing performance of a man requiring immediate memory and coordination of organized speech and thinking. These workers gave relatively high oral doses of Δ^9-THC (20, 40, and 60 mg THC content in an extract from confiscated marihuana) to 8 normal male graduate students with placebo controls (extracted marihuana with virtually all cannabinoids removed). The tests were conducted 1.5, 3.5, and 5.5 hours after ingestion of the diluted alcoholic extract. The effects were considered "temporal disintegration"; the subject has difficulty in retaining, coordinating, and serially indexing those memories, perceptions, and expectations that were relevant to the goal. The goal directed serial alteration (GDSA) task and the short- and long-term memory functions tests employed non-written digit subtraction and addition within a specified time (See Page 44). These tests were developed originally in clinical studies with schizophrenic patients who frequently exhibit symptoms of temporal distortions and disorganized speech.

In these studies high doses of Δ^9-THC produced temporal disintegration, as defined by these workers, that stemmed partly from impaired immediate memory and disorganized speech and thinking (87). As dosage increased, GDSA performance was progressively impaired and higher doses prolonged the effects as measured by the GDSA task. However, the ability to make a regular serial subtraction of sevens from a randomly selected number in a given time (long-term memory), was not significantly impaired by the drug. This task is considered to require sustained attention and long-term memory operations. In addition, errors in addition and subtraction (miscalculations reflecting long-term memory operations) in the GDSA task were not significantly increased by increasing doses of Δ^9-THC. On the other hand, short-term

memory was impaired by Δ^9-THC. In this test, the subject was required to repeat without error in the same or reverse order digits presented at a steady rate. All doses of Δ^9-THC reduced the ability of the subject to repeat digit spans.

In discussing the interpretation of the results obtained in these tests, the authors concluded that Δ^9-THC,

> "significantly impaired the serial coordination of cognitive operations during a task that required sequential adjustments in reaching a goal. This disintegration of sequential thought is related to impaired immediate memory" (87).

They suggest that the temporal incoordination of recent memory with a task to achieve may account, in part, for the speech pattern of the marihuana user. The description of the difficulties of speech wherein the subject is unable to coordinate recent memory and extended temporal goals resembles the experience of the marihuana smoker. It remains to be demonstrated whether these results will be sustained in subsequent studies by other workers. It appears that test measures of this character may be most relevant to the tasks demanded of the man in the military environment. There is an urgent need to extend this work to field studies on communications problems to determine whether the laboratory tests are indeed predictive of the real-life situation. Related studies on speech difficulties after smoking of marihuana have been made by Weil and Zinberg (90).

(2) Inhaled Doses (Smoking)

Most marihuana users prefer to smoke the drug because a prompt and greater effect can be obtained with a small amount of the material. Furthermore, the experienced smoker can titrate his dosage to produce the desired effects. There appear to be differences in the subjective experiences of naive and regular marihuana smokers. In controlled laboratory settings both classes of subjects will experience the typical effects of smoking the drug if the "dosage" is adequate. Some investigators contend there is inadequate evidence for these proposed differences between the subjective experiences of the two groups of individuals (70). The

physiological effects are dose related and similar in the two types of smokers but the question of tolerance in chronic users has not been answered satisfactorily.

The early studies established a number of important facts about the effects of marihuana smoking including performance changes, absence of EEG or biochemical changes and sensory discrimination threshold modifications (63, 83). However, definitive tests with known dosage in terms of the THC content of the marihuana and the composition of the smoke, have been made only recently. Apparently, Δ^9-THC is more potent by smoking than if taken orally (27).

An attempt was made to demonstrate differences between naive and chronic marihuana smokers on the basis of a number of performance and cognitive tests (70). Sustained attention as measured by the Continuous Performance Test with or without distracting strobe light flickering, was unaffected by marihuana smoking in both groups of subjects. On the other hand, the cognition required to complete the Digit Symbol Substitution Test rapidly and accurately, caused the nine naive subjects to perform more poorly than the eight chronic users of marihuana, especially after larger doses. The pursuit rotor test to measure muscular coordination and attention was performed with difficulty by marihuana naive subjects who showed a significant decrement in performance 15 and 30 minutes after smoking. By contrast, regular users did not show the same degree of impairment. Five-minute time estimations for the nine naive subjects changed from 5 ± 2 minutes before smoking to 10 ± 2 minutes for three individuals after smoking a low-dose (approximately 4.5 mg THC) cigarette and four subjects raised their time estimates after a high-dose cigarette (approximately 18 mg THC).

In another study these workers investigated the acute effects of marihuana smoking on speech (90). They related the subtle speech changes to interference with ultra-short-term or "immediate memory" over the past few seconds. It is assumed that once information passes to "recent memory" storage, it seems to be more easily accessible to the consciousness of the subject and can be retrieved. This latter memory phase represents mental activity in a secondary storage role for speaking and thinking in a coherent manner and as such differs from "immediate memory."

After smoking marihuana or a placebo cigarette, chronic smokers and naive subjects were asked to tape an interesting experience. These recordings were analyzed for speech modifications according to a selected group of tests to demonstrate interference with retrieval of information from "immediate memory" storage. The character of the study warrants further work to develop these leads because the results agree with most of the undocumented opinions expressed by observers and writers on the effects of marihuana on speech.

Jones and Stone (52) found significant changes in pulse rate and time estimation of subjects who were regular users of marihuana, after they smoked cigarettes with standardized amounts of THC in the marihuana. The EEG changes were characterized by an increased abundance of low voltage fast (20-30 Hz) activity, decreased alpha abundance and slight alpha slowing. Smoking marihuana had no effect on the rod and frame task and field dependence did not change. There was no influence on a digit symbol substitution task. In evaluating the effects of smoking marihuana, the authors stress the importance of the dose, prior experience of the subject with drugs, the setting, and possible cross tolerance of marihuana and alcohol.

With carefully assayed quantities of Δ^9-THC (5 mg= to an administered dose range of 50-75 μg/kg) in the cigarette smoke and with a standardized manner of smoking, Manno et al. (67) found a significant decrement in motor performance tests in subjects who were either experienced tobacco cigarette smokers or who had previous experience with marihuana. After smoking a single marihauan cigarette, the subjects performed a sophisticated pursuit meter task and nine verbal or cognitive tests executed while listening to a delayed auditory feedback that induced anxiety. Both tasks require constant attention during their performance. These investigators concluded that significant decrements in motor and mental performance were produced in man after smoking a marihuana cigarette that delivered this dose of the drug. In similar studies they reported additive effects of marihuana smoking and alcohol ingestion (5 mg/100 ml blood) in impairing performance of motor and mental tasks (53).

4. Adverse Behavioral Effects

Recent reports, especially in the psychiatric literature, suggest that the smoking of marihuana may precipitate transient but

severe psychotic reactions. The evidence marshalled in these accounts is not complete and numerous factors of importance have not been considered, e.g., true nature of the "marihuana" smoked, prior experience of the user, environmental conditions of stress, and the possibility of psychopathic personality of the subjects.

Although marihuana produces sensations of change in time, distance, and sound, and a free play of the imagination, it requires high doses to achieve hallucinatory effects. Opinions differ, and it is extremely difficult to distinguish between such factors as adverse reactions in naive persons from smoking a single marihuana cigarette (a moderate dose), and true hallucinations resulting from excessive doses. Without biochemical methods to assess the dose consumed, one cannot make a true correlation between effects and dosage.

Murphy reviewed the literature to 1963 on psychiatric sequelae following the use of Cannabis (101). He discussed the personality traits of Cannabis users in different cultures, the reported long-term psychological effects, and the evidence for "Cannabis psychoses." He concluded that while the literature is contradictory and confusing, there is little evidence of a higher incidence of psychoses in Cannabis users than in the general population.

Numerous anecdotal accounts describe marked psychotic reactions or severe hallucinatory effects following the use of Cannabis (94, 102, 103, 104, 105, 106). These include fright, panic, anxiety reactions, and disorganized behavior that may be related to any one of a number of factors. Adverse behavioral effects appear to be the consequence of (a) the presence of an incipient, innate psychotic personality, or a neurotic diathesis of the user (101, 105, 107, 108); (b) the ingestion of a high potency Cannabis (64, 109); (c) the presence of adulterants or additives to the marihuana (110, 111); or, (d) a combination of these factors.

In the past 40 years attempts to classify marihuana users, especially military personnel, in terms of their personality (112, 113, 114, 115). The novel effects of marihuana may cause a transient emotional disturbance in an unstable person that may be mistakenly diagnosed as a psychiatric episode. In addition, especially in military situations, the stress of environmental extremes may interact with

the effects of marihuana to produce a chain of adverse behavioral events in the individual. The older reports on the incidence of marihuana use among inmates in mental hospitals in India and North Africa are difficult to evaluate and are of little value at this time in determining the chronic toxicity of the drug. The Report of the Indian Hemp Drugs Commission concluded that the moderate use of hemp drugs in that country did not cause deleterious mental effects (116) and the Mayor's Committee on Marihuana did not find evidence of psychotic reactions from smoking marihuana (83). It is not easy to appraise the statement frequently found in the literature that chronic use of marihuana leads to a passive attitude toward life stresses, a withdrawal from action-demanding tasks, and lessened ambition, drive, and motivation. If the marihuana smoker is using the drug to escape the demands of daily living or environmental stress, he is not likely to learn how to perform successfully to meet these challenges in the military environment. On the other hand, it may be argued with some basis in fact that the use of the drug is "recreational" and the pleasant experience affords a temporary escape that is concluded with a restful sleep. From this euphoric experience the individual recovers with renewed vitality.

There is a growing body of scientific knowledge that moderate long-term use of marihuana in Western cultures may not necessarily cause an undue degree of interference with productive life activities. McGlothlin et al. (117) studied 29 individuals (7 females and 22 males; mean age of 40) who had smoked marihuana two or more times a week for a minimum of two years prior to 1961. Some used marihuana for 20 years but only a few had used the drug on a regular basis. There was no evidence to support the current idea that marihuana users eschew alcohol. This group did not have a higher accident rate or more traffic violations than a control group. The authors concluded that marihuana may vie with alcohol as a popular intoxicant because these two drugs meet the requirements for wide appeal, are suitable for use over long periods of time, and produce significant physical, psychological or social behavioral change. Their use did not appear to be mutually exclusive and apparently this group of marihuana users were able to use these drugs without producing serious social problems for themselves. These experiences are in contrast to other cultures reviewed by Murphy (101).

Individual differences in patterns of use and reactions to marihuana are significant and it is impossible to draw firm conclusions regarding the adverse behavioral effects. Further research

is needed to elucidate the short- and long-term effects of marihuana on a man's performance. However, the absence of scientific data should not lead to the assumption that long-term marihuana smoking is harmless.

5. Influence of Additives and Adulterants

Until recently, the role of adulterants or additives knowingly or clandestinely incorporated into marihuana cigarettes to enhance their potency, was not considered in assessing severe adverse reactions. In India, the admixture of various additives and adulterants to Cannabis has been a long-standing practice, and it is aptly described in the report of the Indian Hemp Drugs Commission (116). Tobacco, spices, rose leaves, attar, betel nut and leaves have been and perhaps still are common additives:

> "Powerful and noxious drugs are occasionally introduced into the pipe; but this practice is confined to excessive consumers. . . . . on whom hemp alone has ceased to produce the desired effect of exhilaration or stupefaction. The seeds of Datura are by far the commonest ingredient of this class. The next place should probably be taken by opium. . . . ."

The greater availability of jimson weed (Datura stramonium) has made it a common additive, and for years it has been used in combination with marihuana among the dock workers of New Orleans (118). It is said to be present in marihuana used by laborers in South American ports.

There is growing evidence that belladonna and other members of the Solanaceae family such as Hyoscyamus niger (henbane), are used as marihuana adulterants in addition to D. stramonium (98). These plants contain the alkaloids atropine, hyoscamine, scopolamine (hyoscine) that produce cerebral excitation, hallucinations, and disorientation in adequate doses (119). Other adulterants that have been suspected or identified are LSD, mescaline, psilocybin, N, N-dimethyltryptamine (DMT), phencyclidine (Sernyl), and similar compounds. In Southeast Asia Cestrum laevigatum leaves and Mitragyna leaves are suspected adulterants. These are known as plants that elicit behavioral effects but their pharmacology is not well known.

Modern synthetic compounds that produce behavioral effects, e.g., amphetamine, morphine, or heroin, may be suspected, but it is more likely that such substances as quinine or strychnine may be found because these alkaloids are more readily available.

There is every reason to believe that traffickers in illicit drugs will use any means to enhance their trade and sophistication may be expected in the product offered for sale. Recognition of adulteration of marihuana as a common practice calls into question the psychotic-like or bizarre effects ostensibly produced by "marihuana" and reported in the literature as adverse effects of marihuana smoking. For example, additives may have produced the psychotic-like effects in military personnel who had smoked "marihuana" in Vietnam (120).

For an adequate approach to this problem it will be necessary to determine by analysis the composition of products offered as "marihuana." Investigators reporting the effects of drugs that come from such notoriously unreliable sources as narcotics pushers should ascertain the exact nature of the drug used by the subjects. In this respect it is desirable for the military authorities to ascertain the composition of marihuana cigarettes available to the soldier. This information is vital for the physician called upon to treat severe adverse effects of any drug. Indeed, there is a need for a world-wide analysis of drug-abuse substances, including Cannabis, as sold in illicit traffic in much the same way the potency of "street heroin" is assayed to determine the purity and the degree of availability of the narcotic alkaloid. In the case of marihuana, the purity of the product is significant from the standpoint of adequate medical care of the subject poisoned by adulterated Cannabis.

6. Drug Interactions

It is well recognized in clinical pharmacology that two or more substances, therapeutic agents or even dietary items may interact in the body and cause adverse reactions (121, 122). Interactions of this character may be especially hazardous with drugs that act on the central nervous system. The potential interactions of therapeutic agents with marihuana should be investigated because

essentially nothing is known about the possible somatic or behavioral effects of such combinations. These studies should consider the effects of marihuana smoking on the action of drugs, or conversely, the effects of a drug on the response to marihuana. These investigations are particularly important to the military because prophylactic drugs such as the antimalarials may be administered over extended periods of time.

F. MARIHUANA SMOKING AND PERFORMANCE

By definition, human performance denotes a measurable activity that requires expenditure of physical and mental energy in an attempted completion of a task. Both neuromuscular effort and mental activity have been included in the laboratory investigations designed to measure and evaluate the effects of marihuana on a human subject. Work performance or energy output is readily measured by ergometric tests. Cognitive skills, mental alertness, and intellectual performance on the other hand, are evaluated only by comparison with some pre-established or hypothetical norms. These two aspects of human behavior are inextricably mixed in the overall performance of a man. In addition, one must deal with the elusive factor of motivation because it may dominate the apparent physical and mental limits of a person to drive him to extraordinary feats.

Military tasks characteristically test the limits of a man's performance capabilities by exposing him to environmental extremes, fatigue, sleep loss, and the hazards of many forms of stress. These usually cause a performance decrement or some reduced level of performance in fulfilling a specific task. To measure these changes assumes some level of achievement for a given task with established criteria for a normal performance level. Military demands are often more urgent than similar requirements in civilian life, and frequently some performance decrement is recognized as a feature of the task and accepted as a "real life" situation. In extreme circumstances, e.g., in prolonged combat, ability of the soldier to achieve even minimal performance is acceptable. On the other hand, every human performance goal, civilian or military, is to achieve the best performance possible at the least cost in terms of physical and intellectual work. This is especially true of man-machine interactions. In this latter area the Army is increasingly employing complicated technical equipment such as the helicopter or the battlefield computer that require skillful operators.

Successful operation of these and other devices under the constraints of military demands places enormous physiological and psychological burdens on the man. The use of hazardous weapons and machines, continuous operations, and the threat to life are additional perils in the military that highlight the need to

protect the man's performance capability.

Obviously, any element in the life situation of the man that affects his performance either by enhancement or by decrement, becomes significant for study and evaluation. For this reason, the life sciences research programs of the Army include topics such as nutrition of the soldier, sleep, use of therapeutic drugs, the impact of disease, and physical comfort in the face of climatic extremes. The medical officer recognizes that the use of socially acceptable drugs, e.g., tobacco and alcohol, may influence the performance of the soldier. However, the use of illegal drugs such as the opiate narcotics or marihuana may pose special problems. Physical and psychic dependence of the heroin or morphine type will seriously interfere with the ability of a man to complete a task either because he has lost his motivation to perform, is physically unable to work, or is preoccupied by drug-seeking behavior. The marihuana user should not be viewed in a similar light because the pharmacologic effects are fundamentally different. Unfortunately, these two issues have become confused in the literature, in official documents, and in the lay press.

Throughout this report emphasis has been placed on the need to assess the impact, either desirable or undesirable, of smoking marihuana on a man's performance in the military environment. Recognition has been given to the problems of transferring laboratory data to the field situation. Basic facts can best be obtained under controlled conditions of the laboratory; however, eventually experiments must be designed to simulate field exercises if the crucial military questions are to be answered. Prior to this time it was not possible to undertake these studies because the fundamental knowledge about marihuana is just beginning to unfold. It will soon be possible to undertake the crucial studies in which the Army is most interested utilizing the rapidly developing information on the effects of known elements of cannabis on man, the availability of these pure substances for research studies, the solution of the problems of analyzing cigarette smoke, and suitable analytical methods for the detection and measurement of active cannabinols or their derivatives in body fluids.

The evidence at hand suggests that the somatic, subjective, and perceptual effects of marihuana smoking cause a temporary

decrement in a man's performance. Most effects appear to be dose related; however, dosage is influenced by the complex variables that have been described, but dosage estimation has yet to be based on biochemical measures of blood and tissue drug levels. Apparently, low doses of the active components may produce behavioral changes and a performance decrement. However, by ignoring or suppressing the subjective effects, almost at will, experienced users appear to be capable of meeting situational demands. Although chronic smokers insist on their ability to perform adequately on a marihuana "high," this claim remains to be verified scientifically. Thus, the performance abilities of the marihuana smoker pose rather unique problems for the investigator.

There is some evidence that even experienced subjects receiving comparatively high doses of Δ^9-THC in cigarette smoke may have difficulty in performing neuromuscular tasks or in exercising their intellectual skills. On the other hand, some individuals in the United States have reportedly smoked marihuana for as long as twenty years and continue their occupational roles without any recognized deficiency in their performance ability.

The investigations on marihuana supported by the National Institute of Mental Health are related to the research interests of the Army. These basic studies may provide information on performance that could be applied to military needs. Therefore, Army research administrators have an urgent need to be aware of these studies because they have the responsibility to plan and develop future research uniquely related to the requirements of the Army.

Army Edgewood Arsenal research scientists have had many years experience in conducting model field tests to assess the performance abilities of men exposed to incapacitating agents. These substances are designed to impair a man's performance, and certain of these agents are administered by inhalation. In evaluating these substances, the Army field tests simulate real-life situation involving the performance of men required to exercise command responsibilities, make time judgements, operate technically complicated equipment, follow orders, maintain vigilance, and complete other military tasks. If legal and scientific

constraints could be met, the unique capability of this research facility could be used to answer pressing questions concerning marihuana smoking and its influence on performance of the man in the military environment. This knowledge would contribute to a better understanding of the problems of marihuana use in contemporary society.

IV. SUGGESTED AREAS FOR FUTURE RESEARCH

INTRODUCTION

Any future Army research on the effects of marihuana on man in the military environment should be coordinated with the comprehensive programs of the National Institute of Mental Health, U.S. Public Health Service, and the Bureau of Narcotics and Dangerous Drugs, Department of Justice. However, these civilian programs do not include studies on human performance in the military environment. Therefore, it may be necessary for the Army to undertake investigations to meet these specific requirements. If a decision is made to conduct such studies, the Army would have an opportunity to contribute its unique research capabilities to a better understanding of the effects of marihuana use.

BOTANY AND CHEMISTRY

The plant, Cannabis sativa, exhibits a high degree of botanical and chemical variability that is reflected in variations in the pharmacologically active cannabinoids. Greater knowledge of the botany and the chemistry of C. sativa and its constituents are basic to further studies on marihuana.

- The existence of many types of Cannabis cultigens makes it difficult to characterize the plant chemically. Additional research is required on the botany and chemistry of these numerous cultigens.

- The geographic origin and distribution of Cannabis throughout the world should be re-investigated.

- The effects of environment on growth of C. sativa should be investigated in relation to the production of biologically active materials.

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- There is a need to develop specific, rapid chemical tests that identify Cannabis plant materials and products.

- The chemical identity of the numerous Cannabis constituents remains obscure and each should be isolated, identified chemically, and evaluated pharmacologically.

- There is an urgent need to assay the materials sold throughout the world as "marihuana" for the actual Cannabis or tetrahydrocannabinol content. The presence of adulterants may be the cause of adverse reactions attributed to marihuana and these adulterants should be identified. This will require sample collections and accurate chemical analyses.

- Studies of the chemical composition of marihuana smoke should be conducted to relate the constituents of the marihuana cigarette to products of chemical interconversions that occur during smoking. The techniques developed for analysis of tobacco smoke should be used in these investigations.

- The water insolubility of Δ^9- and Δ^8-tetrahydrocannabinols is a major problem in studies on animals and man. Water soluble, pharmacologically active derivatives should be developed for experimental studies on animals and man.

- There are no direct, rapid methods for separation and identification of Δ^9- and Δ^8-tetrahydrocannabinols. Chemical tests for identity, purity, and structural specificity of all the cannabinoids are required.

- The lack of a rapid, accurate biochemical test for identification of marihuana users makes enforcement programs difficult. These tests would be useful in education and enforcement programs.

- Further study of the behavioral effects of marihuana requires chemical analytical methods for the accurate determination of Δ^9- and Δ^8-tetrahydrocannabinols and their metabolites in biological fluids.

PHARMACOLOGY

Fundamental questions on the pharmacology and toxicology of marihuana must be answered before the effects of marihuana smoking on man can be explained.

- Marihuana has unique effects on the central nervous system and needs pharmacologic classification. Additional studies on animals and man are necessary to elucidate the mechanisms of action of the active constituents.

- The pharmacologic effects of Δ^9- and Δ^8-tetrahydrocannabinols and other chemically identified natural Cannabis constituents should be investigated in all possible combinations and permutations. These should be compared to the effects produced by marihuana.

- Studies on absorption, distribution, metabolism, and excretion of Δ^9- and Δ^8-tetrahydrocannabinols in man must be expanded and extended to clarify dose-effect relationships.

- Physical and physiological variables of subjects in experimental studies on smoking should be measured, and should include tidal volume, inhalation volume, and frequency and duration of inhalation. These data will assist in quantifying dosage.

- Pharmacologic studies of the products of interconversions and apparent isomerizations of the constituents of marihuana under the high temperatures of smoking are required and may explain the apparent enhanced potency of the drug when it is smoked.

- Investigations are needed that clearly differentiate between the qualitative effects of marihuana and hashish when these substances are either smoked or ingested.

- Properly controlled experimental studies on the effects of marihuana require the development of standardized marihuana, tetrahydrocannabinol, and placebo cigarettes.

- Preliminary studies of rapid-eye-movement (REM) sleep in man after oral doses of tetrahydrocannabinol have indicated that additional investigations of REM sleep under the influence of marihuana may assist in elucidating the central nervous system effects of this drug.

- Complete histopathologic studies in animals and man after ingestion or smoking marihuana or the tetrahydrocannabinols are needed. These data combined with biochemical and physiological information will provide a basis for assessing the toxicity of these substances.

BEHAVIOR AND PERFORMANCE

A precise evaluation of the effects of marihuana use on behavior and performance presents problems that have not been completely resolved. The reliability of the methodology used for measuring behavioral changes and the effects of "set" and "setting" on performance must be determined. The relation between performance in laboratory tests, and performance in real life situations must be established if current knowledge about the effects of marihuana is to be applied to Army or civilian needs.

- There is a need for more satisfactory animal behavioral tests to screen the effects of isolated constituents of Cannabis. These animal tests should reflect the behavioral actions of these compounds in man.

- Future research programs should develop the criteria for differentiation between recreational use and the abuse of marihuana. Just as the use and abuse of alcohol and the hard narcotics has been separated, the use and abuse of marihuana must be clarified.

- The results of laboratory testing procedures of a man's performance may not reflect adequately his performance using sophisticated military equipment in field operations. Therefore, model field exercises must be conducted with military equipment and include command responsibilities, judgement, and execution of commands to determine the effects of marihuana on man in the military environment.

- The unique facilities and experience at the Army Edgewood Arsenal with incapacitating agents provide an unparalleled opportunity for studies on the effects of marihuana on human performance.

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VI. GLOSSARY

Alluvial	Pertaining to deposits ordinarily occurring on the floodplain of a stream or river.
Axillary	Situated in the area between the stem or branch and leaf petiole.
Bract.	The leaf that subtends a flower.
Cannabinoids	Chemical compounds present in Cannabis sativa. Substituted monoterpenoids related to cannabinol, their carboxylic acids and other natural transformation products.
Cultigen.	A plant variant known only in cultivation or domestic association with man, and not yet recognized as a wild or indigenous species.
Cystolith hairs	Modified epidermal cells of various flowering plants that contain calcium carbonate inclusions.
Dioecious	Stamens (male) and pistils (female) in flowers on separate plants.
Escaped plant	A cultivated plant that has reverted to a wild state and is propagated without human assistance.
Hashish	A mixture of resins exuded by Cannabis plants.
Lanceolate leaf	Shaped as a blade sharpened to a narrow point at one end.
Mainstream smoke . .	That smoke inhaled by the smoker.

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Monecious	Stamens (male) and pistils (female) in separate flowers but on the same plant.
Red oil	An extract of Cannabis containing a concentrated mixture of tetrahydro-cannabinols.
Sidestream smoke	That smoke produced during static burning of a cigarette.
Valsalva maneuver . . .	An increase of intrapulmonic pressure by forcible exhalation against a closed glottis.

VII. LIST OF ATTENDEES

AD HOC STUDY GROUP MEETING, OCTOBER 6 AND 7, 1970

On

A REVIEW OF THE BIOMEDICAL EFFECTS

OF MARIHUANA ON MAN IN THE MILITARY ENVIRONMENT

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13. ABSTRACT

This review documents in detail the current state of knowledge of the effects of marihuana on man. The study examines the relationships between marihuana use and performance of the man in a military environment and identifies opportunities for future research by the Army in this field.

The scope of the study includes the botany and phytochemistry of Cannabis sativa, isolation, characterization, and synthesis of the plant constituents, the pharmacology of these compounds, and the need for quantitative estimation of the tetrahydrocannabinols and their derivatives in biological samples. Special attention is directed to the effects of smoking marihuana, the composition of marihuana cigarette smoke, and the resulting somatic, subjective, perceptual, and cognitive changes that may influence the performance of the smoker.

This review includes a description of behavioral tests used to measure marihuana effects, the influence of an individual's expectations, and effects of environmental setting on human subjects. The anecdotal literature on marihuana is being replaced by reports of controlled laboratory studies; however, investigations that measure performance in real-life situations are required to answer

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crucial military questions on marihuana effects. Information on the chemistry, pharmacology, and behavioral effects of marihuana that is necessary for these future studies is being developed at the present time.

The report identifies and assesses the research opportunities that are related to the requirements of the Army. It is suggested that the unique research experience and facilities of the Army in assessing the performance abilities of men exposed to incapacitating agents may be utilized to answer the pressing questions concerning marihuana smoking and its influence on the performance of the man in the military environment.

14. KEY WORDS	LINK A ROLE	LINK A WT	LINK B ROLE	LINK B WT	LINK C ROLE	LINK C WT
Cannabinoids						
Cannabis						
Botany of						
Chemistry of						
Pharmacology of						
Effects of Cannabis						
Adverse						
Behavioral						
Cognitive						
Perceptual						
Somatic						
Hashish						
Ingestion						
Marihuana						
Smoking						
Tetrahydrocannabinols						