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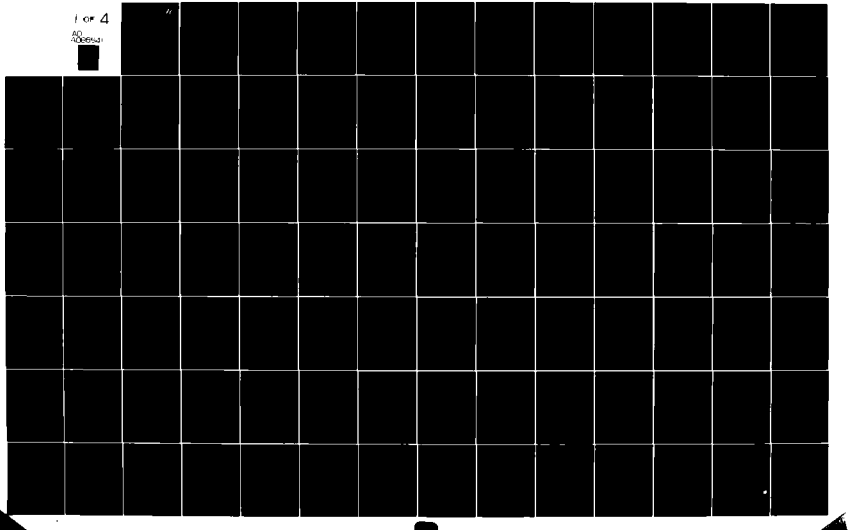

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Final Report

A CRITICAL REVIEW OF THE DRUG/PERFORMANCE LITERATURE

Volume I

Lawrence A. Landry, Project Director

December 1979

Supported by

U.S. Army Medical Research and Development Command
Fort Detrick, Frederick, Maryland 21701

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Associate Consultants, Inc.
1701 K Street, N.W., Suite 501
Washington, D.C. 20006

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Cannabinoids	Drug Addiction	Drugs	Opiates
Cannabinois	Drug Overdose	Drug Interaction	Opiods

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

In anticipation of requirements to perform research on the impact of psychoactive drug use upon military performance, the U.S. Army Medical Research and Development Command (USAMRDC) contracted with Associate Consultants, Inc. to perform and compile a series of original reviews and analyses of the domestic and internaticnal scientific literature of the past 20 years. Reviews were conducted by experts in psychopharmacology with the primary aims of:

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Block 7. Gregory Austin (Univ. of Calif. L.A.); John Bachman (Univ. of Calif. San Francisco); Robert Balster (Virginia Commonwealth Univ.); Brian Brown (Smith-Kettle Institute of Visual Sciences); Karen Gross (Harvard Medical School); Herbert Moskowitz (Univ. of Calif. L.A.); Deborah S. Orzack (Rutgers Univ.); Maressa Hecht Orzack (Boston Univ.); Stephen Rothenberg (McLean Hospital); Charles Schuster (Univ. of Chicago); Ronald K. Siegel (Univ. of Calif. L.A.)

Block 19.

Opium Alkaloids	Physiology	Tranquilizer
PCP - Phencyclidine	Pychomotor Functions	Vision
Performance (Human)	Simulations	Visual Acuity
Physiological Effects	Stimulants	

Block 20

- documenting the current state of knowledge of drug effects upon militarily relevant performance;
- documenting the gaps in knowledge of drug effects upon performance, particularly in situations analagous to those that may be created by rapid deployment of troops into continuous land warfare; and
- making recommendations for future research projects.

The literature reviews are intended to establish a firm scientific basis for subsequent research programs and staff studies concerned with relating militarily-relevant performance capacity to various parameters of drug use.

The eight reviews cover the literature on the major classes of drugs used most frequently in a recreational context: alcohol, cannabinoids, depressants, hallucinogens, opioids, and stimulants. One of the reports concerns phencyclidine piperidine (PCP). In addition, a special review deals with the effects of all these classes of drugs on visual performance and behavior. Volume II of the report includes a cross-index of references cited in the reviews.

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FOREWORD

The following people played a crucial role in the development of the report:

TIMOTHY F. ELSMORE, Ph.D. Department of Medical Neurosciences, Division of Neuropsychiatry, Department of the Army, Walter Reed Army Institute of Research, served as the government representative on the project. Dr. Elsmore's generous advice and counsel, including reading the critical reviews in draft form, was invaluable.

RONALD D. WYNNE, Ph.D. served as a research assistant on the project and was the senior technical person on the project for Associate Consultants, Inc.

BETTY B. BOGART and CHARLENE PYNE served as information specialists on the project.

RICHARD MILLIS, Ph.D. played a key role in selecting the articles for review.

YVES DOUYON, DAHLIA GILL, FRANCIS KILGOUR, DOLORES LANDRY, and IRIS SPENCER served as research assistants on the project. STANLEY BOGART served as a staff consultant.

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INTRODUCTION

In anticipation of requirements to perform research on the impact of psychoactive drug use upon military performance, the U.S. Army Medical Research and Development Command (USAMRDC) entered into a contract with Associate Consultants, Inc. of Washington, D.C. to perform and compile a series of original reviews and analyses of the domestic and international scientific literature of the past 20 years. Reviews were conducted by experts in psychopharmacology, jointly selected by Associate Consultants, Inc. and the USARMRDC. Each was given the task of making a critical evaluation of the research in his or her respective area, with the primary aims of:

- documenting the current state of knowledge of drug effects upon militarily relevant performance;
- documenting the gaps in our knowledge of drug effects upon performance, particularily in situations analagous to those that may be created by rapid deployment of troops into continuous land warfare; and
- making recommendations for future research projects.

These literature reviews, then, are intended to establish a firm scientific basis for subsequent research programs and staff studies concerned with relating militarily relevant performance capacity to various parameters of drug use.

The reviews cover the literature concerning the major classes of drugs used most frequently in a recreational context: alcohol, cannabanoids, depressants, hallucinogens, opioids, and stimulants. One of the reports concerns phencyclidine piperidine (PCP), which has emerged as a major recreational drug in recent years, and is chemically, pharmacologically and behaviorally distinct from the other classes of psychoactive drugs. Reviews concerning drugs and drug classes cover a broad variety of performance areas. In addition, a special review deals with the effects of all these classes of drugs on visual performance and behavior.

The emphasis in these reviews is on the human performance literature. Where there are areas in which there have been no human studies or in which the human studies are clearly deficient, the reviews summarize the animal literature, with an emphasis where possible on primate studies. Where the animal literature was summarized, however, reviewers were asked to generally exclude dose response studies with simple behavioral measures; drug self-administration studies; and gross toxicological, pharmacological and biochemical studies.

In general, the reviews cover the literature of the past 20 years, roughly 1958-78. In some specific cases, the opiates

and stimulants in particular, the reviews cover a longer period because of the importance of earlier work. The alcoholism review, because of the vast size of the research literature, covers only the past decade's studies.

Each review was prepared according to a general outline. Reviewers were asked to be as brief as possible, consistent with a need to summarize what is known and to clearly indicate the research that needs to be done. Each review also includes an evaluation of the quality of the research done to date in these areas.

The performance areas covered in these reviews range from the functionally specific, e.g., general activity, sensory-motor coordination, attention, information processing, and communication processes, to the global, e.g., simulations of driving and other complex behavior. The reviews also cover a variety of performance changes as a function of drug states, e.g., time since administration, chronic administration, effects of withdrawal and termination, interaction of the drugs with other drugs, and with physiological and psychological stressors.

Associate Consultants, Inc. provided each of the reviewers with copies of relevant articles in their areas. The search process (see below) was exhaustive. In addition, reviewers were asked to use their own knowledge of the literature, both published and unpublished, to ensure thorough coverage. To further maximize coverage, as well as to reduce redundancy, reviewers were urged to contact each other during the preparation period (roughly the summer of 1979).

OVERVIEW OF METHODOLOGY FOLLOWED IN PREPARATION OF REVIEWS

An attempt was made to provide each reviewer with "hard copies" of the bulk of the pertinent literature in his/her area. The research papers provided to the experts for review were located through several channels: online searches of databases, manual searches of printed abstract services, and review of card catalogs and other materials in research centers.

The online database searches covered 17 commercially available databases contained in Lockheed's DIALOG system, the applicable Medline-Medlars databases from the National Library of Medicine, and the unclassified database from the Defense Technical Information Center (DTIC, formerly DDC). The manual searches of printed abstract services included 11 titles which correspond to online databases that did not cover the entire time span 1958 through 1978. In these cases, the manual searches covered only the earlier years not available online. The other eight titles were searched to assure comprehensive worldwide coverage of the literature for the time period. Table 1 shows the titles and years covered for the printed abstracts searched. It also shows the relationship between the printed abstract and the online version for those titles where both were searched.

TABLE 1

ABSTRACTS AND DATABASES CONSULTED FOR LITERATURE SEARCH

Printed Abstract Services	Years Covered	Databases	Years Covered
1. Continuations (Print to database)			
Biological Abstracts	1958-68	Biosis	1969-
Chemical Abstracts	1958-69	Chem. Abstracts Condensates Chem. Abstracts Search	1970-71 1972
Excerpta Medica	1958-73	Excerpta Medica	1974-
Monthly Catalog, U.S. Govt. Publications	1958-72	Govt. Printing Office (GPO)	1973-
Readers' Guide to Periodical Literature	1958-76	Magazine Index	1977-
Index Medicus	1958-65	Medlars-Medline	1966-
Government Research Reports	1958-62	Nat. Technical Info Service (NTIS)	1963-
Psychological Abstracts	1958-66	Psychological Abstracts	1967-
Science Citation Index	1961-74	Scisearch Social Scisearch	1974- 1972-
Sociological Abstracts	1958-62	Sociological Abstracts	1963-
Index Medicus	1958-65	Medlars-Medline	1966-
2. Others Consulted			
Abstracts of Soviet Medicine	1958-61	Comprehensive Dissertation Abstracts	1958-
Abstracts of World Medicine	1958-71	Conference Papers Index	1973-
Abstracts of Hygiene	1968-78	Foundation Grants Index	1973-
l'Annee Psychologie	1958-78		
Biological and Agricultural Abstracts	1964-78		
Chemische Zentralblatt	1959-69	Sociological Abstracts	1963-
International Abstracts of Biological Sciences	1958-78	SSIE	1976-
Psychopharmacology Abstracts	1961-78	Defense Documentation Center	-

In addition, the card catalogs, vertical files and other reference materials were reviewed at the following research centers:

In Washington, D.C.: American Pharmaceutical Association
American Psychological Association
Georgetown University
Howard University
Library of Congress
National Clearinghouse for Drug Abuse Information
National Institute on Drug Abuse Reference Library

In Boston, MA.: Francis Countway Library of Medicine

To develop the database search strategy, thesauri for the databases were searched and a word list compiled. The final list was reviewed by project technical consultants and the USAMRDC Project Officer. The word list covered drug names and classes and performance characteristics. The basic search strategy was entered into the system on the first database consulted, stored, and then recalled for execution in each subsequent database search.

After elimination of duplicates, copies of the reports located in the search were retrieved from a variety of sources, including the Library of Congress, National Library of Medicine, and the National Technical Information Service (NTIS).

Abstracts obtained through the search were reviewed by project staff and classified by drug class. Those that passed this screening were retrieved in hard copy form, from a variety of sources, including the Library of Congress, National Library of Medicine, and National Technical Information Service. A final screening was made to eliminate inappropriate articles (e.g., those that were wrongly classified, that had no seeming research value, etc.). The remaining documents, along with an alphabetized list, were sent to the expert reviewers to serve as a major source of input for their reviews.

The drafts of the articles were reviewed by Associate Consultants, Inc. and with the consultant/reviewers before final editing. Following this, a series of cross-indexes were prepared to facilitate the location of information in the review articles.

1. EFFECTS OF CANNABINOIDS ON HUMAN BEHAVIOR

by

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INTRODUCTION: HUMAN STUDIES OF CANNABIS

Consumption of Cannabis sativa (e.g., marihuana, hashish) or its psychoactive constituent, delta-9-tetrahydrocannabinol (THC), can produce stimulation, euphoria, relaxation, sedation, feelings of detachment, subjective enhancement of sensation, altered perception of time and distance, distractability, and disruption of thought sequences and speech. These subjective effects often occur with impairment of perceptual, cognitive, and behavioral functioning and, less often, with gross confusion, anxiety, depersonalization, panic, and psychosis (Goodman & Gilman, 1975).

However, differences in people's responses to cannabis are related to a complex interaction between pharmacological, personal, and environmental factors. These include (1) the composition and interactions of cannabis plant material; (2) the dose(s) consumed and route of administration; (3) the pharmacodynamic and pharmacokinetic properties of the drug; (4) the user's personality, prior experience with, and expectation of the drug's effects; (5) the setting (psychosocial and physical) in which cannabis is taken; and (6) other drugs present.

Until quite recently, the majority of human experiments reported in the cannabis literature involved the administration of single doses to volunteer subjects who varied considerably in their prior use of marihuana. These studies served to elucidate some of the determinants and behavioral consequences of brief periods of cannabis intoxication but were not designed to investigate the effects produced by chronic usage and prolonged intoxication. Inferences regarding tolerance development and dependence that were based on the results of single-dose administrations required confirmation from studies of chronic administration. A recent volume devoted to studies of chronic cannabis use has provided this confirmation (Dornbush, Freedman, & Fink, 1976).

DOSE, ROUTE, AND VEHICLE

The cannabis literature gives the impression that measures sensitive to acute doses of THC reflect consistent dose-response relationships (Borg, Gershon, & Alpert, 1975; Domino, Rennick, & Pearl, 1974; Kiplinger & Manno, 1971). Effects shown to be dose dependent include increased heart rate, performance on simple and complex psychomotor and short term memory tasks, and subjective changes. However, many of the published reports also describe considerable intersubject variability during cannabis intoxication. It is probable that the dose-response consistencies are apparent mainly when different doses are administered to the same person. The interpretation of THC dose-response functions must be made with the recognition that there is considerable differential responsivity between people.

Nevertheless, some general conclusions regarding dose-response relationships and the influence of the route and vehicle of administration can be made. Dosages in the range of 10 to 50 mg of THC orally (Peters, Lewis, Dustman, Straight, & Beck, 1976; Waskow, Olsson, Salzman, & Katz, 1970), 5 to 20 mg of THC smoked[1] (Borg et al., 1975; Domino et al., 1974), and 0.5 to 3 mg of THC intravenously (Bachman, Berkowitz, Herning, & Jones, 1979; Benowitz, Rosenberg, Rogers, Bachman, & Jones, 1979; Gregg, Small, Moore, Raft, & Toomey, 1976; Hollister & Gillespie, 1973; Malit, Johnstone, Bourke, Kulp, Klein, & Smith, 1975; Perez-Reyes, Timmons, Lipton, Davis, & Wall, 1972; Raft, Gregg, Ghia, & Harris, 1977) produced tachycardia, slowed reaction times, impaired short term memory, and caused mood changes that included both relaxation and sedation as well as dysphoria and anxiety. At considerably higher doses (> 80 mg orally, 30 mg smoked, and 5 mg intravenously), anxiety-panic reactions, severe dysphoria, behavioral disorganization, hallucinatory experiences, and psychotic episodes have occurred (Domino et al., 1974; Isbell, Gorodetzsky, Jasinski, Claussen, Spulak, & Korte, 1967; Malit et al., 1975). These latter reactions are more likely to occur in novice users (Tennant & Groesbeck, 1972), in depressed psychiatric patients (Ablon & Goodwin, 1974), or in situations especially conducive to anxiety arousal (e.g., dental surgery--Malit et al., 1975). An important conclusion to be drawn from the above-cited studies is that differences in THC potency vary with dose and route of administration.

Researchers conducted a systematic study of the oral administration of 35 mg of THC in five different vehicles and reported that THC is absorbed at different rates when delivered in sodium glycocholate, sesame oil, Tween-80, ethanol, or a combination of sodium glycocholate plus ethanol (Perez-Reyes, Lipton, Timmons, Wall, Brine, & Davis, 1973). Differences in absorption rate were significant also when the same dose of THC was administered in sesame oil to different subjects. These findings indicate that it is necessary for investigators who administer THC orally (e.g., physicians prescribing oral THC to control glaucoma or nausea) to consider not only the dose but also the vehicle.

PERSONAL AND ENVIRONMENTAL FACTORS

Set and Setting

Variance in people's responses to cannabis is associated with individual differences in prior experiences with the drug, expectation of its effects, and personality, and also with the setting in which it is consumed. Jones (1971) suggested that cannabis is

an ideal drug to study "if one is interested in the more psychological aspects of psychopharmacology." He contended that the relatively low doses of THC consumed by American users facilitates the influence of personal and environmental factors in determining the response to the drug. Jones hypothesized that prior experience with cannabis produces the expectation that intoxication will follow consumption and predisposes frequent users to report feeling "high" whether they smoke placebo or active marihuana, at least in laboratory settings. He suggested that the smell and taste of the burning placebo material served as conditioned stimuli to elicit an internal state that was interpreted by frequent users as a "high." Jones also showed that his subjects' responses to marihuana varied as a function of the psychosocial milieu in which marihuana was smoked. More euphoria, perceptual changes, and thinking changes were reported when the drug was smoked in a group setting than in a solitary setting.

Carlin and colleagues (Carlin, Bakker, Halpern, & Post, 1972; Carlin, Post, Bakker, & Halpern, 1974) suggested that experience with marihuana is a social learning process in which the recognition and appreciation of intoxication is a learned discrimination that, in turn, confers new meaning to the drug effect and modifies subjective ratings of intoxication. Hollister, Overall, and Gerber (1975) reported that the physical setting in which "casual" users smoked marihuana had no significant effect on the subjects' responses to either active or placebo doses. From this, Hollister et al. concluded that "marihuana effects are principally determined by the drug and the subject to whom it is given and that the actual conditions under which the drug is administered do not much alter the effects."

Although personal experience and expectations of THC effects have been shown conclusively to influence the drug's activity, it is necessary to extend the study of the influence exerted by physical setting. An important example of the influence of physical setting, which has received only spotty attention in the literature, concerns the behavioral effects produced by the drug when it is consumed in situations of extreme stress or fatigue. Prolonged combat or radar monitoring are obvious examples. The vast majority of marihuana studies have been conducted either in austere laboratory situations or in social "living room" situations. Studies are needed that assess the drug's effects in the context of (1) prolonged sensory deprivation; (2) prolonged sleeplessness and fatigue; and (3) intense stress produced by demanding, incessant physical and mental activity.

Personality

Individual differences in personality characteristics between people have been shown to influence their subjective reactions to a variety of psychoactive drugs. However, no adequate study has evaluated the effect of personality on responsivity to THC. The cannabis literature contains several reports that have correlated personality attributes with levels of cannabis usage but contains no well-controlled experimental studies on how personality differences might affect the subjective experience and behavioral consequences of cannabis intoxication. These correlational studies were conducted with samples drawn from college students (Brill, Crumpton, & Grayson, 1971; Harmatz, Shader, & Salzman, 1972; Hogan, Mankin, Conway, & Fox, 1970; Knecht, Cundick, Edwards, & Gunderson, 1972; McAree, Steffenhagen, & Zheutlin, 1972; Zinberg & Weil, 1970), people using inpatient and outpatient drug treatment facilities (Burke & Eichberg, 1972), prisoners (McGuire & Megargee, 1974), and labor union members (Khavari, Mabry, & Humes, 1977). Many conceptual and methodological inadequacies limit the generalizability and validity of the findings reported by these authors, but the unanimity of their results offsets the problems to some extent. In most of the studies, subjects were assigned to groups on the basis of their reported use of cannabis and other drugs (usually including hallucinogens, stimulants, barbiturates, and opiates). Univariate statistical comparisons were performed on the group means to determine whether any personality differences existed between them. Personality was measured most often with the Minnesota Multiphasic Personality Inventory (MMPI), the California or Eysenck Personality Inventories, and questionnaire ratings of sensation seeking. By treating personality as the dependent variable and cannabis usage as the independent variable, these studies tend to give the impression that significant personality differences between users and nonusers are related causally to the use of the drug(s). Obviously, any such differences could be attributed to factors other than cannabis or multidrug use. None of the studies report data relevant to the question of whether cannabis use produces the personality differences or is merely a manifestation of them.

Nevertheless, the data reported in these studies support the hypothesis that different patterns of cannabis usage are associated with different profiles on personality tests. Specifically, frequent users scored significantly higher on test scales indicative of psychopathy (i.e., impulsive, antisocial nonconformity) in conjunction with extroversion, sensation seeking, hypomania, esthetic and interpersonal sensitivity, and psychopathology. Infrequent users and nonusers appeared less antisocial and alienated but more introverted, controlled, and neurotic.

One question suggested by these data concerns whether the individual differences in personality between cannabis users are associated with differences between them in the subjective and

behavioral effects produced by the drug. The very few investigation of this question suggest an equivocal "yes." Klapper, McColloch, and Sidell (1972) reviewed the records of army volunteers who were given various doses of synthetic THC-like compounds via different routes of administration. The subjects were classified as either "drug resistant" or "drug sensitive" on the basis of whether their score on a number facility test was above or below the mean for all subjects given the same compound. Statistical comparisons were made of the resistant and sensitive subjects' intelligence test scores and MMPI scores. The resistant subjects were significantly more intelligent than the sensitive subjects (which alone could explain the differences on the number facility test) and also had significantly higher scores on the MMPI's hypochondriasis, paranoia, and schizophrenia scales. Numerous factors in this retrospective study were confounded making any reliable interpretation of the results virtually impossible.

Bachman and Jones (1979) related the personality characteristics of 48 male volunteers as measured by the MMPI to measures of cannabis withdrawal symptoms. The personality variables accounted for 25 percent of the variance in these symptoms. Neurotic introversion, a tendency not to deny anxiety, absence of sensation seeking, and openness were traits found to relate positively to the intensity of cannabis abstinence symptoms. Whether or not these clusters of personality characteristics are predictive of other aspects of cannabis dependence (e.g., compulsive drug-seeking behavior) is a question for further study.

CANNABIS EFFECTS ON HUMAN BEHAVIOR

The complex interactions among drug, personal, and environmental factors influence the intensity and effects of cannabis intoxication. Nevertheless, a person smoking or ingesting a single dose of 5 to 100 mg of THC will experience certain time-limited and dose-dependent changes in perceptual, cognitive, and behavioral capabilities. Frequent, repeated THC use results in tolerance and dependence development (Jones, Benowitz, & Bachman, 1976; Williams, Himmelsbach, Wikler, Ruble, & Lloyd, 1946) which, in turn, modifies the intensity and effects of subsequent doses. Studies of acute and chronic THC effects on general activity levels, sleep-wake cycles, work capacity, attention, psychomotor performance, information processing, complex behaviors, and mood expression show that the drug exerts a pervasive influence on virtually all areas of human functioning.

GENERAL ACTIVITY LEVELS

A crucial and recurring question in the cannabis literature concerns the drug's specific capacity to inhibit users' motivation and activity. A syndrome consisting of "apathy, dullness, and lethargy with mild-to-severe impairment of judgment, concentration and memory" was described by Tennant and Groesbeck (1972) in an uncontrolled study of the psychiatric effects of hashish on American soldiers stationed in West Germany. Kolansky and Moore (1971) also observed evidence of an "amotivation syndrome" in 13 cannabis users they treated. These cannabis users were apathetic and sluggish in mental and physical responses. Goallessness and lack of concern over personal appearance accompanied flattening of mood, confusion, slowed time sense, memory deficits, and inability to complete thoughts during verbal communication.

A common element in Tennant and Groesbeck's and Kolansky and Moore's populations was their frequent and chronic use of cannabis products. The symptoms and their disappearance following cessation of cannabis use, in conjunction with the positive correlation between symptom severity and duration of use, suggested that the amotivation syndrome was the consequence of prolonged cannabis use. The introduction of this clinical phenomenon into social consciousness helped stimulate cross-cultural and laboratory research designed to investigate the behavioral effects of long term cannabis consumption. This research has provided important, new information on cannabis tolerance and dependence in human users. The research results have not, however, confirmed the existence of an amotivational syndrome.

SLEEP-WAKE CYCLES

Jones et al. (1976) conducted controlled clinical studies of cannabis effects on a group of hospitalized male volunteers. In these studies, oral doses of 30 mg of THC were given to subjects every 4 hours for between 11 and 21 days. Seven-day periods of placebo administration preceded and followed the THC period, so that the subjects served as their own controls. Trained nurses made hourly sleep ratings and observations of the subjects each night. Additionally, nurses recorded daily behavioral ratings during subjects' waking hours. These data indicated (1) that the number of hours subjects slept per night increased significantly during the first week of THC administration; (2) that subjects became sedated, sluggish, slow moving, and lethargic during their waking hours after THC administration commenced; and (3) that tolerance to these effects developed so that after approximately 7 to 10 days on THC subjects resumed sleeping normally (i.e., their baseline number of hours) and no longer appeared sedated to the nurses.

Feinberg and colleagues studied a small subset of Jones et al.'s subjects in a sleep laboratory where electroencephalogram

(EEG) and eye movement recordings were made for 3 baseline nights, 3 nights at the beginning of the THC period, 3 nights at the end of the 2-week TCH period, and 3 nights immediately after the THC period (Feinberg, Jones, Walker, Cavness, & March, 1975). THC significantly reduced eye movement activity during sleep and decreased the duration of REM sleep time. THC withdrawal produced increases above baseline levels in both of these measures. Nightmares and increased awakenings were not experienced by subjects in the sleep laboratory, but other subjects in the study, who were sleeping in the relatively noisier hospital environment, did experience increased awakenings and reported vivid dreams and nightmares during THC withdrawal. Feinberg et al. emphasized that no relationship between the behavioral effects of THC and its effects on sleep has been demonstrated. This is an obvious and important line of future research.

WORK CAPACITY AND ENDURANCE

Carter and Doughty (1976) examined 41 working-class Costa Rican males who smoked an average of 10 cannabis cigarettes daily for an average of 17 years. Each cigarette contained approximately 200 mg of THC, of which the smoker derived about 100 mg by inhalation. The 41 users were compared with 41 male nonusers matched for occupation, education, marital status, age, tobacco use, and alcohol consumption. Cannabis usage did not result in behavior that impaired the users' ability to function in areas of their personal and social life. No experimental observations were made of work output by users of successively greater amounts of marihuana, but an obvious inverse relationship existed between work stability and level of use. The most frequent users of the greatest amounts had the highest incomes, the least unemployment, and the most stable job histories of the entire user group.

Boulougouris, Liakos, and Stefanis (1976) interviewed 47 male hashish users in Greece who smoked two or three times a day, nearly every day, for an average of 23 years. Smokers consumed approximately 3 mg of hashish a day, or about 200 mg of THC a day, according to the authors' calculations. The 47 users were compared with 40 male nonusers matched for age, family origin, upbringing, education, and birthplace. Some of the relevant results include: (1) 55 percent of the users and 95 percent of the nonusers served in the army ($p < .001$); reasons for exemption from service were cannabis use and antisocial behavior; (2) no differences existed between number of occupations or changes of jobs in the two groups; (3) at the time of the interview, however, 42 percent of the users and 15 percent of the nonusers were unemployed ($p < .01$), and 25 percent of the users versus 62 percent of the nonusers were skilled workers ($p < .001$); (4) 63 percent of the users versus 26 percent of the nonusers had prison records for offenses other than cannabis violations. It is difficult to determine if the differences between the two groups reflect the influence of chronic cannabis use or the social milieu of Greece

when the interviews were conducted. It is possible that the basic problem associated with hashish use in Greece during the early 1970's was police harassment, imprisonment, and identification as a socially undesirable person not fit for employment or military service. This stigma may result more from social attitudes concerning morality and the need of a dictatorship to enforce social conformity than from any direct, long term effect of the drug. This study emphasizes the interactions between culture and presumed drug effects that often make such field studies difficult to interpret.

Comitas (1976) studied 30 male Jamaican ganja smokers with 10 or more years of cannabis experience (daily doses not specified) and 30 male nonusers matched for age, socioeconomic status, and residence. The 60 subjects were lower class agricultural workers. They were observed and tested in their actual work settings and in a hospital laboratory. The ganja users reported that the drug enhanced their ability to perform hard manual labor for prolonged periods (e.g., cutting sugarcane, weeding, and turning soil). Video-taped observations of the workers showed that smoking cannabis before working resulted in (1) greater numbers of movements or more variations in numbers of movement per unit of time and a higher kilocaloric expenditure per task and (2) more social cohesiveness during work in group situations. Despite the expenditure of more energy by the smokers, no differences were found in the overall work productivity of users and nonusers. Also, no differences were found between the groups in ownership and control of property and possessions or in weekly income. Comitas concluded that these data indicated there were no signs of apathy, ineffectiveness, nonproductiveness, or deficits in general motivation among Jamaican laborers, regardless of ganja use.

It is possible that the ganja smokers became dependent on the drug to perform their work and that for them not smoking may be disruptive. This possibility was not addressed by Comitas but deserves attention. Field investigations of chronic cannibas users could be more informative if subjects' behaviors are observed during a period of drug abstinence.

Chopra and Jandu (1976) reported that in India the greatest percentage of chronic cannabis users comes from the unemployed, low-income classes and from the student population. These people are passive, nonproductive, and prone to psychosis. The authors claimed that these characteristics were indicative of the amotivational syndrome, and since "there were no other common factors beyond the use of the drug," they concluded chronic cannabis use caused the syndrome. Unfortunately, Chopra and Jandu did not study a control sample of nonusers derived from the same socioeconomic and educational backgrounds. Without these appropriate comparisons, their data remain questionable.

Soueif (1976) reported that in Egypt a group of very frequent, chronic hashish users tended to work for longer hours

daily than did a group of more moderate, less frequent users. Again, however, no control group of matched nonusers was studied.

Results of the controlled cross-cultural studies indicate that culturally appropriate activity level and work capacity do not differ between chronic cannabis users and nonusers. The important finding is that long term use of cannabis preparations renders users tolerant to the drug's behaviorally disruptive effects which occur in infrequent users after single doses. The effects of single or acute doses on sensory, cognitive, and behavioral functions in nontolerant users are reviewed next, followed by a review of cannabis tolerance and dependence.)

ACUTE EFFECTS ON SENSORY, COGNITIVE, AND BEHAVIORAL FUNCTIONS

If cannabis tolerance appears so readily in populations of chronic, frequent users, a reasonable question is why the phenomenon is not observed more frequently in the "real world" of North American users. The answer is, because, at the relatively low doses and intermittent dosage schedules used presently in our culture, the conditions necessary for tolerance to develop are not met. The vast majority of cannabis users questioned in this country and Canada said that after they stop smoking marihuana they either do not experience (or, at least, do not report) changes that are indicative of either tolerance or dependence (Adamec, Pihl, & Leiter, 1976; Halikas & Goodwin, 1971; Hollister & Overall, 1975/76; Klonoff, 1973; Tart, 1971; Weil et al., 1968). These questionnaire and interview data suggest that the experience of most cannabis users in our culture is with acute effects produced by single doses of THC to which little or no tolerance has developed. Experienced users inevitably acquire expectations and some behavioral tolerance that alter THC effects, but such tolerance is probably lost quickly between smoking sessions (Babor, Mendelson, Greenberg, & Kuehnle, 1975; Jones et al., 1976).

Early Studies

The acute effects of different cannabis preparations and doses on perception, cognition, and behavior in casual and chronic users have been studied experimentally in literally hundreds of investigations commencing with the LaGuardia Report (Mayor's Committee on Marihuana, 1944). In studies conducted for the Report, 72 prisoners (48 of whom reported using cannabis previously), housed under police guard on Welfare Island, were given a battery of psychophysical and intellectual tests while intoxicated from different doses of orally administered cannabis extract. No control conditions were included and the doses and THC content of the cannabis were unspecified. The drug produced dose (i.e., quantity) dependent impairments of body and hand steadiness, choice reaction time performance, memory function,

and problem-solving ability. The Report concluded that the higher the dose and more complex the task, the greater the cognitive or behavioral impairment. With few exceptions (Borg et al., 1975; Weckowicz, Fedora, Mason, Radstaak, Bay, & Yonge, 1975), the Report's conclusion has been confirmed repeatedly in many subsequent controlled experiments (Herning, Jones, & Peltzman, 1979).

Some precedent-setting studies demonstrated dose-response relationships of cannabis effects in human subjects and stimulated other investigators to pursue cannabis research (Clark, Hughes, & Nakashima, 1970; Jones & Stone, 1970; Manno et al., 1970; Melges, Tinklenberg, & Hollister, 1970; Weil et al., 1968). The results of these early controlled studies showed that THC can interfere adversely with attention, recent memory, time perception, temporal organization of thought processes, rapid decisionmaking, and motor quickness.

Attention and Psychomotor Performance

Alterations in attention and impairment of various psychomotor tasks that require sensorimotor coordination (e.g., tracking) have been reported consistently by users and investigators of cannabis (see table 1, p. 35). Alteration of time perception appears to reflect a shift in focus of attention during cannabis intoxication. This alteration is characterized by an acceleration of subjective time so that clock time seems to pass more slowly. The data reviewed in table 1 indicate that when subjects are instructed to produce an interval of time from a specified beginning point during THC intoxication they tend to underproduce the interval. This suggests an acceleration of the internal passage of time. When asked to estimate (i.e., evaluate) the duration of an interval, THC-intoxicated subjects tend to overestimate the duration. This suggests a subjective slowing in the passage of external time. Recognition of the reciprocity between time production and time estimation measures of temporal perception is important in interpreting these data.

A consequence of the cannabis-induced alteration in time sense is "temporal disintegration" or "difficulty in retaining, coordinating and serially indexing those memories, perceptions and expectations that are relevant to the goal" (Melges et al., 1970, p. 1118). These investigators and later Casswell et al. (1973) and Casswell (1975) used the goal-directed serial alteration (GDSA) task, which depends on storage, coordination, and serial indexing of recent information and memories to reach a numeric goal, in assessing temporal disintegration during cannabis intoxication. GDSA was profoundly affected with a dose-dependent impairment of performance. Casswell et al. (1973) also reported no difference in performance between naive and experienced cannabis users on the GDSA task. Casswell (1975) again found no effect of prior use on GDSA performance but did report a trend

suggesting that increased motivation (i.e., monetary reward for good performance) decreased the impairment. Cappell and Pliner (1973) reported that their subjects compensated partially for intoxication effects on a time estimation task but not on a short term memory task. Temporal disintegration, at least when uncompensated for, may account, in part, for the disruption of speech patterns that occurs with cannabis intoxication in some people (Weil & Zinberg, 1969). Coherent speech requires that words and phrases, syntax and grammar, verb tenses and singular/plural nouns, be coordinated and organized hierarchically in a goal-directed manner. Disruption of short term memory and attention to temporal perspective can result in forgetting what one is going to say next and a tendency to follow irrelevant associations derived from past memories, present perceptions, and future expectations.

In summary, the data reviewed in table 1 indicate that alterations in attention and time perception, slowing of complex reaction times, disruption of information processing that requires simultaneous cognitive operations, and impairment of recent memory (see below) can result from cannabis intoxication. However, confidence in specifying acute cannabis effects will increase with an increased number of similar findings derived from replications that use valid measures. Unfortunately, many investigators persistently use disparate test instruments or incomplete samples of subtests from different test batteries whose sensitivity, reliability, and validity as measures of central nervous system function, let alone CNS drug effects, have yet to be established. There has been no uniformity in the selection of measures from study to study.

Even with measures that seem to reflect cannabis effects consistently (i.e., time judgment and complex reaction time tasks), differences in their form and content can make interpretation of changes difficult. That is, time judgment tasks consist of time estimation, time production, and time reproduction. Complex reaction time tasks measure perceptual, cognitive, and motor functions all in one number. Thus, different studies, using or emphasizing one or the other of these measures, can produce seemingly incompatible results that are more the result of differences in methodology and terminology than cannabis effects. As table 1 clearly demonstrates, differences in THC dose, route of administration, and type of task have complicated the understanding of acute cannabis effects. In addition, differences in the times of testing after dosing and in subjects' attributes contribute to the complexity. The amount of undrugged practice of a specific activity affects the subject's subsequent performance of the task while intoxicated; likewise, practice while intoxicated improves the subject's performance (Peeke, Jones, & Stone, 1976).

The use of electroencephalographic (EEG) measures of CNS function and cannabis effects is a good example of the caveats presented above. Fink (1976) reviewed the EEG effects produced

by cannabis: a slight decrease in dominant frequency, an increase in alpha power, a decrease in beta power, with a peak effect occurring quickly after smoking. But the scalp-recorded EEG measures only about one-third of the brain's activity (i.e., its outer shell and a small portion of the undersurface and medial surface of the cerebrum). The EEG is influenced by several factors other than psychoactive drug intoxication: neuropathology; mood; level of consciousness; vigilance; age; sex; metabolic state; sensory excitation; and genetic, cultural, and educational variables; to name a few. These factors may readily obviate or obscure presumed drug effects. Thus, reliance on "firmer" neurological measures as predictors of cannabis effects must be viewed cautiously (Dornbush, 1975).

Memory and Information Processing

Disruption of memory function is a frequently reported consequence of cannabis intoxication (Abel, 1971a, 1971b, 1971c; Darley, 1973, 1977; Darley, Tinklenberg, & Roth, 1974; Darley et al., 1973; Miller, 1972, 1977; Miller & Cornett, 1976; Miller, Cornett, Drew, McFarland, Brightwell, & Wikler, 1977; Miller, Cornett, & McFarland, 1978; Miller, McFarland, Cornett, & Brightwell, 1977; Peeke, Jones, & Stone, 1979; Pfefferbaum, 1977). These studies demonstrated that (1) verbal information presented during intoxication is not recalled as well as information presented following placebo or no-drug treatment; (2) to-be-remembered information presented prior to intoxication is equally well recalled subsequently during intoxication and after placebo or no-drug treatment; (3) retrieval of nonexperimentally presented information from long term memory is unaffected by cannabis intoxication; and (4) during recall intoxication increases the number of intrusions (irrelevant information not part of the original to-be-remembered presentation).

Two hypothetical models of memory function provide the theoretical framework in which these results have been interpreted. One model postulates a process called storage which refers to the operations engaged when information is initially learned by an individual. The major effect of cannabis is to inhibit the transfer of incoming information from a short term storage site to a long term storage site. Transfer is completed successfully, under normal circumstances, when information is rehearsed overtly or covertly until it becomes linked to preexperimental associations stored in long term memory. Rehearsal is disrupted by cannabis' effect on the individual's attention level and capacity to concentrate on the information. Thus, transfer is incomplete and the individual fails to store (and later recall) the information.

However, the extant data do not support the latter predictions of the above hypothesis. Reference to table 1 shows no study reporting a decrement in intoxicated subjects' Continuous

Performance Test scores, a measure of ability to sustain attention. Also, Darley et al. (1974) reported that cannabis intoxication impaired the storage of information even when overt rehearsal in the drug and no-drug states was manipulated and equated.

Virtually all the studies of acute memory deficits associated with cannabis intoxication show that the effect is produced at the time of presentation of the information to be learned. The finding that cannabis also increases the number of intrusions in recall tests suggests that the drug acts to alter the formation of associations between incoming information and those in long term memory during rehearsal. Formation of these associations can result in clusters of conceptually related responses being emitted during recall. Peeke et al. (1979) and Pearl et al. (1973) reported that conceptual clustering is reduced by cannabis during recall of wordlists. Of course, the conceptual clusters used experimentally are imposed by the investigators. Intoxicated subjects may either fail to recognize these clusters or employ their own coding strategies. In either case, their ability to recall task-relevant items later is impaired.

The study of cannabis intoxication on memory function requires extension in at least two important directions. Virtually nothing is known about cannabis effects on memory systems that do not rely on linguistic or verbal mediation. Also, the influence of practice, in both drugged and undrugged states, on memory function and psychomotor performance needs further attention. This latter area includes studies of state-dependent learning and behaviorally augmented tolerance. Researchers reported evidence that state-dependent learning of word associations, spatio-temporal relationships, and pattern recognition occurs with cannabis (Cohen, Rickles, & Naliboff, 1975; Rickles, Cohen, & Whitaker, 1973; Stillman et al., 1974). That is, information learned in either the drugged or undrugged state is recalled better in the same state that it was learned in. Beautrais and Marks (1976) reported no evidence for state-dependent learning tasks' requiring simple sorting and dexterity skills. Such studies are very relevant to military contexts if and when personnel learn codes, maps, or other information while sober (or intoxicated) and then have to recall and use the information in a subsequent drugged (or sober) state.

Vigilance, Tracking, Driving, and Flying

Complex behaviors such as driving and flying require continuous integration of vigilance and tracking skills. Vigilance consists of an acute sensory awareness of the surrounding environment with an ability to detect subtle changes almost instantaneously. Tracking involves the coordination of sensory input and motor output to keep a moving vehicle on target. Together with recalling where one is going, successful vigilance and

tracking determine the efficiency of driving and flying performance. Several experiments conducted in the last decade investigated the influence of cannabis intoxication on vigilance, tracking, simulated automobile driving, real automobile driving, and simulated airplane flying (Crancer et al., 1969; Hansteen, Miller, & Lonero, 1976; Janowsky, Meacham, & Blaine, 1976; Klonoff, 1974; Moskowitz & McGlothlin, 1973; Moskowitz et al., 1973; Rafaelsen, 1973; Rafaelsen, Bech, & Rafaelsen, 1973; Rafaelsen, Christup, & Bech, 1973; Sharma & Moskowitz, 1974).

Moskowitz and McGlothlin (1973) studied performance changes in an auditory signal detection task under conditions of both concentrated and divided attention after 23 healthy male college students received either no drug, a placebo, or three active doses of smoked cannabis. Doses of 0, 50, 100, and 200 µg/kg of THC were used. In the concentrated attention condition, subjects listened to a tape that contained a series of random noise bursts of 3-second durations each, separated by a 7-second silent intertrial interval. Half of the noise bursts contained a 1,000-Hz signal of 1-second duration, 15 decibels below the level of the noise. The tone occurred randomly within the 3-second noise burst on 50 percent of the trials. Subjects were instructed to report the presence or absence of the tone. In the divided attention condition, subjects heard a series of lists of six random digits which occurred at 0.5-second intervals during the same 3 seconds that the 3-second noise burst occurred on the other tape channel. Subjects were instructed to attend to information coming to both ears, reporting the presence or absence of the tone in the noise burst and also repeating the six random digits. No differences in performance were found between the no-drug and the placebo treatment conditions. Cannabis produced a significant decrement in signal detection under both attention conditions. The degree of impairment was greater under the more complex demands of divided attention. However, digit recall in the divided attention task was minimally affected by cannabis. The impairment of signal detection performance occurred from both a failure to detect the tone (misses) and a tendency to report the tone as present when it was not (false alarms). The increased false alarm rate is similar to the increase in intrusions reported in the memory experiments reviewed above. In the language of signal detection theory, the effect of cannabis is both to reduce perceptual discrimination sensitivity and to alter the criterion used by subjects to determine a signal's presence. Similarly, Sharma and Moskowitz (1974) reported increasing performance decrements in successive time periods when subjects were required to detect infrequent visual signals which occurred in a circular sequential pattern of light after the subjects received 200 µg/kg of THC.

Hansteen et al. (1976) investigated the effects of cannabis and alcohol, in two different doses given alone and together, on psychomotor tracking performance. Each of 22 male subjects received placebo treatment (extracted cannabis and a nonalcoholic

drink), two doses of cannabis (21 and 88 µg/kg of THC), two doses of alcohol that yielded blood alcohol levels of 0.03 percent and 0.07 percent, and the low cannabis and alcohol doses combined. After drinking and smoking, subjects performed the tracking task. The task consisted of manipulating a hand-operated "joy stick" in such a way as to keep a small target circle as close as possible to a fixed central horizontal target line. The circle and line were displayed in front of the subject on an 3- by 10-inch screen. In addition to this simple tracking task, a more complex task tested subjects' abilities to compensate for unexpected reversals of polarity in the joy stick's control plus a secondary attention-reaction time task which required subjects to respond with their foot each time a light appeared without warning on a tube above the target screen. In each session (one for each treatment), the first trial consisted of four simple tracking tests and two complex tracking tests.

Compared to the placebo, alcohol produced a clear dose-related increase in errors in the simple tracking test. The higher cannabis dose, but not the lower dose, also resulted in a significant increase in error scores. The combination of low-alcohol and low-cannabis doses produced error scores that were not significantly different from those obtained in the low-alcohol dose alone condition. There were no consistent drug effects on error scores in a trial given 4 hours after drug administration. The higher alcohol and cannabis doses and the combination of the low doses produced increased error scores for complex tracking compared to the placebo effects. The combination of the low doses of the two drugs produced greater error scores in the complex tracking test than the errors that resulted from the corresponding doses of each drug given alone. Blood alcohol levels obtained after the administration of the low-alcohol dose alone were not different from the corresponding levels in the low-alcohol low-cannabis combination condition. This finding suggests that at the low doses studied cannabis does not have a significant effect on the bio-availability of alcohol. Foot choice reaction time was faster in the placebo condition than in any of the drug conditions; however, only the decrement due to the higher alcohol dose was significant. Hansteen et al.'s results indicate that alcohol, cannabis, and the combination of these drugs can result in decreased psychomotor tracking performance. The more pronounced performance decrement that resulted from the combination of the two drugs suggests an additive interaction between them. The relevance of these vigilance and tracking performance deficits to simulated and real automobile driving and simulated airplane flying is seen in studies of these phenomena.

Crancer et al. (1969) compared the effects of cannabis intoxication (dose unspecified, subjects smoked two cigarettes of approximately equal weight and totaling 1.7 grams), alcohol intoxication (0.10 percent blood alcohol level), and no treatment on simulated driving performance over a 4½ hour period. Thirty-six subjects received each treatment and were tested in a

console mockup of a recent-model automobile containing all the control and instrument equipment relevant to driving. The console faced a 6- by 18-foot screen upon which a test film was projected. The film depicted normal and emergency driving situations on freeways and urban and suburban streets. Speedometer, steering, brake, accelerator, and signal errors during the driving sequence were monitored. Error scores for the cannabis and the no-treatment conditions were not different. Alcohol produced significantly more errors than the other two treatments. Separate analyses of the individual types of driving errors revealed that alcohol increased accelerator, signal, braking, and speedometer errors compared with an increase in speedometer errors only for the cannabis treatment.

Rafaelsen and colleagues also compared the effects of cannabis and alcohol on simulated automobile driving (Rafaelsen, 1973; Rafaelsen, Bech, & Rafaelsen, 1973). Both cannabis (8, 12, and 16 mg of THC oral) and alcohol (70 grams) increased the time required to brake and start, whereas alcohol increased and cannabis decreased the number of gear changes.

Moskowitz and colleagues conducted a double-blind examination of the effects of three doses of smoked cannabis and a placebo treatment on performance in a complex driving simulator which used a film projection system (Moskowitz, Hulbert, & McGlothlin, 1973; Moskowitz et al., 1973). Driving in the simulator yielded speed, accelerator, braking, steering, and tracking scores. During the simulation, subjects also performed a visual reaction time test designed to provide a sample of the greater search-and-recognition task demanded by actual driving situations. In each of four sessions, each of 23 male college students smoked two marihuana cigarettes of approximately 0.5 gram each that contained either 0, 50, 100, or 200 µg/kg of THC. Immediately after smoking, subjects entered the simulator and drove the 31-mile projected drive which required between 45 and 70 minutes, depending on the speed subjects selected. The data provided no evidence that cannabis significantly affected car control performance as measured by the driving simulator. However, the data did indicate a dose-related impairment of reaction time to visual stimuli presented during the drive.

Conclusions about the effect of cannabis on actual driving behavior are difficult to draw from studies of simulated driving. No driving simulator is a truly complete sample of all the elements that enter into the demands of real driving. Each simulator selects some sample of driving behavior that the investigator considers relevant to the driving task. The validity of simulated behavior is a crucial methodological issue in all of these studies. For example, Crancer et al. (1969) instructed subjects to manipulate the steering wheel and turn signals and to brake and accelerate. These actions, however, had no effect on the presentation of the driving film. The accelerator did control the speedometer reading, and maintaining the speedometer reading

within given limits was one of the response measures. The evidence presented by Crancer et al. that speedometer monitoring was affected adversely by marihuana agrees with the results of Sharma and Moskowitz (1974). That is, cannabis has a consistent effect on vigilance. Since the other responses had no effect on the projected drive, they seem to have no face validity for actual driving.

In the studies by Rafaelsen and colleagues the simulator was equipped with a steering wheel, an accelerator, a brake, a gearshift, and a clutch. The accelerator controlled the speed of the circular landscape and the steering wheel shifted the image projected onto the windshield. Red and green lights above the windshield signaled the driver to stop and start. Response measures were brake time, start time, number of gear changes, and mean speed. These measures were thus more characteristic of a real driving situation. The adverse effect of cannabis on braking and starting times in response to the lights corresponds with Moskowitz et al.'s (1973) findings and indicates that cannabis interferes with the perceptual aspects of driving and the monitoring of the environment. Evidence is less strong for a loss of car control or of tracking decrements under the influence of cannabis. Car control performance, however, is best tested in actual automobile driving situations.

Car handling and tracking were examined in on-the-road tests using a closed course and street traffic (Klonoff, 1974; Hansteen et al., 1976). Klonoff's study compared 4.9 and 8.4 mg of THC, smoked, with placebo cannabis. The experiment involved a driving course and a driving test on city streets. Subjects' abilities to weave between poles, drive through tunnels of different lengths, assess the risk that would be involved in passing between two rows of cones, back up, negotiate turning a corner and react to an emergency braking situation were assessed in the driving course. On the city streets, subjects' general driving habits, including posture, starting and stopping, carelessness with driving regulations, turning, lane changes, traffic signal detection, cooperation, attitude, irritability, judgment, speed, carelessness, confidence, tension, aggressiveness and concentration were assessed by a trained observer who sat in the car while the subject was driving. On the driving course, cannabis, in a dose-related fashion, impaired driving performance as compared to pre-drug trials and the placebo treatment. Driving scores declined 29 percent from predicted for the group of subjects smoking low doses and 54 percent for the group smoking high doses. On city street driving, greater variability in subjects' driving performance was noted by the observers. Driving performance of some subjects receiving the low dose actually improved compared to placebo while performance for subjects receiving the high dose declined compared to placebo. Klonoff concluded that the effect of cannabis on driving is bidirectional and dependent on compensatory ability and dose.

Hansteen et al.'s (1976) study compared 21 and 88 μg/kg of THC, smoked, with a blood alcohol level of 0.07 percent and placebo treatments. The experiment involved subjects' driving six circuits of a 1.1-mile course through lanes marked off with cones and poles. Both forward and backward maneuvering were involved. The mean number of objects struck per lap under placebo treatment was 13.2. This number rose to 16.8 for the higher marihuana dose and to 17.4 for the alcohol treatment. The low dose of cannabis had no effect. However, trained observers in the car and on the course were unable to discriminate between driving behaviors for the four treatment conditions. This finding suggests that, at the doses given, the drugs' effects on driving performance were not dramatic.

On the whole, the results of all these studies emphasize the possibility that cannabis may adversely affect traffic safety and driving performance. The locus of the impairment seems to be in the perceptual functioning of intoxicated drivers and in their monitoring of the environment. Evidence of a loss of car control or of tracking decrements under the influence of cannabis is more tentative. It is not clear to what extent the car control and tracking tasks that showed performance impairment after subjects ingested cannabis are representative of actual car control and tracking demands of driving.

Obviously further research is urgently required to better understand the effects of acute cannabis intoxication on complex behavioral skills. Only one study of simulated flying performance after cannabis intoxication has been reported (Janowsky et. al., 1976). Ten experienced pilots smoked, in counterbalanced order on a double-blind basis, 0.09 mg/kg of THC and a placebo cigarette after they were trained to fly a specific sequence on a standard flight simulator. In contrast to the placebo treatment, cannabis caused a gross decrement in flying performance, with increased prevalence of major errors, minor errors, altitude deviations, heading deviations, and radio navigation errors. These effects persisted for at least 2 hours and generally disappeared by 4 to 6 hours after the drug administration. All the subjects in this experiment had smoked marihuana socially for several years. No mention is made of the pilots' previous flying experience while under the influence of cannabis. As with driving, it is possible that pilots learn to compensate for the drug's effects while flying. Further research is required to determine the effects of altitude and pressure changes in conjunction with cannabis on the performance of intoxicated pilots. The authors' description of the intoxicated pilots is informative: "Subjects often forgot where they were in a given flight sequence or had difficulty recounting how long they had been performing a given maneuver, in spite of the presence of written instructions and a stopwatch. Marijuana also appeared to cause alterations in concentration and attending behavior, so that pilots would concentrate on one variable to the exclusion of other variables or perhaps attend to intrusive thoughts" (p. 127).

In summary, the impairment of driver and pilot performance probably reflects cannabis' ability to affect complex learned psychomotor skills involving memory, attention, concentration, time sense, perceptual orientation in three-dimensional space, and the simultaneous performance of multiple complex tasks. The implications of these cannabis effects on militarily relevant performance are obvious but require substantial additional experimental study. A critical question concerns adaptation to cannabis' acute effects with repeated use.

CHRONIC USE: TOLERANCE AND DEPENDENCE

The term tolerance refers to the diminution of an initial effect with repeated exposure to the same dose. Conversely, tolerance also refers to the reproduction of an initial effect with an increase in dose. Ideally, experimental studies of tolerance should incorporate both definitions into research designs. Also, the phrase behaviorally augmented tolerance (Kalant, LeBlanc, & Gibbins, 1971) refers to the finding that tolerance to a drug develops more rapidly if the user performs or attempts to perform a task or complex behavior while under the influence of the drug.

The term dependence refers to (1) the occurrence of abstinence phenomena following cessation of drug use and (2) the occurrence of repetitive drug-seeking and drug-taking behaviors. Abstinence phenomena consist of physiological, behavioral, and/or subjective symptoms that are terminated by administration of the drug. Although drug seeking and drug taking may occur in the absence of obvious abstinence symptoms, the behavior may be reinforced strongly by the drug's ability to terminate incipient withdrawal symptoms.

There is considerable evidence that tolerance to cannabis develops in animals (Ferraro et al., 1972; Wikler, 1976). Several studies comparing frequent and infrequent cannabis users in the United States showed that, after acute doses of THC, experienced users were less affected and performed better on behavioral tasks than persons with minimal or no cannabis experience (Mayor's Committee on Marihuana, 1944; Weil et al., 1968; Meyer, Pillard, Shapiro, & Mirin, 1971; Jones, 1971). Other studies with similar rationales and designs failed to find evidence to suggest tolerance development in experienced users (Hollister & Tinklenberg, 1973; Perez-Reyes, Timmons, & Wall, 1974; Renault, Schuster, Freedman, Sikic, deMello, & Halaris, 1974). Another group of studies provided for experimental administration of placebo and active THC doses in controlled, live-in laboratory settings for extended periods of time (Babor et al., 1975; Dornbush, Clare, Zaks, Crown, Volavka, & Fink, 1972; Jones et al., 1976; Nowlan & Cohen, 1977; Williams et al., 1946). The most recent studies have provided the clarification necessary to draw some reliable conclusions regarding the necessary and sufficient conditions for development of cannabis tolerance and dependence.

Williams et al. (1946) administered synhexyl (a synthetic THC, 60-2,400 mg a day in one to eight divided doses for 26-31 days) and marihuana cigarettes (THC content not assayed, 1 to 26 cigarettes a day for 39 days) to groups of imprisoned marihuana users. Initial effects produced by synhexyl included sedation, euphoria, dry mouth, increased appetite, slowed reactions, and difficulty expressing thoughts verbally. After 4 to 6 days, all subjects chose to increase their dosage, with reappearance of the initial effects that had dissipated. Initial marihuana-smoking effects also included euphoric or silly behavior, but this behavior quickly changed to decreased activity and sedation. The subjects did not choose to increase their smoked dosage to the same extent that they increased their oral dosage of synhexyl. Tolerance developed to the initial increase in pulse rate produced by smoking. By the third day following abrupt cessation of synhexyl administration, most subjects became restless, slept poorly, lost their appetites, felt hot flashes, and perspired. Only transient jitteriness occurred after cessation of marihuana smoking.

Dornbush et al. (1972) administered one marihuana cigarette (1,000 mg of cannabis containing 1.4 percent THC or 14 mg of THC) daily for 21 consecutive days to five experienced cannabis users. Tolerance developed to the initial impairment of short term memory (i.e., recall of trigrams after 6- to 18-second delays), the increase in pulse rate, and subjective effects.

Babor et al. (1975) studied "moderate" and "heavy" users of marihuana over 21 consecutive days during which the subjects "worked" (i.e., button pressed) for money with which they could purchase marihuana cigarettes (1,000 mg of cannabis containing 1.8 percent to 2.3 percent THC or 20 mg of THC). The moderate users smoked an average of 3.2 cigarettes a day and the heavy users smoked an average of 5.7 cigarettes a day. Throughout the 3-week smoking period, there was no diminution in intoxication ratings or in duration of increased pulse rate for the moderate users after smoking. However, there was a progressive decrease in intoxication ratings and in duration of increased pulse rate for heavy users. The authors concluded that tolerance to marihuana's effect on pulse rate and subjective sense of intoxication develops only when large amounts are smoked daily.

In a paper based on the same experiment as Babor et al.'s (1975), Mendelson and colleagues reported that all the moderate user subjects and most of the heavy user subjects increased the amount they smoked during the 21 days (Mendelson, Babor, Kuehnle, Rossi, Bernstein, Mello, & Greenberg, 1976). Both groups worked on the button-pressing task between two and five times as many hours a day as was necessary to earn the number of cigarettes smoked. Subjects earned and saved a lot more money than was spent for marihuana. The authors concluded that the increase in marihuana consumption without any accompanying behavioral disruption may reflect behavioral tolerance. Their data do not support

the hypothesis that daily marihuana use produces an amotivational syndrome. Mendelson et al.'s (1976) findings are consistent with those of the cross-cultural studies in suggesting that tolerance develops to cannabis-induced disruption of simple, although strenuous, behavioral tasks.

It should be noted, too, that Mendelson et al.'s subjects exhibited weight loss, lessened appetite, increased finger tremor, and increased irritability after the smoking period. These changes were not interpreted by Mendelson et al. as abstinence phenomena or evidence of dependence.

Nowlan and Cohen (1977) studied 30 hospitalized marihuana users for a 94-day period during which the subjects smoked at least one marihuana cigarette (900 mg of cannabis containing 2.2 percent THC or 19.8 mg of THC) for 64 days. Tolerance developed to the initial increases in heart rate and intoxication. Similar to Mendelson et al.'s study, there was a minimum of 9 to 12 hours of sleep-imposed abstinence between smoking the last cigarette of one day and the first cigarette of the next day. During the week of abstinence following the smoking period, restlessness, sleeplessness, appetite loss, mild nausea, and irritability were observed in the subjects. These changes were interpreted as mild withdrawal reactions.

With the exception of Williams et al.'s (1946) use of repeated oral doses of synhexyl, the studies reviewed above administered smoked doses of cannabis that contained approximately 14 to 23 mg of THC per dose. On the assumption (made by Kiplinger & Manno, 1971) that only 50 percent of the THC content of a cigarette is actually available in the smoke, the delivered doses in the above studies ranged from 7 to 11 mg of THC. Furthermore, in each of these studies, between one and six or seven cigarettes were smoked per day. There was always a sleep-induced period of abstinence in each of these studies. All this is to emphasize the relatively low doses that were (relatively) infrequently administered in these studies. The doses and dosage schedules used in these North American studies were certainly lower and more infrequent than the usage patterns of cannabis reported in Costa Rica, Jamaica, Greece, Egypt, and India. That tolerance was shown to develop at such low and infrequent doses suggests the phenomenon is an important characteristic of cannabis pharmacology.

Jones et al. (1976) used a different dose, dosage schedule, and route of administration to study cannabis tolerance and dependence. Oral doses of 30 mg of THC were given to 53 hospitalized male volunteers, every 4 hours, for 11 to 21 days. Three- to 9-day periods of placebo (i.e., sesame oil) administration preceded and followed the THC period. The total daily dose administered to the subjects was 210 mg, or, on a per kilogram basis, 3.1 mg/kg/day (range = 2.2 to 4.2 mg/kg). This total dose is about equal to the dose self-administered by Mendelson et al.'s

subjects when certain considerations are taken into account. Kiplinger and Manno (1971) estimated that the potency of THC when smoked is about three times greater than when ingested orally. Thus, when Mendelson et al.'s "heavy" user subjects smoked seven 1-gram cigarettes that contained 20 mg of THC and delivered 10 mg of THC, they self-administered about 70 mg of THC a day. With the conversion to oral potency (70 mg x 3), this dose approximately equals the dose that Jones et al.'s subjects received daily (i.e., 210 mg of THC). Thus, although the dose of THC was comparable for the two studies, the distribution of its administration throughout the day was entirely different. Jones et al.'s dosage schedule produced and maintained a consistent tissue level of the drug for a prolonged period of time. This variable appears to be crucial to the development of tolerance and dependence to many psychoactive drugs (e.g., opiates, barbiturates, ethanol), and it is not surprising that constant, prolonged tissue levels of THC are necessary to produce tolerance.

Jones et al. (1976) found that tolerance developed to THC-induced mood changes, tachycardia, orthostatic hypotension, skin temperature decrease, body temperature increase, salivary flow decrease, intraocular pressure decrease, EEG slowing, EEG-evoked potential alterations, sleep EEG changes, sleep time and quality, eye-tracking deficits, psychomotor impairments, and behavioral disruptions (i.e., sedation). Furthermore, signs and symptoms of abstinence phenomena after abrupt cessation of the prolonged THC administration included increased feelings of anxiety, anger, and vigor; insomnia; decreased appetite; restlessness; irritability; perspiration; weight loss; nausea; abdominal distress; hemoconcentration; increased salivation; tremor; body temperature increase; sleep EEG eye movement rebound; waking EEG changes; and intraocular pressure increase. Although drug-seeking behavior was not measured, administration of either smoked or oral doses of THC terminated all these changes. The onset of some of these symptoms began as soon as 4 hours after the last dose (e.g., sleep EEG changes -- see Feinberg et al., 1975). Most changes reverted to basal, predrug levels by 96 hours, although sleep disturbances in some subjects lasted for 1 week. Jones et al. also demonstrated that tolerance is lost very rapidly after cessation of THC administration. Within 24 to 48 hours after the last THC dose, subjects' heart rate increase after smoking a marihuana cigarette was equal to the increase produced by a cigarette before oral THC. During the period of oral THC administration, no heart rate increase occurred after smoking a marihuana cigarette. This is evidence of cross-tolerance between oral THC and smoked cannabis.

One important aspect of cannabis tolerance and dependence that has not yet received adequate experimental attention concerns the effect of tolerance development on cannabis-seeking and cannabis-taking behaviors. The question is whether tolerance development to the subjective changes users seek necessitates an increase in consumption to achieve previous levels of intoxication or produces a switch to another drug. The cross-cultural studies of chronic cannabis users were not longitudinal, and hence data

are not available concerning users' tendencies to increase their doses. Mendelson et al.'s studies showed that both groups of users increased their consumption of marihuana over the 3-week smoking period, but tolerance development was not independently manipulated, as in Jones et al.'s study. A study that incorporated both Jones et al.'s dose and dosage schedule and Mendelson et al.'s marihuana self-administration paradigm would allow systematic manipulation of tolerance and dependence while cannabis consumption was measured as a function of these independent variables. Selection and use of other drugs could easily be incorporated into the experiment.

CANNABINOID INTERACTIONS WITH THC AND OTHER DRUGS

CANNABINOID COMPOSITION AND INTERACTIONS

Cannabinoid composition varies in plants grown in different areas (Paton, 1975). Three basic phenotypes are characterized by a high delta-9-tetrahydrocannabinol (THC) to cannabidiol (CBD) ratio, an equal THC to CBD ratio, or a low THC to CBD ratio. Studies with human subjects have shown consistently that THC produces a broad spectrum of pharmacologic activity (see below), but CBD produces little or no effect when given alone. Studies of the interactions between various cannabinoids indicate that the botanical differences can produce pharmacological differences, although the results have not been consistent (Bachman et al., 1979; Dalton, Martz, Lemberger, Rodda, & Forney, 1976; Hollister & Gillespie, 1975; Karniol, Shirakawa, Kasinski, Pfefferman, & Carlini, 1974).

When single doses of THC and CBD are given together, both attenuation and potentiation of THC effects have been reported. The use of different doses between studies is one reason for the inconsistency of results, but the particular response system assessed is also a factor. In Karniol et al.'s (1974) study, 30 mg of THC plus 15 mg of CBD, taken orally, produced an even greater heart rate increase than THC alone, but resulted in less subjective changes. In the same study, when the dose of CBD was increased to 30 or 60 mg, the heart rate increase was lessened, as were subjective changes. These results confirm that the ratio of THC to CBD dose, the absolute dose levels, and the response systems measured all contribute to the cannabinoid interaction.

Dalton et al. (1976) also reported that subjective changes were diminished when THC and CBD were given together. Psychomotor effects were not significantly altered, however, when the cannabinoids were combined. Dalton et al. used a combination of 150 µg/kg of CBD plus 25 µg/kg of THC in a single smoked dose. Hollister and Gillespie (1975) reported a delay in the onset of activity but a prolongation of subjective effects when 20 mg of THC were combined with 40 mg of CBD, given orally. Bachman et al. (1979) found no evidence for an interaction between THC and CBD at

the level of subjective and cognitive effects when subjects smoked cannabis cigarettes (containing 2.2 percent THC) before, during, and after a 7-day period of chronic oral CBD administration. Only the immediate heart rate increase produced by the cannabis cigarettes was diminished during the CBD period.

Results of these studies indicate a small interaction between THC and CBD when the two cannabinoids are consumed simultaneously. In addition to dosage differences, route of administration (oral versus smoked) could also contribute to the interaction, particularly if the bio-availability of one cannabinoid is affected by coadministration of the other. Simultaneous versus sequential administration of single doses may influence the interaction, too, as demonstrated by Dalton et al. (1976). They showed that when CBD preceded THC by 30 minutes there was no interaction effect.

No definitive study designed to clarify the mechanisms mediating the THC-CBD interaction has been conducted. Such a study would require intravenous administration of radioactively labeled TCH given in a dose sufficient to produce reliable effects, either alone or in combination with various doses of intravenously administered CBD. In this way, the pharmacokinetics of THC could be studied and related to the responses produced by THC when the dose of CBD and the interval between CBD and THC are manipulated systematically. The intravenous route allows known doses to be administered and permits control of differences in absorption rates and/or smoking techniques. In such a study, the influence of CBD on THC effects, blood levels, and metabolism could be determined. This information is needed to determine (1) if CBD competitively inhibits binding of THC at common sites of action and (2) if CBD accelerates or retards the formation of active THC metabolites. A CBD-produced delay in the formation of active THC metabolites and/or a CBD-related prevention of THC binding at activity sites could be responsible for the reported diminution of THC effects.

A study similar to the one described above conducted by Hunt, Bachman, and Jones (1979) showed that pretreatment with 1,500 mg of CBD, given in 500-mg oral doses 9, 6, and 3 hours before an intravenous injection of radioactively labeled THC (2 mg), had no influence on THC effects or blood levels. This result, analogous to that of Dalton et al. (1976), emphasizes the importance of manipulating the interval between CBD and THC to clarify the drugs' interaction.

Studies of the interaction between cannabis and other frequently used (and abusable) drugs are important for two reasons: (1) combined use of cannabis and one or more other drugs is a frequent consumption pattern and (2) people tolerant to cannabis effects and either unable or unwilling to increase cannabis consumption may take other drugs to reproduce or modify cannabis effects. Studies reviewed above, in table 1, and in the section on driving compared the effects produced by different doses of THC

and ethanol (Bech et al., 1973; Cappell et al., 1972; Crancer et al., 1969; Hansteen et al., 1976; Hollister & Gillespie, 1970; Jones & Stone, 1970; Rafaelsen, 1973; Rafaelsen, Bech, & Rafaelsen, 1973; Tinklenberg, 1972; Tinklenberg, Roth, & Kopell, 1976). With the exception of Hansteen et al. (1976), none of these studies administered the two drugs together to evaluate the effect of their combination on human performance. Only a few studies have done this and fewer studies yet have investigated the effects of cannabis combined with other drugs, such as barbiturates, stimulants, or opiates. Further research is needed to evaluate the effects on human performance of different doses of THC combined with different doses of the other drugs frequently used with cannabis.

CANNABIS-ALCOHOL INTERACTIONS

This section reviews studies that have administered cannabis and alcohol alone and in combination. Adams et al. (1978) reported that the time course of light adaptation after intense light exposure (i.e., glare recovery) is significantly delayed by alcohol (0.75 ml/kg), cannabis (8 and 15 mg, smoked 10 minutes after subjects begin to drink), and a combined dose of alcohol and the higher THC cigarette. The difference between glare recovery times after the combined doses versus after either drug alone was not significant. This lack of difference suggests that the combined treatment may produce some antagonism between the two drugs. A cannabis-alcohol interaction was evident in the significantly lower blood alcohol levels obtained when the two drugs were combined than after alcohol alone. The cannabis was smoked 10 minutes after subjects began to drink and may have interfered with the absorption of the alcohol. THC has been shown to decrease gastrointestinal motility in animals (Chester, Dahl, Everingham, Jackson, Marchant-Williams, Starmer, 1973). This may account for the effects on alcohol absorption reported by Adams et al. (1978). Altered rates of absorption are important in evaluating interactions between THC and other psychoactive drugs, because the rate of rise of blood and brain levels contribute to the maximum effects of these drugs. Benowitz and Jones (1977) also reported that chronic doses of THC delayed absorption of both ethanol and pentobarbital in human subjects.

Chesher et al. (1977) administered an oral dose of ethanol (0.54 g/kg) with approximately 15 mg of THC, given orally 1 hour before drinking. THC pretreatment had no effect on subsequent blood alcohol levels. However, the effects of THC plus ethanol were greater than those of either drug alone, and these additive effects occurred within 40 minutes of THC administration. Additive effects of the two drugs were observed in tests of standing steadiness, complex reaction time, simple visual reaction time, and numerical reasoning. Belgrave and colleagues also reported additive effects on these measures after a higher dose of THC (Belgrave, Bird, Chesher, Jackson, Lubbe, Starmer, & Teo, 1979).

In a brief report, Sulkowski, Vachon, and Rich (1977) reported that 1 g/kg of ethanol plus 18 mg of THC (smoked 1 hour after drinking) produced significantly more nausea and vomiting in four out of seven subjects than was produced by alcohol alone. They did not report blood alcohol levels following the combination of drugs or alcohol alone.

As reviewed above in the section on driving, Hansteel et al. (1976) reported that ethanol, given in a dose sufficient to produce a 0.03 percent blood alcohol level plus 1.6 mg of THC, smoked 15 minutes after drinking, produced a greater performance decrement in psychomotor tracking than the decrement produced by either drug given alone. Hansteen reported that blood alcohol levels obtained after the administration of the low-alcohol dose alone were not different from the corresponding measures in the low-alcohol plus cannabis combination condition. From this finding, they concluded that, at the low doses studied, cannabis does not have a significant effect on the rate of alcohol appearance in and disappearance from blood. However, they administered ethanol in doses sufficient to produce a given blood alcohol level in each individual. That is, they did not administer a predetermined, fixed dose to each individual. This technique precluded determination of the effect of cannabis on ethanol blood levels.

Manno and Kiplinger (1971) gave 15 ml per 50 pounds of ethanol plus either 0, 2.5, or 5 mg of THC (smoked in cigarettes 30 minutes after drinking) and measured pursuit rotor tracking and delayed auditory feedback mental performance in 12 human subjects. The high dose of THC produced significant impairment in performance of both the mental and motor tasks. The combination of the two drugs generally produced an additive decrement in performance. Unfortunately, no data regarding blood alcohol levels after either alcohol alone or the combination of the two drugs were reported.

In the study conducted by Benowitz and Jones (1977), 22 hospitalized, healthy subjects received 60 to 180 mg of THC a day in divided doses for 14 days. Body weight increased and plasma volume expanded significantly during the period of THC administration. A within-subject comparison of the pharmacokinetics of antipyrine, pentobarbital, and ethanol given before, during, and after THC showed that antipyrine plasma half-life increased during THC in five of six subjects, pentobarbital half-life increased in seven of eight subjects, and blood ethanol disappearance rate decreased in seven of eight subjects. The effect of THC on the disappearance rate of these drugs appeared to be due to a combination of (1) increased volume of distribution due in part to expansion of extracellular fluid volume during THC ingestion and (2) diminished metabolic clearance. The subjective effects produced by pentobarbital and ethanol during THC administration were substantially diminished compared with the effects before and after. This finding indicates that cross-tolerance develops between cannabis and, at least, ethanol and pentobarbital in the doses administered. This finding is significant because it implies that chronic cannabis use and, hence, cannabis tolerance

may make people tolerant to other depressant drugs, such as alcohol and barbiturates. This, in turn, may lead to the use of increased doses of the latter two drugs. Again, however, drug self-administration studies in people tolerant to cannabis have not been conducted experimentally.

MISCELLANEOUS STUDIES OF CANNABIS' INTERACTIONS WITH OTHER DRUGS

Given the widespread usage of cannabis, surprisingly few experimental studies of its use in combination with barbiturates, opiates, and stimulants have been conducted. Secobarbital and smoked cannabis had additive effects on subjective responses and psychomotor impairment (Dalton, Martz, & Lemberger, 1975). Subjects had difficulty distinguishing 150 mg of secobarbital from 25 µg/kg of THC. When amphetamine and smoked cannabis were combined, additive effects on heart rate, blood pressure, and subjective symptoms were reported, but no interaction of the drugs was found on psychomotor performance (Evans, 1976). Based on the assumption that THC interferes with cholinergic brain mechanisms, physostigmine was administered after THC. It decreased the tachycardia and conjunctival injection but had little effect on psychological changes (Freemon, Rosenblatt, & El-Yousef, 1975). Based on the evidence that THC-induced tachycardia is blocked by the beta-adrenergic antagonist propranolol, Drew, Kiplinger, and Miller (1972) and Sulkowski et al. (1977) evaluated the effect of propranolol on THC-related cognitive impairment and subjective changes. Although Drew et al. reported no evidence of an interaction, Sulkowski et al. found that propranolol prevented tachycardia and THC-related learning impairment and attenuated the subjective changes. They interpreted these results as supporting the hypothesis that THC action in the brain may be mediated, in part, through beta-adrenergic receptors. Bachman et al. (1979) administered 30 to 44.8 µg/kg of THC, intravenously, alone or in combination with atropine, propranolol, or both autonomic blocking drugs together. Heart rates, subjective intoxication and symptom rating, time production, and EEG activity were measured. In the absence of autonomic blocking drugs, THC produced characteristic tachycardia, subjective intoxication, and EEG effects. After combined autonomic blockade, THC had no effect on heart rate, while subjective and EEG changes remained as intense. These findings argue against the hypothesis that the subjective and EEG effects of THC are mediated by autonomic receptors. Finally, Johnstone, Lief, Kulp and Smith (1975) studied the psychologic, respiratory, and cardiovascular interactions of THC with oxymorphone and pentobarbital in healthy volunteers. THC doses were 27, 40, 60, 90, and 134 µg/kg, given intravenously. The combination of oxymorphone and THC caused increased sedation and a neutral to pleasant experience that was greater than that produced by oxymorphone alone, although four of the eight subjects vomited toward the end of the study. The combination of THC and pentobarbital produced anxiety and hallucinations of such intensity that four of the seven subjects could not continue with

the study. The authors concluded that as a preanesthetic sedative THC does not have therapeutic advantages. They suggested that anesthesia for the patient acutely intoxicated with cannabis presents several hazards. Barbiturate administration can exacerbate THC mood changes. Opioid premedication should quiet the patient, although the combination may depress ventilation severely, so that ventilatory support may be necessary.

AGGRESSION, EATING, AND SEX

As with other areas of complex human behavior, very few experimental studies of cannabis effects on drive states have been conducted. Salzman, Kochansky, and Porrino (1974) studied the subjects hospitalized and tested by Mendelson et al. (1976). As reviewed above in the section on cannabis tolerance and dependence, these subjects smoked cannabis cigarettes that they purchased with money they earned during a 3-week period preceded and followed by no-smoking control days. Saltzman et al. measured three aspects of aggression and hostility: (1) hostile inner states (using the Buss-Durkee Hostility Inventory), (2) interpersonal perception of hostility (using a scale developed by Salzman), and (3) an observer rating system of verbal interpersonal hostility. Cannabis intoxication was characterized by decreased hostility even under conditions of mild frustration. Tinklenberg and colleagues reported that extremely aggressive and sexually assaultive behavior in a population of adolescents occurred much more frequently during ethanol intoxication than during cannabis intoxication, despite the fact that the adolescents reported using both drugs with almost equal frequency (Tinklenberg, Murphy, Murphy, Darley, Roth, & Kopell, 1974). Bachman and Jones (1979) reported a significant decrease in anger and hostility scores on mood and behavioral questionnaires by 48 male subjects during a period of prolonged THC intoxication. Abel (1977) reviewed the relationship between cannabis and violence and reported that the consensus is that marihuana does not precipitate violence in the majority of those using it sporadically or chronically. Abel noted, however, that in certain individuals, such as those suffering from temporal lobe epilepsy, and in certain situations of set and setting cannabis use may result in violence. In sum, the experimental literature suggests that, if anything, cannabis tends to reduce the expression of aggression and hostility. Further research is required to evaluate the interaction between cannabis intoxication and the expression of aggression in situations that are conducive to producing anger and hostility (e.g., frustration or authority conflicts).

Anecdotal evidence supports the notion that cannabis intoxication produces hunger and increased eating. However, there is no evidence that cannabis lowers blood glucose levels (Jones et al., 1976; Weil et al., 1968). Jones et al. (1976) did report significant increases in body weight during the prolonged period

of THC intoxication. This increase resulted from the retention of water which served to compensate for the initial orthostatic hypotension produced by the oral doses of THC. With the cessation of THC administration, Jones et al.'s subjects quickly lost between 10 and 15 pounds, almost entirely through loss of water. Mendelson et al. (1976) reported a similar weight loss in subjects following the 3-week period of cannabis smoking.

No experimental studies of cannabis effects on sexual arousal, receptivity, or functioning have been published. Again, anecdotal evidence suggests that acute cannabis intoxication enhances sexual pleasure but reduces sexual performance. There have been reports that acute cannabis intoxication and chronic cannabis use lowers serum testosterone levels in male users. These reports have produced inconsistent results; the relationship between serum testosterone levels and sexual performance is unclear.

In sum, it appears that cannabis tends to produce aggression, anger, and hostility, perhaps through its sedative-relaxant properties. Sedation may be conductive to eating, but weight gain following cannabis use seems to result more from shifts in fluid retention and water balance than from overeating and increased caloric intake. Sexual activity under the influence of cannabis has not been studied.

SUMMARY

ESTABLISHED FINDINGS

The effects produced by single doses of cannabis on human perception, cognition, and behavior vary with (1) the amount of THC consumed (Domino et al., 1974; Kiplinger & Manno, 1971), (2) its route of administration (oral--Peters et al., 1976; smoked--Borg et al., 1975; intravenous--Benowitz et al., 1979), (3) the user's prior experience with and acquired tolerance to the drug (Jones, 1971; Jones et al., 1976; Peeke et al., 1976), and (4) other drugs present with which THC interacts (Bachman et al., 1979; Belgrave et al., 1979). The onset and duration of cannabis effects vary primarily with dose and route of administration. After a single 30-mg oral dose of THC, effects become apparent in 45 to 75 minutes and last approximately 4 hours (Jones et al., 1976). After a single smoked dose of cannabis with 10 mg of THC actually delivered, effects become apparent within 5 to 10 minutes and last approximately 90 to 120 minutes. After an intravenous dose of 2 mg of THC, effects begin within 3 minutes and last approximately 45 to 60 minutes (Hunt et al., 1979).

Acute and subchronic doses of THC produce significant changes in general activity levels, sleep-wake cycles, and work capacity. These changes include psychomotor retardation, lethargy, sedation, increased sleep time, and diminished rapid eye movement (REM) sleep (Feinberg et al., 1975; Jones et al., 1976). However, with repeated doses of THC or chronic use, the initial effects dissipate as tolerance develops, so that psychomotor activity and sleep time return to predrug levels that, in cross-cultural studies of chronic users, are indistinguishable from nonusers' levels of activity (Dornbush et al., 1976; Mendelson et al., 1976).

Laboratory studies of nontolerant users, conducted over the last 35 years, have shown consistently that the higher the THC dose and more complex the task, the greater the cognitive and behavioral impairment as compared with either nonuser's or placebo performance. Percpetual, cognitive, and behavioral functions shown to be susceptible to disruption by THC include temporal judgments (Tinklenberg et al., 1976), simultaneous performance of multiple and complex tasks (Casswell, 1975; Hansteen et al., 1976; Janowsky et al., 1976; Klonoff, 1974; Melges et al., 1970), simple and complex reaction time performance (Peeke et al., 1976), memory and learning (the work of Abel, Darley, Miller, and Peeke), signal detection and vigilance (Moskowitz & McGlothlin, 1973), and psychomotor tracking (Evans et al., 1973; Hansteen et al., 1976).

These performance deficits are not absolute, however. Instructions to compensate for the drug's effects, rewards for good performance, and practice while intoxicated have been shown to diminish some of the behavioral impairments produced by THC (Cappell & Pliner, 1973; Casswell, 1975; Peeke et al., 1976). Similarly, evidence for state-dependent learning in the cannabis literature suggests that material learned while intoxicated is recalled better while intoxicated (again) rather than while sober (Cohen et al., 1975; Rickles et al., 1973; Stillman et al., 1974).

In addition to the diminution of impairment that occurs with repeated doses or chronic use of THC, dependence on the drug also develops. Cannabis withdrawal symptoms include restlessness, behavioral hyperactivity, insomnia, loss of appetite, weight loss, and increased feelings of anxiety and anger (Jones et al., 1976). These symptoms are reversed by administration of THC.

The most consistent finding from studies of cannabis interactions with other drugs is the additive effect produced by other nervous system depressants (THC plus ethanol--Belgrave et al., 1979; THC plus secobarbital--Dalton et al., 1975; THC plus oxymorphone or pentobarbital--Johnstone et al., 1975).

Cannabis use, unlike alcohol use, has been related to decreased expression and feelings of anger, hostility, and aggression (Abel, 1977; Bachman & Jones, 1979; Salzman et al., 1974; Tinklenberg et al., 1974).

NEEDED RESEARCH

Further work in two conceptually distinct lines of research is needed to clarify and extend the established findings. One line of research involves elaboration of the nonpharmacological contributions to cannabis intoxication. The other concerns study of the pharmacological determinants and the behavioral consequences of cannabis tolerance and dependence. Also of importance is research to investigate behavioral interactions between cannabis and a broader range of other drugs that are used in combination with THC.

The influence of the physical and psychosocial environment in which cannabis is used and the psychophysiological state of the user at the time of consumption are factors known to interact with THC dose in determining the drug's behavioral effects. However, much of what is known about these factors was learned from testing healthy human volunteers in relatively nonstressful laboratory environments. Subjects are usually tested at basal levels of arousal, and the outcome of their performance on the relatively menial laboratory tasks usually has no consequences. As reviewed above, intoxicated performance has been manipulated by providing practice, monetary rewards, and instructions to offset the drug effects. This type of research should be extended to situations that are directly relevant to military-related environments and tasks. Experiments designed to compare the effects of different THC doses on behaviors such as radar vigilance, rifle shooting, tank driving, and jet plane flying should be conducted with volunteers in different physiological states produced by, for example, situations of extreme stress, prolonged sleep and sensory deprivation, and physical and mental fatigue, and in situations where obedience to authority is expected. If cannabis use by military personnel is a reality, then its effects on military behaviors performed in military environments must be evaluated.

Further studies of the conditions that are necessary and sufficient to produce cannabis tolerance and dependence are needed. Such work is important in evaluating the therapeutic potential of THC and similar molecules used experimentally to treat nausea and vomiting, glaucoma, asthma, hypertension, and, perhaps, certain psychiatric illnesses. Of equal importance is a better understanding of the relationship between tolerance, dependence, and the subsequent use of cannabis and other drugs. That is, does the acquisition of tolerance to the effects the user seeks cause the user to increase the dose or to switch to another drug? Does the relief from cannabis withdrawal symptoms afforded by using more THC sufficiently reinforce compulsive cannabis use? With drugs like alcohol, heroin, and nicotine, the answer to the above questions is yes. Another crucial question concerns the behavioral effects produced by cannabis dependence and withdrawal symptoms. It is possible, as suggested by the cross-cultural studies of chronic cannabis use, that once a user has acquired behavioral tolerance to cannabis, performance

is unaffected by successive doses. However, users may become dependent on cannabis to continue performing without disruption. Their behavior may be affected adversely only when cannabis use is stopped. This appears to be true of individuals dependent on tobacco. Finally, research is needed to determine which perceptual, cognitive, and behavioral functions return to predrug levels with tolerance development and which remain impaired.

Interactions between THC and other drugs used with cannabis have just begun to receive adequate experimental attention. Simply developing a list of these other drugs with data on the incidence and prevalence of their use with cannabis would be an important contribution. To date, most of the research in this area has involved depressant drugs only. Experiments must be designed so that potentiation or antagonism of cannabis' behavioral effects can be detected. Interaction studies should be conducted in which both tolerant and nontolerant cannabis users are given another drug. The specific aim of all such drug interaction studies is to determine if and how the behavioral effects produced by various doses of THC are modified by the presence of another psychoactive drug. Thus it is imperative to know definitively what the cannabis effects are and what their time course is before evaluating the effects of the additional drug. The converse is true if one is evaluating the effects of different doses of another drug.

TABLE 1 SUMMARY OF ACUTE CANNABIS EFFECTS ON TIME PERCEPTION AND PSYCHOMOTOR PERFORMANCE

Author(s) and Date of Study	Route of Administration	THC Dose	Control Condition and/or Comparison Drugs	Tests Used	Results
Weil et al. (1968)	Smoked	4.5 & 18 mg	Placebo marihuana (mh)	Time estimation (TE)	Overestimation of 5-min interval
				Continuous Performance Test (CPT)	Unaffected
				Digit Symbol Substitution (DSS)	Dose-related impairment for naive subjects
				Pursuit Rotor (PR)	Dose-related impairment for naive subjects
				Verbal sample	Speech disruption
Clark et al. (1970)	Oral	0.03 cc/lb (w/10mg/cc=) 0.66 mg/kg	No-drug testing 1 week prior	TE	Overestimation of 15-, 90-, & 180-sec intervals
				Complex visual Reaction Time (RT)	Increased variability proportional to complexity
				Digit-code memory	Impaired
				Reading comprehension	Impairment proportional to complexity
Hollister & Gillespie (1970)	Oral	0.5 mg/kg	Placebo THC 1 ml/kg ETOH 0.2 mg/kg dextroamphetamine	TE	Overestimation of 3.5-sec interval by THC only
				Number facility (NF)	Impaired by THC & ETOH; improved by dextroamphetamine
				Simple RT	Increased by ETOH & THC
Jones & Stone (1970)	Smoked Oral	4.5 mg 90 mg	Placebo mh 1 ml/kg ETOH Placebo ETOH	TE	Overestimation of 15-sec interval by smoked & oral THC; underestimation by ETOH
				Time production (TP)	TP unaffected
Manno et al. (1970)	Smoked	5 mg	Placebo mh	PR	Impaired; more errors
				Delayed auditory feedback (DAF)	Impaired; greater percentage of errors

TABLE 1 SUMMARY OF ACUTE CANNABIS EFFECTS ON THE PERCEPTION AND PSYCHOMOTOR PERFORMANCE (Continued)

Author(s) and Date of Study	Route of Administration	THC Dose	Control Condition and/or Comparison Drugs	Tests Used	Results
Melges et al. (1970)	Oral	20, 40, & 60 mg	Placebo THC	Goal directed serial alteration (GDSA) Digit span memory Serial subtraction of 7's	Impairment proportional to dose Impaired Unaffected
Dornbush, Fink, & Freedman (1971)	Smoked	7.5 & 22.5 mg	Placebo mh	Time reproduction Recall of 3-letter trigrams	1-, 2-, & 5-sec reproductions unaffected Impaired
Cappell et al. (1972)	Smoked	4, 8, & 16 mg	Placebo mh 0, 0.48, 0.72, & 0.96 ml/kg ETOH	TP	Underproduction of 20-sec intervals proportional to increased THC dose TP unaffected by ETOH
Tinklenberg (1972)	Oral	0.35 mg/kg	Placebo THC 0.7 ml/kg ETOH	TP GDSA Memory Span	Underproduction of 30-, 60-, & 120-sec *intervals by THC only; overproduction* by ETOH Unaffected Unaffected
Casswell et al. (1973)	Smoked	3.3 & 6.6 mg	Placebo mh	GDSA Digit span memory Serial subtraction of 7's	Impairment proportional to dose Unaffected (cf Melges et al., 1970) Impaired (cf Melges et al., 1970)
Evans et al. (1973)	Smoked	0, 3, 6, & 9 µg/kg	Placebo mh	PR DAF Body steadiness	Impaired; effect equal at all doses Unaffected (cf Manno et al., 1970) Increased ataxia proportional to dose
Pearl et al. (1973)	Smoked	0 & approx. 10 & 20 mg	Placebo mh	9 measures of 7 different concept formation tasks	Increased variability of performance proportional to dose; dose-related impairment of number of words recalled in Conceptual Clustering Test
Galanter (1973)	Smoked	10 mg	Placebo mh, natural mh, & placebo + synthetic THC	RT Digit recall Recall of free associations	Unaffected Impaired Unaffected

TABLE 1 SUMMARY OF ACUTE CANNABIS EFFECTS ON THE PERCEPTION AND PSYCHOMOTOR PERFORMANCE (Continued)

Author(s) and Date of Study	Route of Administration	THC Dose	Control Condition and/or Comparison Drugs	Tests Used	Results
Bech et al. (1973)	Oral	8, 12, & 16 mg	Placebo THC 1 ml/kg ETOH	TE	Overestimation of 3-min intervals increasing w/dose; no difference between ETOH and placebo
				Digit span memory	Impaired by THC, not by ETOH
Hollister & Tinklenberg (1973)	Oral	20 mg	Placebo THC	TP (same as Tinklenberg, 1972)	Underproduction of 30, 60, & 120 sec
Cappell & Pliner (1973)	Smoked	12 mg	Placebo mh	TE (half the subjects instructed to offset drug effects volitionally)	Overestimation of 50-, 90-, & 1500-sec intervals only in noninstructed Ss; Ss instructed to offset effects performed equally well on THC as on placebo
				Short-term memory	Impaired regardless of instructions
Vachon (1974)	Smoked	25 mg	Placebo mh	TP	Underproduction of 10-sec interval
				CPT	Unaffected
				DSS	Impaired due to slowed response time
Borg et al. (1975)	Smoked	0, 70, 130 190, & 250 µg/kg	Placebo mh & no-smoking control session	TE	Overestimation at low dose, underestimation at high dose
				TP	Underproduction of 10- & 30-sec intervals
				DSS	Impairment proportional to dose
				Word associations	Speed of associations decreased
				Simple & complex RT	Increasing RT's w/increasing dose
Weckowicz et al. (1975)	Smoked	3 & 6 mg	Placebo mh & no-smoking group	Wechsler Adult Intelligence Scale (WAIS): Block Design Memory-for-Design Vocabulary	Performance on tests requiring concrete & specific solutions was impaired in dose-dependent manner
				Oral word fluency	Performance on open-ended verbal task (oral fluency) was improved

TABLE 1 SUMMARY OF ACUTE CANNABIS EFFECTS ON THE PERCEPTION AND PSYCHOMOTOR PERFORMANCE (Continued)

Author(s) and Date of Study	Route of Administration	THC Dose	Control Condition and/or Comparison Drugs	Tests Used	Results
Casswell (1975)	Smoked	3.96 & 9.24 mg	Placebo mh & no-smoking control session	DSS CPT GDSA Serial subtraction of 7's RT	Impairment proportional to dose Unaffected Impairment proportional to dose Impairment proportional to dose Dose-related increase
Peeke et al. (1976)	Smoked	18 mg	Placebo mh & no-smoking groups	Complex RT	Initial impairment with improved performance over 5 practice sessions; Ss who practiced after smoking placebo for 4 sessions showed no impairment after smoking mh on fifth session
Beautrais & Marks (1976)	Smoked	7 mg	No-drug control group	Card sorting time Block turning PR	Unaffected Impaired regardless of previous practice while intoxicated; initial effect not tested Impaired regardless of previous practice while intoxicated
Peters et al. (1976)	Oral	0.0, 0.2, 0.4, & 0.6 mg/kg	Placebo THC	Ten Reitan Test Battery tests used clinically to evaluate neurological damage	Slight impairment of proficiency and increase in variability of performance
Tinklenberg et al. (1976)	Oral	0.7 mg/kg	Placebo THC 1 ml/kg ETOH	TP	Underproduction of 30-, 60-, & 120-sec intervals by THC; overproduction by ETOH (cf Tinklenberg et al., 1972)
Schaefer, Gunn, & Dubowski (1977)	Smoked	0, 10 & 20 mg	Placebo mh	Perceptual (visual) accuracy Complex RT	Impairment proportional to dose; addition of irrelevant stimuli eliminated THC effect Slowed only by high dose
Bachman et al. (1979)	Intravenous	30-45 µg/kg	Saline placebo Atropine (0.04mg/kg) Propranolol (0.2 mg/kg)	TP	Underproduction by THC only; effect unaffected by pretreatment with autonomic blocking drugs

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2. A REVIEW OF SELECTED RESEARCH STUDIES FROM THE LAST DECADE ON THE EFFECTS OF ALCOHOL ON HUMAN SKILLS PERFORMANCE

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INTRODUCTION

In 1973, two reviews of skills performance under alcohol were published by Moskowitz and Perrine, respectively. Perrine (1973) found evidence for the effect of alcohol on neuromuscular control with standing steadiness a particularly sensitive measure of alcohol intake. However, clear evidence of significant impairment of motor control did not arise until blood alcohol concentration levels (BAC's) became considerably greater than those levels associated with impairment of driving. Similarly, his review of sensory factors ranging from visual acuity to critical flicker fusion indicated significant impairment at BAC's considerably greater than those levels associated with many driving accidents.

Moskowitz (1973) reviewed the areas of vision, tracking, and attention. He reported that, when vision or tracking performance was examined in studies isolating the function, impairment failed to occur until moderate or high BAC's. However, when the same visual or tracking functions were component tasks within a more complex requirement for joint performance of several functions, large performance decrements occurred at low blood alcohol levels. The article concluded that alcohol primarily impaired more central processes that required considerable information processing. Under the requirements of division of attention, significant impairment was found at BAC's below 0.02 percent.

In 1975, a review by Levine, Kramer, and Levine charted the degree of impairment versus dosage for a large number of studies grouped into cognitive, perceptual-sensory, and psychomotor categories. The psychomotor tasks appeared the most resistant to the effects of alcohol, whereas the perceptual and cognitive tasks were the most impaired by alcohol.

Thus, these three independent reviews reached roughly the same conclusions based on examining different sets of studies. The basic conclusions of Moskowitz and Perrine, formulated roughly 6 years ago, remain intact today after the examination of more recent literature. Although alcohol appears to affect many functions, and at very high dosages nearly all functions, it remains true that in terms of skills performance the primary effects of alcohol are on central mechanisms of perception and cognition, including response selection, rather than on sensory input receptors or motor effectors.

The main contribution of recent literature has been to define further the areas of central impairment by alcohol, the interaction of alcohol with factors such as chronic use, and the interaction of alcohol with other drugs. Alcohol appears to be the common solvent most frequently present when other drugs are used. A short review of some of the more prominent articles in the alcohol-drug interaction field is included here, but this area requires an extensive review of its own. Further, the massive

number of studies conducted in the past decade can be only partially reviewed in the time allocated for this review. Few animal studies are reported here because there are sufficient alcohol studies using human subjects to cover the areas of skills performance.

WORK CAPACITY AND ENDURANCE

Studies of the effects of alcohol on human physical performance have indicated that consumption of large amounts of alcohol leads to a deterioration of physical working capacity, even long after ingestion. Hebbelinck (1963) investigated the effects of low to moderate doses of alcohol on the performance of somatic tasks. He observed that most of the earlier investigations using low doses were not carried out very systematically, the number of subjects was low, much emphasis was put on the psychological aspects of the problem, and few of the investigators referred to the concentration of alcohol in the blood prior to the test. Hebbelinck compared the performances of 21 healthy male subjects on a set of tests before and a half hour after they ingested 0.6 ml of 94 percent ethyl alcohol per kg/bw (body weight). Results indicated that static strength was not changed. Dynamic strength, or power, as demonstrated by executing a vertical jump, decreased by 5.8 percent. Speed in performing an 80-meter sprint resulted in longer running times, with a performance decrease of almost 10 percent. Posture control, as measured by an equilibrium test, was considerably affected. Neuromuscular incoordination and poorer reflectory control seemed to be mainly responsible for the deteriorative effects of alcohol on these basic components of human physical performance.

Research involving the physiological effect of acute ethanol ingestion on oxygen uptake and heart rate response during exercise has been controversial, yielding contradictory findings in large part because of discrepancies regarding experimental methodology and data analysis (Williams, 1972). In regard to heart rate, Hebbelinck (1959) evaluated the effect of a moderate dose (0.6 cc/kg) of absolute alcohol on the cardiac response before, during, and after a 5-minute workload at 1,500 kpm. He noted an increase of 4 systoles per minute during rest and recovery and a marked average increase of 23 bpm during the early stages of the workload. In a subsequent report, Hebbelinck (1962), using a small dose of ethanol and a workload of 1,000 kpm, obtained identical results. In this experiment, the heart rate responses of 19 healthy male subjects were examined at rest, during a 5-minute workload of 1,000 kg/m/min, and during recovery, and then compared with the records of the same subjects under similar conditions after the intake of 0.6 ml of 94 percent alcohol per kg/bw. A slight average increase of the heart rate (4 bpm) at rest appeared 40 minutes after ingestion; a significant average increase of 23 bpm was recorded in the work experiments with alcohol compared with the experiments when sober. This increase was particularly

evident during the first 2 minutes of the adjustment of the cardiac rate to exercise. However, although the data are indicative of a significant cardiac response, no statistical analysis was performed.

Blomqvist (1970) reported that 150 ml of 86 proof alcohol elevated the heart rate 12-14 bpm during submaximal exercise but during maximal exercise left the rate unchanged. However, he did not counterbalance the order of administration of treatments in this repeated-measures design. Furthermore, the control phase, which involved a maximal workload, was conducted on the same day, 2 hours prior to the experimental phase. Previous research has indicated a relative increase in heart rate response during a light submaximal workload if preceded by exercise at a heavier workload. Thus, as the author noted, the results of the study may have been influenced by the prior maximal workload. In addition, Blomqvist reported that the resting heart rate was elevated during the alcohol phase, which has been found previously to affect cardiac response during the early stages of work.

To resolve the contradictions in the literature on heart rate response, Williams (1972) investigated the acute effects of low and moderate doses of alcohol on heart rate and oxygen consumption before, during, and after a progressive workload. Nine male university faculty members and students underwent three separate trials of a 9-minute work task consisting of 3 minutes each at 500, 1,000, and 1,500 kpm. Prior to each trial, the subjects consumed either a placebo or a low (0.2 cc/lb) or moderate (0.4 cc/lb) dose of ethanol. Generally, findings supported the conclusion that neither a low nor a moderate dose of alcohol significantly affected the heart rate or oxygen uptake during rest, exercise, or recovery.

SENSORIMOTOR COORDINATION

REACTION TIME

In an early review of the research on the effects of alcohol on reaction time (RT), Carpenter (1962) concluded that RT changes were not universally obtained and that design weaknesses vitiated the conclusions of several studies. For example, in some cases, the definition of simple RT was questionable (e.g., failures in a driving simulator were classified as RT). Approximately a decade later, Sutton and Burns (1971) found little change in the situation. Heimstra and Struckman (1972), in a review of 14 driving simulator studies, found that the effects of alcohol on brake reaction time were at best inconsistent.

Despite his recognition that RT impairment was not universally obtained, Carpenter (1962) concluded that simple RT and motor performance are impaired even at low doses of alcohol

(0.40-0.50 ml/kg). Lolli, Nencini, and Misiti (1964) and Teichner (1954) concluded that moderate doses of alcohol increased choice RT. Heacock and Wikle (1974) found impairment of reaction time in both the placebo group and the moderately dosed alcohol group and found impairment of distance judgment in alcohol groups. They suggested, however, that alcohol may lead to a misperception of when to react rather than to an actual physical impairment of RT.

Most reports indicate that impairment of RT by alcohol is not an obligatory relationship, at least under some conditions. Sutton and Burns (1971) studied 10 subjects performing finger extension and finger flexion in a RT paradigm at dose levels of 0.03 percent and 0.06 percent BAC's for females and 0.02 percent and 0.04 percent BAC's for males. Their aim was to study the influence of low doses of alcohol on two different RT tasks in a practice group of subjects, all of whom received performance feedback. Although the BAC values were low, the higher doses were in the range employed by other studies, some of which had detected alcohol effects on RT. Two stimulus modes--visual and auditory--were investigated and trial-by-trial display of RT was provided. RT's were found to be briefer to auditory than to visual stimuli, and flexion and extension responses were approximately equal in RT latency. Alcohol impaired the females' performance of each response, but not the males' performance because of the males' more competitive attitude toward feedback display. This suggests that the effect of alcohol dosage does not necessarily affect RT but that factors interacting with alcohol may.

Obitz, Rhodes, and Creel (1977) studied the effect of an ingestion of alcohol producing a mean BAC of 0.09 percent under high- and low-motivation conditions. They found that simple visual-motor reaction time was slower in a low-motivation, nonreward condition but that it was not affected in a high-motivation, monetary reward condition. It appears that, at this BAC, subjects motivated by monetary reinforcement were capable of responding as fast as they responded under the control condition, whereas reaction times in the nonrewarded condition were significantly slower following the ingestion of alcohol. The authors suggested that the debilitating effect of moderate doses of alcohol (BAC of less than 0.10 percent) on the performance of a visual-motor task is probably the result of "inattention." This "inattention" may be overcome by using a positive reinforcer such as money to increase the subject's motivational arousal level.

Huntley (1973) studied the notion that alcohol increases RT to extrafoveal stimulation and that these increases (which may represent decreases in visual sensitivity) become greater as stimulus eccentricity increases. Second, he sought to test whether an increase in the difficulty of a concurrent high-priority foveal task would result in similar increases in RT, which would also become greater as stimulus eccentricity increased. In nine males under BAC's of 1, 50, and 100 mg/100 ml,

he found that choice RT to extrafoveal stimulation increased, but the alcohol's effects were independent of target eccentricity--a finding contrary to that reported by Hamilton and Copeman (1970). Choice RT to stimulus of retinal periphery was thus an increasing function of the relative difficulty of high-priority foveal tasks.

Some researchers found increased reaction time under alcohol in response to stimuli presented in parallel with another task. (Rafaelsen, Bech, & Rafaelsen, 1973; Rafaelsen, Christup, & Bech, 1973; Sugarman, Cozad, & Zavala, 1973).

Shillito, King, and Cameron (1974) studied RT of five subjects performing a key-pressing task at mean BAC's of 0, 0.011, 0.037, and 0.055 percent. Task load was systematically varied by the use of information "alphabets" of different sizes. Choice RT was not affected by BAC's up to 0.055 percent. There was some evidence that accuracy of performance was impaired at BAC's of 0.037 and 0.055 percent while BAC's of 0.011 percent had a slight facilitating effect on performance. Thus tasks in which accurate performance is the main criterion are more likely to be sensitive to alcohol effects than tasks which involve information processing. Finally, it was found that different subjects employed different strategies to maintain performance. In particular, many subjects showed a willingness to trade off accuracy against speed.

Jennings, Woods, and Lawrence (1976) continued the research of Shillito et al. (1974) on the speed-accuracy tradeoff in choice RT. Complete speed-accuracy tradeoff functions were generated for each of five doses of alcohol (0, 0.33, 0.67, 1.0, and 1.33 ml 97 percent alc/kg). Such functions permitted RT differences resulting from changes in performance efficiency to be distinguished from those due to changes in subjects' speed-accuracy criteria. Results indicated that alcohol reduced performance efficiency by decreasing rate of growth of accuracy per unit of time. Change in the speed-accuracy criteria was combined with a decrease in efficiency at the highest alcohol doses. This suggests that, if mean RT is considered without respect to accuracy, alcohol produces no discernible decrement in performance, but when accuracy is considered, subjects may maintain roughly constant RT performance by sacrificing accuracy at higher alcohol doses.

These results clarify two aspects of past research. First, the obtained decrease in performance efficiency under alcohol strongly supports the conclusions that alcohol decreases choice RT performance. Unassessed changes in speed-accuracy criteria may have obscured efficiency effects and may account for the past inconsistency of previous results. Second, the absence of effects at low doses (below 80 percent mg) in the past may have been associated with unassessed changes in the speed-accuracy criteria at these doses (Carpenter, 1962; Shillito et al., 1974). Although these results clarify the influence of alcohol on choice RT performance, they do not identify the specific functional processes

impaired, as the authors noted. Since there was no decrement in mean RT with increasing dose, it is unlikely that alcohol produced a simple motor effect.

To summarize, the inconsistency in past findings can be explained by taking into account the information-processing demands of the experimental tasks involving reaction time. Motor performance involves more than RT. It appears that there is a small effect on simple reaction time if the experiment is designed well; a larger effect is apparent when the experiment calls for other information processing. It also appears that the inconsistency in RT results may be due to undetected variations in speed-accuracy criteria.

TRACKING

Reviewing the area of tracking, Wallgren and Barry (1970) found fairly general agreement that alcohol does produce a decrement in tracking performance but that such a deficit is more likely or more prominent when the tracking task is accompanied by another task that serves to divide the attention of the subjects. Research since then has essentially supported their conclusions (Moskowitz, 1973). Relatively straightforward compensatory tracking tasks comparable to the task difficulty of driving have not exhibited performance decline under alcohol when subjects' attention was devoted solely to the tracking task (Chiles & Jennings, 1970; Collins, Schroeder, Gilson, & Guedry, 1971; Newman, 1949; Pearson, 1968). On the other hand, noticeable tracking performance declines have been observed under even low BAC's when the task involves pursuit tracking, which requires monitoring two or more sources of information, or when the tracking task is performed concurrently with another subsidiary activity. Under such circumstances, most studies have reported impairment by 0.05 percent BAC (Aksnes, 1954; Binder, 1971; Hamilton & Copeman, 1970; Hughes & Forney, 1964; Loomis & West, 1958; Mortimer, 1963; Newman & Fletcher, 1940; Newman, Fletcher, & Abramson, 1942; Russell, 1951; Von Wright & Mikkonen, 1970).

Compensatory Tracking

Five studies on compensatory tracking found that the effect of alcohol was significant only when the tracking task was performed concurrently with another task or while the subjects were influenced by another stressor, such as anoxia.

Newman (1949) examined the effects of alcohol and alcohol in combination with decreased oxygen supply upon performance on a two-dimensional compensatory tracking task. The average BAC at which a significant impairment first appeared was 0.182 percent, although in combination with a reduction of oxygen to 10 percent, impairment appeared at 0.127 percent. (This oxygen level is equivalent to an altitude of 18,000 feet).

Pearson (1968) examined a compensatory tracking task combined with concurrent monitoring of two meters. Alcohol effects were examined at ground level and at an altitude of 12,000 feet. Subjects achieved a mean peak BAC of 0.085 percent. Alcohol failed to significantly affect the tracking task at ground level, although under the stress of the hypoxia, a trend toward an alcohol effect appeared. The subsidiary monitoring task, however, did show an alcohol effect.

Collins et al. (1971) also used a compensatory tracking task to examine the effects of an alcohol dose which produced a mean peak BAC of 0.074 percent. Subjects were examined under two conditions: while stationary and while subjected to 48-second cycles of angular acceleration reaching a peak velocity of 120° per second. Under the stationary condition, there was a significant increase in tracking errors in only one of five test sessions, whereas under angular acceleration, tracking errors increased in three of five sessions. The authors concluded that "although eye-hand coordination may show little or no impairment following alcohol ingestion in a static situation, it may be seriously degraded during motion." They suggested that studying alcohol impairment requires presentation of the "total array of stimuli that will impinge upon the individual."

A study by Chiles and Jennings (1970) examined performance in a compensatory tracking task while the subjects were simultaneously and intermittently required to perform a series of subsidiary tasks. Peak BAC's were near 0.10 percent. Since the subsidiary tasks were intermittent, the authors analyzed the tracking performance with and without the presence of a subsidiary task. They reported that "the results of these tests showed that for no measure (there were several measures of tracking) was tracking significantly affected by alcohol when tracking was performed by itself." Tracking was impaired by alcohol, however, when the subject was concurrently performing some of the subsidiary tasks. The authors concluded that "a decrease in the ability of the subject to time-share the performance of tasks requiring the exercise of different psychological functions may be the most important detrimental effect of alcohol on trained subjects. Motor effects may be somewhat less important."

Reid and Ibraham (1975) studied the application of human operator describing functions in an investigation of the influence of alcohol and marihuana in combination and of alcohol alone on subjects performing a compensatory visual-manual tracking task. They found that at peak BAC's of 0, 0.03, and 0.07 percent, the effects of increasing the BAC were (1) degraded tracking performance; (2) increased noise injection (remnant); and (3) decreased effective gain and crossover frequency.

Pursuit Tracking

In contrast to the simple compensatory tracking tasks, which generally have failed to find alcohol impairment except at high BAC's, most studies that have examined pursuit tracking, like those that have combined a compensatory tracking task with a concurrent subsidiary task, have found impairment at BAC's of 0.05 percent to 0.09 percent.

For example, Newman and Fletcher (1940), using a pursuit tracking task combined with a subsidiary visual recognition task, administered 0.79 grams alc/kg bw to most of their subjects and obtained impairment of performance at a mean BAC of approximately 0.095 percent.

Newman et al. (1942) used the same pursuit tracking task as did Newman and Fletcher (1940). No mention was made of the simultaneous recognition task. Although the study used inadequate statistical analysis, the scatter plot of BAC versus change in performance on the tracking task suggests that impairment is significant by the 0.07 to 0.08 percent BAC level.

Aksnes (1954) examined performance in a Link trainer. Subjects flew blind and were required to monitor seven instruments and a map of the course they were required to maintain. The course imposed limits with regard to altitude, airspeed, vertical speed, turning speed, and time. Subjects were administered either 0.2 or 0.5 gram alc/kg bw. The larger dose produced about 0.05 percent BAC and appeared to cause an impairment, although no statistical analysis was reported.

Another study of pursuit tracking was reported by Loomis and West (1958). They combined a pursuit tracking task with a subsidiary recognition and response task and found impairment by 0.05 percent BAC.

Mortimer (1963) used an alcohol dose that produced a mean BAC above 0.06 percent and found substantial impairment of pursuit tracking performance.

Hughes and Forney (1964) tested performance on a pursuit tracking task with four levels of complexity of the function to be pursued. They administered 0.52 gram alc/kg bw resulting in about 0.05 percent BAC and reported that all functions showed large degrees of impairment at this dose level. A later study by Manno et al. (1971), using the same instrument and the same dosage again producing 0.05 percent BAC, failed to replicate the deficit. However, still another study by Forney and Hughes (1964), using the same instrument and a 0.5 gram alc/kg bw dose producing 0.046 percent BAC, reported impairment on two of the four test pursuit patterns.

A pursuit tracking task was combined with simultaneous signal detection in the study by Von Wright and Mikkonen (1970).

Tracking was impaired at the 0.8 gram alc/kg bw dose but not at the 0.4 gram alc/kg bw dose. Signal detection was impaired at both dose levels.

Another study by Hamilton and Copeman (1970) also combined pursuit tracking with signal detection. They included a condition where additional stress was introduced by noise. Under the quiet condition, the lower alcohol dose of 0.21 gram alc/kg bw did not affect tracking scores, but the higher dose of 0.63 gram alc/kg bw did impair tracking performance. With the additional stress of noise, both alcohol doses produced impairment.

Binder (1971) utilized a pursuit tracking task combined with a subsidiary cue recognition task to examine subjects recruited from local bars. Although statistical analysis did not test the lowest blood alcohol group versus controls, the figures indicate that subjects with an average peak BAC as low as 0.06 percent showed impairment.

Although most studies of the effects of alcohol on pursuit tracking have found impairment, a few studies have equivocal results. In an experiment by Gibbs (1966) using a pursuit step-tracking apparatus, which involved steps of unequal probabilities, alcohol treatment resulting in a peak BAC of 0.10 percent showed impairment on improbable steps but no impairment on probable steps. Using a modified version of Gibbs' pursuit step-tracking task, Landauer, Milner, and Patman (1969) failed to find any evidence for an alcohol deficit at a BAC near 0.05 percent.

Conclusions

Three general conclusions can be drawn from the above-cited studies. First, there is little evidence that a compensatory tracking task will exhibit a significant performance decline under alcohol when attention can be devoted solely to the tracking task. Second, tracking performance declines are very likely to occur under alcohol when the tracking task is a pursuit tracking task that requires monitoring two or more sources of information. Third, alcohol-induced impairment is demonstrated under a tracking task (of any type) when it is performed concurrently with another activity with which it must time-share the brain's capacity to process information. Under these circumstances, impairment will be exhibited at very low BAC's, with most studies reporting impairment by 0.05 percent.

REFLEXES

It is generally accepted that the acoustic reflex acts as a protective mechanism for the inner ear against high-intensity sounds at the lower frequencies. Several investigators have shown a direct protective relationship between the presence or

magnitude of stapedius muscle contraction and the concomitant decrease in temporary threshold shift (TTS) from intense auditory stimulation. Alcohol has also been found to alter this protective mechanism. Thus Robinette and Brey (1978) sought to determine if the presence of alcohol in the human system would increase susceptibility to TTS associated with noise exposure. Stimuli consisted of a narrowband noise of 500 to 1,000 Hz and a 500-Hz pure tone. Measurements were made at BAC's from 0.05 percent to 0.15 percent. Blood alcohol levels between 0.09 percent and 0.15 percent were found to reduce the protective action of the acoustic reflex in five human subjects with normal hearing. Specifically, under alcohol conditions acoustic reflex thresholds increased, reflex magnitude decreased, and temporary threshold shift increased. Temporary threshold shift at 1,000 Hz was determined 3 minutes after a 10-minute exposure to narrowband noise at -5, +5, and +20 decibels relative to the subject's prealcohol acoustic reflex threshold.

Peiterson (1966) investigated the effects cf alcohol on various forms of vestibulospinal reflexes in light of the evidence that small amounts of alcohol induce a sensation of motor uncertainty and slight, uncharacteristic dizziness. Peiterson studied 10 normal persons using the stepping test before and 20 and 55 minutes after alcohol ingestion. BAC's of 0.043 percent and 0.084 percent were produced in the subjects. For all the subjects, the rotation angle on their own axis increased significantly from spontaneous 58° to 85° at 20 minutes and 132° at 55 minutes (mean values). The forward movement did not show significant alterations, whereas sideways movements increased. All the subjects exhibited a very slight unsteadiness at the low BAC, usually manifested as a sideways sway. At the high BAC, all subjects showed a definite unsteadiness.

VISUAL PERFORMANCE

Much of the early literature on the effects of alcohol on visual functions reported equivocal, contradictory findings (Carpenter, 1962). Frequently, automobile drivers under the influence of alcohol have reported a decreased ability to perceive objects in their peripheral visual field, a condition known in the extreme as "tunnel vision" (Drew, 1963). However, early laboratory attempts to demonstrate tunnel vision in such conditions produced uniformly negative results. Subsequent research has provided more conclusive evidence that, under the influence of alcohol, a subject's visual disturbances are relatively trivial (Grant, 1970; Wallgren & Barry, 1970). In their extensive review of the actions of alcohol, Wallgren and Barry (1970) concluded that visual acuity is "relatively insensitive to alcohol." They also found little impairment of peripheral vision, glare recovery, or critical flicker fusion. The only exception was in color perception, but even here the results varied greatly.

Moskowitz, Sharma, and Schapero (1972) examined subjects' visual acuity, dark adaptation, binocular fusion, phoria, and duction performance under a dose of 0.69 grams alc/kg bw. The only statistically significant effect was a change of a few diopters in lateral phoria at far distances, i.e., esophoria.

Thus, the experimental literature provides little evidence that the visual sensory processes per se show alcohol-induced impairment at moderate BAC's. Most of the experimental studies carefully isolated some visual function and then tested for possible ethanol impairment. In regard to those studies that found no impairment of peripheral vision, the usual laboratory testing technique required attention to only one task, using a standard optometric technique wherein the subjects were required to fixate upon a continuously lit central light while detecting the appearance of lights in the peripheral visual field. In such a situation, the fixation light presents no information-processing requirements and attention can be allocated primarily to the periphery. Recent studies examining peripheral vision under circumstances involving complex situations more analogous to the demands for information processing in driving have uniformly reported extensive impairment by alcohol (Buikhuisen & Jongman, 1972; Hamilton & Copeman, 1970; Huntley, 1970; Moskowitz & Sharma, 1974; Von Wright & Mikkonen, 1970).

Von Wright and Mikkonen (1970) studied the effects of moderate amounts of alcohol on the detection of visual signals and found impairment at about 0.05 percent BAC for combined tracking and visual recognition tasks at treatment doses of 0, 0.4, and 0.8 gram alc/kg bw. All subjects demonstrated impairment at both alcohol doses.

Further evidence for the susceptibility of peripheral vision to alcohol impairment, when examined in a complex perceptual situation, is offered by Hamilton and Copeman (1970). The study involved a central visual tracking task combined with signal detection of lights in a horizontal peripheral visual field. Signal detectability was examined under placebo and 2 alcohol treatments (mean peak BAC's of 0.017 percent and 0.055 percent). Under both alcohol treatments performance decrements were statistically significant.

Huntley (1970) examined the effects of doses of 0.58 and 0.96 gram alc/kg bw in a combined central visual fixation task (counting blinks of a central fixation light) and a peripheral vision task. The two doses produced approximately 5 percent and 8 percent increases in the time required to perceive and respond to the signals.

Studying the effects of alcohol on eye movements at a BAC of 0.08 percent, Buikhuisen and Jongman (1972) found that subjects concentrated their visual fixations more on the center of the field and significantly failed to perceive objects on the

periphery of the visual scene. Failures to see objects in the center also increased, but to a much smaller extent.

Moskowitz and Sharma (1974) also examined peripheral vision signal detection while subjects were occupied with a variably blinking central fixation light. This study specifically tested the hypothesis that the appearance of an alcohol-induced deficit in peripheral vision is a function of the attention or information-processing demands placed on central vision or, for that matter, the demands from any source of information occupying the central processing mechanisms. The study failed to find any impairment in peripheral vision at doses of either 0.41 or 0.83 gram alc/kg bw when central vision was occupied with a steady, unblinking fixation light. However, when central vision was occupied with counting blinking lights, there were significant deficits in peripheral light detections at the dose of 0.41 gram alc/kg bw, which produces less than 0.05 percent BAC. A statistically significant interaction term indicated that the effect of alcohol on peripheral vision is a function of the information load on central vision. Nearly all the errors were failures to detect the signals; few false alarms occurred under any treatment. Results thus confirmed the hypothesis that alcohol restricts visual perception by reducing the number of peripheral lights detected when a subject is required to divide attention between two visual tasks requiring information processing.

In other words, when peripheral vision is examined in isolation with no other demands on the subject, alcohol will produce no impairment. When peripheral vision is examined while the brain is occupied with processing information from some additional source, then alcohol will impair peripheral vision. The results confirm for the visual modality the findings of Moskowitz and DePry (1968) on the auditory modality that alcohol affects central processing of information when attention is divided and has little or no effect on the sensory input system. The authors demonstrated that, when examined singly, separate auditory tasks were unaffected by alcohol, but when examined as a combined divided attention task, they exhibited a large and significant deficit. This suggests that the impairment, when it occurs, is not a direct effect on the sensory transducer or transmission system but is an indirect result of the impairment by alcohol of the central system.

In summary, it thus appears that the conflicting reports in areas of visual research found by Carpenter (1962) may be due to the ways in which the various experiments were performed so that the results of some studies are contaminated with excessive demands for information processing. In many situations where the demands for processing information are simple, alcohol has no apparent effect on visual inputs. However, in situations such as driving, which requires complex information processing and division of attention, subjects under the influence of ethanol exhibit a failure in visual perception.

It should be noted that the above studies have emphasized sensory processes. Considerable literature demonstrates that oculomotor control is readily impaired by drugs, including alcohol. A recent study of this genre (Baloh, Sharma, Moskowitz, & Griffith, 1979) demonstrated that alcohol at both 0.05 and 0.10 percent produced impairment of saccade maximum velocity and response time, the velocity of smooth pursuits, and the slow component velocity of optokinetic nystagmus. Similar findings have been reported by Flom et al. (1977) and Guedry et al. (1975).

COGNITIVE FUNCTIONS

ATTENTION

In a discussion of the effects of alcohol on attention, it is important to stress that attention refers to 2 functions, which are differentially affected by alcohol. Attention refers to arousal or vigilance, terms describing the state of the organism's ability to process information. Attention also refers to selective attention, or divided attention, which deals with the selective mechanisms involved in determining which input or processes will be attended to in preference to others in situations where the amount of information is greater than can be processed centrally at a given time. In general, it appears that, for non-fatigued or non-sleep-deprived individuals, the effect of alcohol on arousal or vigilance defined in terms of monitoring low quantities of information over long periods of time is very slight for low to moderate levels of alcohol. On the other hand, selective attention or the ability to divide attention is sharply impaired even at the lowest levels of alcohol detectable within the body.

In a typical experiment on vigilance under alcohol, Colquhoun (1962) presented subjects with a vigilance task that required detection of a possible difference in hue intensity of 1 of 6 small lights presented simultaneously. There were 2,000 such trials in 1 hour. A moderate dose of alcohol failed to produce any evidence of impairment. Similar results were found in a study by Mayer, Naitoh, and Smith (1966), using normal subjects, and in a study by Talland, Mendelson, and Ryack (1964), employing chronic alcoholics undergoing sustained alcohol [illegible] have been some reports of vigilance decrements [illegible] but the context of the experiments suggests that [illegible] in vigilance might have been due to an interaction [illegible] other factors such as fatigue. These possibili- [illegible] tested adequately in a well-controlled ex-

[illegible] insensitivity of vigilance to the effects [illegible] dies (some of which were discussed in the [illegible] rate that divided attention is partic- [illegible] ects of alcohol. Gruner and colleagues

(Gruner, 1955, 1963; Gruner, Gruner, Ludwig, & Domer, 1964) found evidence of impairment under moderate doses of alcohol in subjects required to perform a cancellation task on every "E" in a long stream of printed letters while simultaneously responding as rapidly as possible to two lamps on the periphery of their vision, which required a different response depending on which lamp was flashed. Under alcohol, there was an increase in the reaction time to the lamps being flashed and a decrease in the accuracy of the cancellation task.

Moskowitz and DePry (1968) specifically tested the issue of whether alcohol has a differential effect on vigilance versus divided-attention tasks in the auditory modality. Their subjects performed a dichotic listening task in a series of 3-second trials over roughly 1 hour. In one ear channel, subjects were required to detect the presence or absence of a 1,000-cycle tone whose presence was hidden below the level of a concurrent random noise burst. In the second auditory channel, a series of six randomly chosen digits was presented at 0.5-second intervals. The experiment was run under two conditions. In the vigilance condition the subjects were required to ignore the presence of the numbers in one ear and simply attend to the presence or absence of the 1,000-cycle tone and report after each trial on its presence or absence. In the divided-attention condition, subjects were required to report on the presence or absence of the tone in the noise burst presented in one ear while simultaneously memorizing the series of six numbers, which were reported back immediately after the 3-second presentation.

Under a 0.52 gram alc/kg bw treatment, which resulted in roughly 0.07 percent blood alcohol concentration, there were no effects on the vigilance task performance, whereas there was a highly significant impairment in the divided-attention situation. In a drug dose replication reported by Moskowitz (1973) which used dosages ranging from 0.2 to 0.83 gram alc/kg bw, only insignificant decrements in vigilance behavior were found at roughly 0.10 percent BAC, whereas deficits in the divided-attention condition were found at 0.015 percent. Similar results for visual modalities have been found (and are reported in the section on information processing below).

PROBLEM SOLVING

No studies of changes in intellectual performance under alcohol were submitted for this review. This reflects a declining interest in this area during the past decade. From the 1940's to the early 1960's, a considerable number of studies were done on the subject. These studies are well summarized in Wallgren and Barry (1970). The majority of intellectual tasks involved arithmetic problems, and although results were variable, in general, there was a decrease in performance with greater frequency of errors and increased time necessary for performance.

INFORMATION PROCESSING

Many of the studies reviewed above, especially those involved in visual performance, suggest that one reason for the deficit in division of attention and in skills performance generally may be a decrease in the rate of information processing under alcohol. Several studies by Moskowitz and associates have directly tested this hypothesis.

A study performed by Moskowitz and Burns (1971) used as a measure the psychological refractory period, defined as the increased delay in reacting to the second of two stimuli presented in rapid succession with the response delay being a function of the interstimulus interval. In this experiment subjects responded to a tone and a light by pressing corresponding keys. If the interstimulus interval (ISI) is less than 300 milliseconds, the response to the second stimulus is longer than to the first. The greatest increase in response time to the second stimulus occurs for the shortest ISI. This increase has been interpreted as a measure of the time required for the central processor to complete the processing of the first stimulus prior to initiating processing of the second stimulus. Alcohol slowed central processing as shown by an additional increase in reaction time to the second stimulus under alcohol. It is apparent that this is not merely an increase in motor reaction time, because the reaction time to the first stimulus increased only slightly.

This work was continued by Moskowitz and Roth (1971), who examined the latency in naming a visually presented object. Naming an object is an information-processing event which takes from 400 to 1,500 milliseconds. With an alcohol dose of only 0.52 gram alc/kg bw, there was a very large increase in the length of time required to perform this naming. It should be noted that in these experiments the slowing of central processing under alcohol is not dependent on division of attention. The study on latency of single responses by Moskowitz and Roth is clearly under a concentrated-attention condition. However, it takes unusual situations for this alcohol slowing of information processing to exhibit itself. It is more clearly exhibited in divided attention where it results in an inability to switch to alternate channels rapidly enough because of the slowing of the information processing of the first channel.

The above two experiments involved a reaction time measure. Moskowitz and Murray (1976) examined the rate of information processing uncontaminated by a reaction time measure. The experiment employed backward masking of visual stimuli. The experimental procedure involves presenting a row of four letters in a tachistoscope for 15 milliseconds. After a variable interstimulus interval, the four-letter stimulus is followed by a masking stimulus. The masking stimulus consists of random elements cut from letters. The visual mask effectively wipes out the iconic image. For the information in the visual image to be retained, it must

be transformed and placed in short-term memory. This transformation is a linear serial process. At 0.05 percent and 0.10 percent BAC's, there was an increase in the time necessary to transfer the four letters. Transforming the image, or iconic memory, into short-term memory requires time, and alcohol impairs the rate at which that process occurs.

Another aspect of information processing which has been examined for possible alcohol effect is the direct influence of alcohol on the rate of switching attention. The technique used for this study involved matching the rate of clicks presented either monotically, where the clicks are presented in one ear, or dichotically, where the clicks are presented alternately to each ear. Under these conditions, the apparent subjective equality is reached when a greater frequency of clicks is presented dichotically for a monotic comparison because apparently the brain cannot switch back and forth without losing some information.

Moskowitz and Keller (1979) reported that subjective equality between monotic and dichotic presentations was reached at a greatly increased dichotic presentation rate for a monotic standard when subjects were under the influence of 0.05 percent and 0.10 percent BAC, low to moderate levels of alcohol.

EYE MOVEMENT STUDIES

Attempting to understand the characteristics of impairment to central information processing or cognitive performance, several investigators have used eye movement studies to determine how alcohol affects target detection, search and scanning behavior, and focus of attention. The basic premise is that fixations (or dwells) and pursuits are the information-sampling aspects of the eye movements. They are the "looks" without which one cannot see. From their frequency, duration, and distribution, one can investigate many aspects of visual search behavior. The information obtained in these studies has relevance to alcohol effects on information-processing rates. Because an observer must look directly at an object to bring it to the central (or foveal) area of the retina for best resolution, measuring the patterns of looking behavior during performance of a visual task provides valuable data on the individual's information-seeking strategy. The point on the visual scene brought to focus at the fovea is termed the eye point of regard (EPR). In addition to providing information as to where an observer is looking, EPR measurements provide data on the duration of each look; these data are important because they indicate the time required to acquire and process information.

Fixation Duration

An increase in fixation duration under alcohol has been consistently reported (Beideman & Stern, 1976; Belt, 1969; Buikhuisen & Jongman, 1972; Kobayashi, 1974; Mortimer & Sturgis, 1972; Moskowitz, Ziedman, & Sharma, 1976; Schroeder, Ewing, & Allen, 1974). This finding is consistent with laboratory work showing that alcohol slows the information-processing rate (e.g., Moskowitz & Murray, 1976). Thus, the longer fixation times found in the studies could be attributed to the additional time needed for processing data during each fixation.

Belt (1969) measured visual search patterns of two subjects under three levels of alcohol for three different driving conditions. The nominal BAC's were 0, 0.037, and 0.075 percent. The three on-the-road tasks were car following, short-interval open-road driving, and long-interval open-road driving. Only about 1 or 2 minutes of data were analyzed per test session. The results showed no effect of alcohol level on mean eye travel distance (distance between successive fixations). The increased amount of fixation time that occurred under alcohol in the most populous 3^{o} times 3^{o} visual angle block indicates that subjects under alcohol looked less often outside a central region. Mean fixation duration increased under alcohol under the open-road mode but not under the car-following mode. The results of this study must be taken as tentative due to the small amount of data collected.

Mortimer and Sturgis (1972) studied visual scan patterns of two experienced drivers for three BAC levels: 0, 0.05, and 0.10 percent. Driving on a two-lane road at 35 mph and driving on an expressway at 60 mph were compared, as were car following and open-road driving. They found an increase in mean fixation durations at the 0.10 percent alcohol level and an indication (not statistically significant) that preview distances were decreased under alcohol (viewing was closer to the vehicle). No alcohol effects were found on the horizontal distribution of fixations.

Kobayashi (1974) also found indications of longer fixation durations in two subjects while they were driving a test course under alcohol, but the author did not report the spatial pattern of fixations.

Buikhuisen and Jongman (1972) conducted a laboratory study in which eye movements were measured while a subject was viewing a video display of a 4.5-minute film made from a car moving through typical suburban traffic. Twenty staged situations were included in the film in order to control the type and location of potentially hazardous events that should be noticed by a driver. In all, 86 such "critical events" were selected for analysis. Fifty-five subjects at 0 percent BAC were compared with 50 subjects at 0.08 percent BAC. The results indicated that under alcohol subjects looked at the sides somewhat less (concentrated more on straight ahead) and that fewer "critical

events" were seen in cases of simultaneous occurrences of such events. The sober driver made more attention shifts and could divide attention more efficiently. In the central region of the roadway scene, intoxicated subjects saw about as many "critical events" as did sober subjects. It appears that a major effect of alcohol was to change the subjects' scan priorities so that more attention was paid to the central field; within this region the extra attention paid off for the intoxicated subjects as they were able to maintain a normal detection rate. However, this effort was paid for by poorer performance in the periphery. A particularly significant result in this regard is the finding that subjects under alcohol shifted their focus of attention toward the right side of the road. In Holland the vehicle on the right has the right of way, without qualification. This rule is rigidly enforced and apparently has sufficient weight in driving experience to have caused the subjects to pay extra attention to this area. Thus, under alcohol, subjects concentrated attention on those areas that (1) were most sensitive to the basic task of driving (straight ahead) and (2) were emphasized by learned reinforcement of critical events (a traffic citation or accident due to not yielding the right of way).

Schroeder et al. (1974) examined the combined effects of alcohol and methapyrilene and chlordiazepoxide on performance of a simulated driving task. Male subjects, viewing a 6-minute 10-second movie in an Aetna-Driver-Trainer, were required to operate the steering wheel, accelerator, and brake in response to nine critical events. Alcohol alone was found generally to suppress eye movement activity and to decrease the proportion of saccades greater than 5^{o} compared with those less than 5^{o}; i.e., more attention was paid to central visual regions under alcohol. The frequency of driving errors did not increase under alcohol.

Beideman and Stern (1976) examined visual search behavior in a Link Driver Simulator at 0 percent and 0.075 percent BAC. Twenty subjects operated the brake, the steering wheel, and the accelerator while viewing two films in succession (49-minute total viewing time). A variety of visual search measures and measures of control performance were recorded. Under the intoxicated condition subjects demonstrated (1) a decrease in the frequency of saccades, (2) an increase in the percentage of long duration fixations, (3) a decrease in large amplitude saccades, (4) an increase in the duration of saccadic eye movements, and (5) a decrease in the peak velocity of saccades. On motor performance tasks alcohol increased the amplitude, velocity, and variability of responses on the accelerator, brake, and steering wheel. A tendency for subjects to "stare into space" was noted. Beideman and Stern concluded that their results support the hypothesis that alcohol affects information-processing capability as exhibited by a less efficient division of attention in the complex simulation task.

Moskowitz et al. (1976) examined visual search behavior in 27 subjects who were watching a 17-minute traffic movie (congested

urban scene) at 0, 0.075, or 0.15 percent BAC. Subjects were required to watch the movie for potentially hazardous events and also to perform a secondary task requiring turn-signal responses to "right" or "left" arrows projected on the screen. The results showed an increase in mean dwell or fixation time and a corresponding decrease in dwell frequency under alcohol. Fewer points in the visual field were examined and fewer shifts of attention occurred under alcohol. Pursuit or eye-following activity increased under alcohol. An analysis of the various categories of traffic events looked at by subjects indicated differential effects of alcohol on different categories of events (duration of looks for flashing lights and traffic lights increased under alcohol whereas duration of looks for pedestrians decreased or remained the same). A "fixation of gaze" phenomenon apparently similar to the tendency to "stare into space" reported by Beideman and Stern (1976) was also found. Moskowitz et al. (1976) concluded that the longer dwell times found under alcohol were the consequence of a decreased information-processing rate and that visual search efficiency decreased as the need to examine each area for a longer time resulted in a decrease in the amount of the visual field that can be examined.

Allocation of Attention

Less consistent findings were reported regarding whether allocation of attention is changed under alcohol. Belt (1969), Buikhuisen and Jongman (1972), Beideman and Stern (1976), and Schroeder et al. (1974) found indications of increased attention to central areas, whereas Mortimer and Sturgis (1972) and Moskowitz et al. (1976) did not. This apparent inconsistency could be related to differences in the task demands between studies and to the strategies adopted by the subjects toward their tasks. Note that a possible shift in attention when driving under alcohol need not only be a shift in the focus of visual scanning from the peripheral scene toward the central area but also increased attention on any subtask to the exclusion of others. The specific aspects of a shift in attention would be determined by the driver's "set" as influenced by previous experience and the reward/penalty structure of the current situation.

COMMUNICATION AND AWARENESS

Smith, Parker, and Noble (1975) studied the effects of alcohol on formal aspects of social communication by scoring transcripts of verbal discussions between dyads (18 male-female couples) in alcohol and placebo sessions. At a low dose (0.83 to 1.0 ml/kg), alcohol significantly increased the amount of, and overlap in, communications and tended to decrease subjects' acknowledgment of their partners' statements. At a high dose (1.5 ml/kg), the rate of overlap in speech was additionally increased, but there was a leveling off or reversal of the drug's

effect on amount of communication. The subjects' blood alcohol levels were not related to the drug's effect. A number of theories are proposed by the authors regarding the possible mechanisms by which alcohol exerts these effects, such as general "disinhibition" and specific deficits in cognitive processing. However, no direct evidence was available from which to draw any conclusions.

Early research suggested that levels of alcohol that impair perceptual and psychomotor skills also reduce awareness of the impairment (Wallgren & Barry, 1970). However, the experimental evidence concerning the effects of alcohol on awareness is contradictory. The results from some laboratory studies and closed course driving studies suggest that subjects are generally unaware of the impairing effects of alcohol on performance. However, other studies indicate that performance judgments and awareness are independent of subjects' level of intoxication and the extent of the alcohol-induced impairment. The results of these studies lead to the conclusion that subjects are aware of both relative intoxication and the extent of alcohol-induced impairment.

In reviewing these studies, Lubin (1977) observed that unfortunately many of the attempts to assess alcohol effects on performance awareness have considered the measure of awareness to be of secondary importance to actual performance and that the contradictory findings in this area of research may be attributed to the procedural variations among the studies. It is possible that subjects in the latter studies were responding to cues provided by feedback in the experimental paradigm, rather than their judgmental acumen, in assessing personal levels of performance. The former studies contained experimental contingencies that either limited or eliminated extraneous sources of feedback.

Lubin (1977) designed a study to test whether the affective value of experimental feedback, i.e., positive or negative with regard to the previously established standard, could largely account for variations in performance awareness. If increasing levels of alcohol induce subjects to be both less aware of performance quality and more dependent on feedback cues, then systematic manipulation of the affective value of the feedback could be used to identify the extent and direction of this effect. Thus it was hypothesized that increasing doses of alcohol would impair actual performance, impair subjects' ability to perform accurate self-judgments, and increase subjects' dependence on the affective value of available performance cues. Using 15 male subjects responding to extra foveal visual signals, a series of RT's and response-speed judgments were recorded over three experimental sessions which differed in target BAC's of placebo, 0.05 percent, and 0.10 percent. Spurious performance feedback was presented to five subjects in each of three groups representing either fast, average, or slow RT's. Data supported the hypothesis that alcohol impairs both performance and performance

awareness. In all groups, alcohol significantly increased RT's and significantly impaired the accuracy of response-speed judgments. The measures of awareness (i.e., correlations between RT's and response-speed judgments) showed that alcohol and spurious feedback significantly impaired performance awareness.

MEMORY

Hutchinson et al. (1964) found that not all mental functions were uniformly affected by alcohol but that alcohol dosage did significantly affect mental functions requiring sophisticated strategies for analyzing and organizing stimulus information such as attention, abstract thinking, and learning efficiency. Impairment of such functions seemed to occur at relatively low BAC's.

Both clinical and experimental evidence suggests that memory impairments can occur as a result of alcohol intoxication. Acute alcohol intoxication is commonly followed by partial or total amnesia (the so-called alcohol blackout) for events occurring during the drinking period. Alcoholics frequently experience blackouts or amnesia in connection with a drinking episode, and even nonalcoholics often have difficulty remembering events that occurred during intoxication (Rosen & Lee, 1976). Although a plethora of research exists showing the detrimental effects of alcohol on various aspects of memory functioning, results have been equivocal, in large part because of methodological differences. Such differences include imprecisely measured BAC's, failure to recognize that the action of alcohol may be more pronounced on some aspects of memory than others, use of insensitive measures of memory, and possible changes in levels of subject motivation under alcohol (Miller & Dolan, 1974). The general conclusion of the research is that alcohol produces an impairment in the short term memory (STM) which is followed after the early information storage by the immediate memory.

Reviewing seven previous studies on short term memory and the alcoholic blackout, Goodwin and Hill (1972) found that the studies varied widely in experimental design and the types of observations obtained and showed little agreement with regard to distinctions between "immediate" and "short term" memory. They concluded that STM deficits were correlated with alcoholic blackouts and that those studies which had found contrary evidence did so because large enough quantities had not been consumed. They further observed that the STM/blackout phenomenon is a threshold rather than a graded phenomenon, more closely resembling "sudden" amnesia from head injury than the gradual forgetfulness of increasing senility; that is, lesser degrees of STM loss and amnesia do not appear to result from smaller amounts of alcohol.

Goodwin, Othmer, Halikas, and Freeman (1970) studied 10 volunteers drinking between 16 and 18 ounces of bourbon in a 4-hour

period during which memory was monitored and four types of memory were tested: remote, immediate, short term, and recent. STM was defined as the ability to remember events for 30 minutes. They found that STM deficits and ensuing amnesia were correlated with a rapidly rising blood alcohol concentration, with the memory deficits beginning in the 200 to 300 mg/100 ml range. It appeared that STM deficit alone was correlated with subsequent amnesia when sober.

Ryback (1970a) observed seven drinking inpatient alcoholics and reported a correlation between STM deficits and failure to later recall events that happened during the STM deficit period. Even though the subjects could carry on a conversation during the amnesiac state, they could not remember what they said or did 5 minutes earlier. STM deficit appeared to be associated with rapidly rising BAC exceeding 150 mg percent.

Tamerin et al. (1971) made the first attempt to examine the alcoholic blackout during a sustained period of experimental intoxication (12-14 days) and found STM significantly and progressively impaired with increasing levels of intoxication.

Lisman (1972) found deterioration in STM as BAC increased, but immediate and remote memory appeared intact. Mendelson and LaDou (1964) found that, for alcoholics maintained on high levels of alcohol for extended periods, only when the alcohol consumption reached 40 ounces of bourbon a day was memory disturbance observed through STM. Even at these high levels attention span remained, more or less, providing further evidence "that STM impairment is the sine qua non of alcoholic amnesia" (Goodwin & Hill, 1972).

Mello (1973) suggested that STM deficits and blackouts may not be linked. She found that, even when severely intoxicated, a sample of alcoholics with a history of blackouts showed no sign of STM deficit on a matching-to-sample test. But Goodwin and Hill (1972) suggested that in her study the alcoholics, albeit having a history of blackouts, were able to perform the task as well drunk as sober and did not experience subsequent amnesia.

Most studies have not found any effect on immediate and remote memory. Ryback (1971) reviewed 104 studies dealing with the effects of alcohol on memory and concluded that alcohol does affect immediate and remote memory but it most severely and selectively disrupts the STM. Even in normal subjects with BAC's similar to those commonly produced at cocktail parties, shorter spans of STM were produced with a rise of mean BAC from 79 to 102 mg/100 ml. He concluded that disruption of STM is the specific memory deficit common to cocktail party drinking, alcoholic amnesia, and the Wernicke-Korsakoff syndrome.

Similarly, Jones (1973b), in a comprehensive study of alcohol's amnestic properties, concluded that immediate, short term, and long term memory are all influenced by alcohol ingestion but that STM seems to be particularly susceptible to disruption,

especially on the ascending limb of the BAC. He found that long term memory impairments were not due to a change in drug state (state dependency) but perhaps were secondary to the effect of the alcohol on STM.

Miller and Dolan (1974) supported the earlier finding of Carpenter and Ross (1965) and Ryback et al. (1970) that alcohol-treated subjects displayed significantly poorer short term memory during the treatment session when compared with controls. This inferior performance was attributed to a combination of improved STM on the part of controls and inferior performance by the alcohol-treated subjects from the first to the second session. Miller and Dolan suggested that alcohol may have interfered with the effects of practice and that it has nonspecific actions on human STM. They further suggested that the findings of STM indicate that task parameters may be an important factor determining whether alcohol impairs performance. In their own study they employed measures of memory that did not involve active rehearsal or a dependence on consolidated information. These rather "pure" measures of STM may be more sensitive to effects of drugs than measures normally used. Results also suggested that alcohol may have impeded a practice effect that normally would have occurred.

An experiment by Moskowitz and Murray (1976) examined the effects of alcohol on iconic memory. Iconic memory lasts less than a few seconds. Subjects were presented with cards containing three rows of four letters each. A 50-millisecond presentation limited viewing to a single fixation. At time intervals from 1 millisecond to 1 second after stimulus presentation, the subject was given an auditory signal indicating which row to report and only had to report that row. The subject was then able to report a substantially higher percentage of the letters than if asked to report the entire set of letters immediately following stimulus presentation. This demonstrates that the sensory memory system, or iconic memory, decays in a period shorter than that required to verbalize all the information originally available. In an experiment with administration of 0, 0.41, and 0.8 gram alc/kg bw, the effects of alcohol were examined. The results demonstrated that while alcohol impairs the original acquisition of material, it does not affect the rate of decay for the iconic memory system. The study concluded that the effect of alcohol on divided attention cannot be ascribed to effects on the <u>immediate</u> memory system.

MEMORY AND INFORMATION PROCESSING (RETRIEVAL VS. STORAGE)

Research indicates that the immediate memory, the early sensory information storage system (as opposed to the STM which follows after the storage system), is not significantly affected by alcohol. However, the central processors' ability to extract information and place it in short or long term memory is impaired. It would appear that STM is impaired because information that

enters the short term buffer is lost before it can be transferred to long term storage (Goodwin et al., 1970; Ryback, 1971). However, in terms of information processing, the underlying mechanisms of the effect of alcohol on memory are still unclear. Of particular interest is whether the memory for a particular event fails to be recalled because the information is not sufficiently stored in memory or because the information is stored but just cannot be retrieved at the time of the test. In other words, does alcohol primarily affect storage or retrieval, or both? It is important to know whether information and events occurring during intoxication are forgotten because they are not stored or because they are stored but are subsequently irretrievable (Gerrein & Chechile, 1977). The primary conclusion that can be drawn from the storage-retrieval literature is that this distinction needs more research.

The findings of Tamerin et al. (1971) that the immediate memory remained intact, even with high BAC's, led to the conclusion that either retrieval or retention is the basis of the STM deficit, not registration. Using their own data, Goodwin et al. (1970) independently reached the same conclusion.

Wickelgren (1975) theorized that alcohol-induced forgetting was due solely to storage difficulties. Rosen and Lee (1976), while finding both storage and retrieval adversely affected, did find that retrieval processes were somewhat responsive to experimental manipulation. In the transfer process between the short term buffer and long term memory, their evidence suggested that impairment of memory was caused by an impairment in the ability to organize recall by semantic categories, that is, a failure to encode effective retrieval cues, an ability which is considered a requirement for efficient storage of stimulus information.

Gerrein and Chechile (1977) found that the effect was primarily one of retrieval decrement, not storage. Separating recall into independent storage and retrieval components, they illustrated that alcohol intoxication impairs both processes, thus contradicting Wickelgren (1975). But they also found that the absolute retrieval decrement due to alcohol was nearly twice as large as the absolute storage decrement. This suggested that much of what the sober patient cannot recall is in fact stored in memory and that state-dependent learning is really state-dependent retrieval.

On the other hand, Parker, Birbaum, and Noble (1976), studied the effects of acute alcohol intoxication on the storage phase of memory with two tasks that minimized response retrieval; they concluded that storage processes were sensitive to disruption by alcohol. Tasks that minimized the need for retrieval were impaired by acute doses of alcohol at the time the new material was initially encoded; once the material had been encoded, the level of intoxication at the time of testing had no effect. They suggested that alcohol may influence recall of previously

learned material when retrieval of that material is difficult; when retrieval is easy, alcohol impairs only the storage phase of memory.

The numerous studies on the mechanism of alcohol-induced deficits in short term memory are a reflection of one portion of the increased number of studies on information-processing stages under alcohol produced during the last decade. The work on alcohol's effects on memory, visual search, and attention are a reflection of the increased interest in these areas as their importance is more widely recognized. Definitive conclusions about memory are harder to come by than conclusions about attention and visual search, but the efforts devoted to the area may produce a better integration of the literature in the near future.

STATE-DEPENDENT LEARNING

A number of studies finding alcohol-induced memory loss in humans and animals have attributed this deficit to dissociation or state-dependent learning. This refers to the phenomenon whereby an individual who acquires information in one cognitive state, such as alcoholic intoxication, can then recall that material more effectively later if once again in that same state. Although this has been one of the major areas of alcohol-memory research, here again results have been inconsistent; although much research on humans has been concerned with demonstrating the existence of state dependency, relatively little research has been directed toward explicating the nature of the memory deficits.

Most studies indicated that alcohol does produce state-dependent learning in humans with the degree of state dependency seeming to depend on the particular drug, the dosage, and the type of task the subject is required to perform (Goodwin, Crane, & Guze, 1969; Peterson, 1977; Storm & Caird, 1967; Tarter, 1970; Weingartner & Faillace, 1971; Weingartner et al., 1976).

However, Mello (1973) observed that it is difficult to understand some of the evidence pertaining to memory loss under alcohol in terms of dissociation interpretation because original learning is impaired in the drug state over relatively short time intervals. Jones (1973) and Parker et al. (1976) did not find any state dependency, although their studies were not designed to detect potential dissociative effects. Jones (1973) found that long term memory impairments were not due to a change in drug state but perhaps were secondary to the effect of the alcohol on the STM. Parker et al. (1976) found that when the retrieval task was easy, once material was encoded (stored), the level of intoxication had no effect on recall. They suggested that the disparate findings regarding state-dependent decrements

can be explained by the fact that such decrements occur only when a considerable amount of retrieval is required and disappear when retrieval needs are minimal.

Peterson (1977), studying retrieval tasks on 28 human subjects in either an alcohol state (1.0 ml/kg) or sober, found that state dependency existed on two tasks that did not involve recall cues and that no state dependency appeared to be present on two tasks involving cues. This finding suggested that memory failures resulting from a changed drug state can be reversed by appropriate experimental cuing or prompting and implies that a learner's drug state has stimulus properties for recall.

DRIVING

Much of the research using driving simulators has been contradictory. Heimstra and Struckman (1972), reviewing 14 studies and classifying alcohol effects into seven categories, concluded, "There appears to be no behavior on which the effects of alcohol have been reported more than once with complete consistency. In many cases, alcohol appears to have had opposite effects on the same behaviors in different investigations." Moskowitz (1975) emphasized that despite the value of simulators in the study of drug-driving interactions, such comparisons are difficult because all current simulators sample only a restricted range of the possible behavioral demands met on the road. No simulator adequately samples the totality of behavioral driving demands, and because the simulators in current use differ so greatly, it is unlikely that they make the same behavior demands on the subjects (Binder, 1971; Buikhuisen & Jongman, 1972; Landauer et al., 1969; among others). This limits the conclusions that can be drawn from the presence or absence of any drug-performance interaction found in a given simulator. Thus, to examine the reliability and validity of drug-simulator studies, it is necessary (1) to understand the specific behavioral demands of the simulator used and (2) to compare drug-performance changes in the simulator with the nature of accidents that occur when people are under the influence of the drug. Unfortunately, there has been no systematic analysis of what various simulators require from the behavior of subjects.

Nevertheless, those simulator studies that require concurrent performance on several subtasks (as is typically found in driving between tracking and environmental search and perception tasks) agree that performance is impaired at low to moderate BAC's (Aksnes, 1954; Chiles & Jennings, 1970; Loomis & West, 1958; Moskowitz, 1971; Newman & Fletcher, 1940; Von Wright & Mikkonen, 1970). When the emphasis is on the psychological function affected by the drug, rather than on the response variable in which the particular psychological function is exhibited, there is considerable agreement that the most

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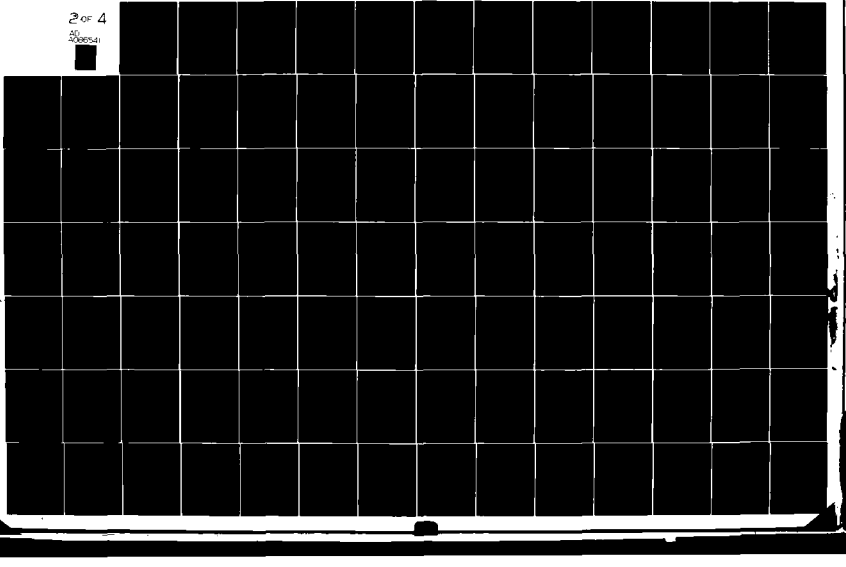

common alcohol effect is impairment of the capacity for information processing, especially in time sharing of several concurrent tasks (Billings, Wick, Gerke, & Chase, 1972; Clayton, 1972).

Newman and Fletcher (1940) found impairment when subjects performed a pursuit tracking task and a subsidiary visual recognition task at 0.095 percent BAC. Aksnes (1954) found impairment at 0.05 percent BAC in a Link trainer when subjects had to track a course, monitor seven instruments, and map their course. Loomis and West (1958) found impairment at 0.05 percent BAC for a combined tracking task with a visual recognition and response task. Von Wright and Mikkonen (1970) found impairment at approximately 0.05 percent BAC for a combined tracking and visual recognition task.

In studies by Moskowitz (1971) and Chiles and Jennings (1970), the presence of the additional tasks was experimentally manipulated, and it was shown that the primary tracking tasks were unaffected by alcohol except in the presence of the secondary task.

Chiles and Jennings (1970) studied the effects of alcohol on a primary tracking task in the presence of additional tasks which were experimentally manipulated. The primary tracking task was unaffected except in the presence of the subsidiary second task, leading the researchers to conclude that "a decrease in the ability of the subject to time-share the performance of tasks requiring the exercise of different psychological functions may be the most important detrimental effect of alcohol."

Moskowitz (1971) reported similar findings from two studies on the effects of about 0.10 percent BAC on 25 performance measures of car control and tracking in a film simulator. In the first study none of the car control and tracking measures showed impairment under this rather high alcohol intake. The study was then replicated with the inclusion of a simple subsidiary task (responding to colored lights). Under the additional information-processing requirement of the subsidiary task, alcohol produced impairment on the subsidiary task as well as on 12 of the 25 car control and track measures which formerly demonstrated no alcohol affect.

Heimstra and Struckman (1972) found that the only primary point of agreement between 14 studies on the effects of alcohol on performance in driving simulators was performance deficits in six of seven studies that included demands for higher mental processes. And Rafaelson, Bach, and Rafaelsen (1973) and Sugarman et al. (1973) found an increase in reaction time under alcohol in a simulator in responses to stimuli presented with another task.

These findings were essentially supported by Huntley's (1972) review of research on closed course driving performance. Contrary to the inconsistent results found in driving simulators, studies of alcohol influences on drivers on closed courses have consistently found impaired performance. Huntley's review concludes that, as alcohol impairment shows up in various performance measures, relatively unstructured task situations may be more susceptible to alcohol impairment than highly structured situations such as a gymkhana course. His observations about unstructured situations may be important in that task performance may be degraded more when the task is randomly embedded in an overall scenario, with the scenario providing an effective division of attention from individual tasks.

Allen, Jex, and McRuer (1975) studied the effects of divided attention on 18 subjects in a fixed-base simulator at BAC's of 0, 0.06 percent, and 0.11 percent. The simulator included both lateral steering control and discrete visual detection, recognition, and response tasks set up to provide the workload and division of attention typical of real world driving. Alcohol was found to cause large heading deviations and increased detection and reaction times on the discrete task. Manual control theory measures showed that the driver's control gain decreased, but stability margins were maintained, while driver remnant increased. Performance on the steering control task decreased when concurrently combined with the discrete peripheral "sign" response task to test divided attention. Results showed a general deterioration in performance with increasing BAC for both continuous and discrete tasks, whether performed singly or in combination. The divided attention aspect of the combined tasks did not seem to affect the general sensitivity of results to BAC, except for path deviation. BAC level effect was highly significant for all parameters except phase margin. Performance of the steering task was significantly impaired by the presence of the discrete task, but the reverse was not true. The authors suggested that this occurs because the discrete task interrupts the continuous nature of steering whereas the discrete task is always performed on demand, so the detection process is not interferred with.

Allen et al. (1978) conducted two experiments on the effects of alcohol on driver decisionmaking, as opposed to control capability. More specifically, they sought to determine whether alcohol increases the willingness to accept risk or merely deteriorates perceptual and psychomotor properties. The first experiment was a laboratory study involving a complex interactive driver simulator. The second was a field validation experiment employing an instrumented car and an interactive test course duplicating many of the driving simulator tasks and conditions. Risk taking did increase at 0.10 percent BAC, but decision making analysis indicated that the increased risk taking was caused by degraded perceptual and psychomotor capabilities, not by increased acceptance of risk. Below BAC's of 0.15 percent subjects did not appear to be aware of the increased risk and did not exhibit compensatory behavior.

FLYING

Important substantiation for the above-cited driving findings is found in a study of flying under the influence of alcohol (Billings et al., 1972). Sixteen subjects took off, instrument flew, and landed a plane under four alcohol treatments resulting in 0, 0.04, 0.08, and 0.12 percent BAC. Eight subjects were highly experienced professional pilots; the other eight were nonprofessional inexperienced pilots. Flignts took place with a safety copilot plus a physician behind the pilot to incapacitate him, if necessary. Although the tracking demands of flying are far more difficult than those of driving, the experienced pilots suffered no significant decrement in their tracking ability, even at the highest dosage. However, even at the lowest dosages they committed procedural errors which were hazardous to flight. At the highest dose level, the safety copilot had to take command of the plane 11 times to prevent an imminent accident. The inexperienced pilots exhibited impairment in their tracking skills and accumulated far more procedural errors than the experienced pilots. Major procedural errors included taking off with full flaps, flying without lights, taking off with carburetor heat on, turning the wrong way in response to instructions, and flying a landing approach tuned to the wrong frequency.

Catastrophic procedural errors included loss of control in flight, turns toward oncoming traffic, and landing errors that would involve striking the ground.

The authors commented, "If we assume that instrument-rated pilots, flying ILS approaches, consider the job of guiding their aircraft to a position from which a visual landing can safely be made as their primary task, then it follows that the other, discrete, procedures involved, while no less essential to safe operations, are relegated to a secondary role. The evidence is clear this is in fact the hierarchy which exists. It is equally clear that as pilots are progressively affected by alcohol, they become progressively less able to cope with the various facets of their task, and it is the secondary tasks which suffer first and most."

The prime alcohol deficit does not impinge on the tracking task because more attention is paid to it than to the search and recognition task.

EMOTIONAL STATES

AGGRESSION

It is commonly assumed that expression of physical aggression is related to the ingestion of alcohol, and there is

evidence to support the assumption that alcohol and violent crimes are related. This evidence has contributed to the theory that alcohol serves as a stimulator or releaser of aggressive behavior. Several competing theoretical positions have been proposed to explain the correlation between drinking and aggression. The first position is predicated on the assumption that alcohol affects aggression-related behavior through some physiologically based mechanism. But research so far has produced only indirect evidence of any directly stimulating effect. Another position suggests that alcohol does not elicit aggression directly but instead "disinhibits" and facilitates its expression by acting to reduce fear and anxiety. Research in this area has also yielded equivocal results.

A third position suggests that the drinking-aggression relationship is mediated by a psychological expectancy set regarding the effects of alcohol consumption or by an ability and a tendency on the part of many people to attribute their antisocial acts to their intoxicated state instead of to themselves.

Unfortunately, there is a paucity of experimental evidence concerning the relationship between physical aggression and the quantity of alcohol ingested, as early reviews emphasized (Carpenter & Armenti, 1972; Wallgren & Barry, 1970). The majority of experimental investigations of these effects have been performed only within the last few years. Furthermore, much of the recent data from studies in which alcohol ingestion was manipulated and elicited physical aggression have yielded contradictory results. On the whole, the evidence from reports regarding alcohol and aggressive behavior tends to support the position that alcohol can promote aggression, but the effect apparently is not physiologically based. Nevertheless, the conclusions are tenuous because of questions arising from the number and type of subjects used, as well as the definition of aggression and varying experimental conditions.

Bennett, Buss, and Carpenter (1969), utilizing the "aggression machine" paradigm, sought to find a relationship between alcohol consumption and physical aggression as measured by the intensity of electric shocks that subjects were willing to administer to another person. To control for expectation, they employed a placebo condition along with three alcohol dosage conditions. They concluded that "alcohol as a pharmacological agent . . . does not lead to aggression." These negative results, however, may still have been due to the fact that all subjects in the experiments had the same beverage expectation.

On the other hand, Shuntich and Taylor (1972) reported that undergraduate subjects who received moderate doses of alcohol (0.9 ml 100 proof bourbon/kg bw) were willing to administer significantly higher intensity shocks to another individual in a competitive reaction time situation than subjects in either

placebo or no-control conditions, which did not differ significantly from each other.

The procedures employed in these two studies differed in two respects. First, the paradigms used to assess harming behavior were quite different. In the Bennett et al. study, one participant was the helpless recipient of noxious stimulation from another. In the Shuntich and Taylor study, both parties could initiate an attack and retaliate. Second, and least likely to be of importance, the subjects in the Shuntich and Taylor study ingested bourbon, an intoxicant of relatively high congener content, while the subjects in the Bennett et al. study ingested vodka, an intoxicant of minimal congener content.

To test whether the discrepancy between these studies was due to the different types of alcohol being used, Taylor and Gammon (1975) conducted a study in which subjects received high or low doses of either bourbon or vodka. Aggressive behavior was found to be related mainly to the quantity of alcohol ingested, not the type of intoxicant: high doses of 100 proof vodka and bourbon. The acting-out behavior evidenced by intoxicated persons may be due to hyperactivity of various subcortical areas of the brain, a "pseudostimulation" which occurs when relatively primitive areas of the brain are freed from the inhibitory control of the cortex.

Taylor, Gammon, and Capasso (1976) tested whether this discrepancy could possibly be attributed to the greater threat inherent in the competitive reaction time situation in the Shuntich and Taylor study. Forty intoxicated (1.5 ounces of 100 proof vodka/40 lb bw) and nonintoxicated subjects competed in a reaction time situation against either a potentially threatening opponent or a nonthreatening opponent. The results indicated that the intoxicated subjects initiated higher levels of attack than the nonintoxicated subjects in the threatening situation only. It was concluded that aggression is not just a consequence of the pharmacological action of alcohol. Instead, alcohol-induced aggression appeared to be a function of the interaction of alcohol consumption and the degree of threat or provocation inherent in a particular situation. These findings did not support the "pseudostimulation" or simple physiological disinhibition hypothesis. The authors speculated that alcohol disrupts various perceptual and cognitive processes thus impairing the subjects' ability to judge the degree to which they are being threatened; the alcohol causes an intoxicated person to attribute more aggressive intent to another's actions than a nonintoxicated person would.

Comparing the effects of alcohol and cannabis (THC) on physical aggression, Taylor et al. (1976) found that, when 40 males were provoked following their ingestion of high or low doses of either drug, the high dose of alcohol instigated more intense aggression than the low dose. The high dose of THC, on the other

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Taken together, these findings indicate that alcohol can contribute to more aggressive behavior, but they strongly challenge the energizing and disinhibition theories, both of which hold that some physiological effect of alcohol accounts for a major portion of the positive correlation between drinking and aggression. Rather, the increases in aggression following the consumption of alcohol appear to be the result of the drinker's expectations concerning the effects of alcohol. Expressions of aggression may be attributed to the effects of alcohol, thus reducing the individual's own responsibility for his or her actions.

The research of Boyatzis (1974) on male subjects in a party situation provides further evidence as to the possible role of expectancy. At experimental "parties" where either distilled spirits or beer was available, men demonstrated more interpersonal aggressive behavior than at parties where nonalcoholic beverages were served. Although their blood alcohol levels were similar, the distilled-spirits drinkers were more aggressive than the beer drinkers. This suggests that controlling for beverage content may lead to discriminable differences in behavior but does not rule out the role of expectancy. Boyatzis observed that expectations about the effects of alcoholic beverages are probably influenced by subcultural norms and economic factors of availability. The subjects in this study may have felt that drinking distilled spirits was "serious drinking" while drinking beer was a social act.

In a reanalysis of previously published material, Bruun (1955) found that individuals with a relatively permissive attitude toward aggression tended to increase the proportion of negative reactions while under the effect of alcohol more than others. Thus, the norms of the individual seem to have an important bearing on alcohol-related behavior. This finding was independent of individual differences in blood alcohol level. He also found that individuals permissive with respect to aggression while intoxicated tended to increase the proportion of their negative reactions in brandy sessions as compared with beer sessions in conformity with their norm as in this particular situation.

There is consistent evidence that moderate and high doses of alcohol suppress intraspecies attack and threat behavior in a number of animal species. Under certain experimental conditions, however, several investigators, using mostly lower doses, have demonstrated that alcohol can facilitate intraspecies attack and threat behavior in mice, fish, and monkeys. Miczek and Barry (1977) noted that these few demonstrations of an aggression-facilitating effect of alcohol are not altogether surprising. Many drugs have been shown to facilitate attack and threat behavior at low doses and suppress these reactions at higher doses. Miczek and Barry (1977) studied the effects of alcohol on fighting behavior in pairs of rats when either the dominant or the

subordinate animal was given the drug. A low dose (0.5 gram/kg) given to the dominant animal increased the frequency of biting attack and prolonged the display of the aggressive posture. Higher doses of alcohol (1.0-1.5 grams/kg) suppressed attack behavior and, when given to the subordinate animal, impaired defensive upright postures. In another experiment, naive animals without fighting or drug experience were subjected to attack by a nontreated dominant animal. When treated with alcohol (1.0-1.5 grams/kg), naive rats were more frequently attacked and injured but reacted more readily to initial attacks with submissive supine postures. The authors concluded that these results demonstrate differential effects of alcohol depending on the type of drug recipient (dominant, experienced subordinate, or naive) and that the alcohol has a greater effect on attack behavior than on defensive-submissive reactions.

Tamerin and Mendelson (1969) reported a significant increase in the general level of assertiveness in four alcoholics during sessions of programed drinking. The aggression disappeared as the subjects returned to sobriety. The authors interpreted certain forms of the observed aggression as defensive displays of hypermasculine behavior.

DRUG STATES

ACUTE DRUG EFFECTS

Acute drug effects have been discussed in the preceding sections of this review.

CHRONIC USE

As is true of many drugs, repetitive use of alcohol produces some degree of tolerance on some behavioral skills. As Hurst (1973) demonstrated from an extensive examination of accident records for drinking drivers, the probability of being involved in an accident at any given blood alcohol concentration varies for different drinking frequency groups. Thus, at any given BAC level, infrequent drinkers are more likely to have an accident than individuals who drink more frequently. Hurst was able to demonstrate quite different curves of accident probability for a given BAC for individuals whose self-reported drinking frequency ranged from yearly or less to daily, with the most frequent drinkers least likely to have accidents at any given BAC level. (It should be noted that this does not mean that frequent drinkers are less likely to have accidents overall. Note that we have reported accident rates in terms of a given blood alcohol concentration.) Heavy drinkers tend to achieve blood alcohol levels far beyond those which any moderate or infrequent drinker is capable of achieving without serious incapacity. Moskowitz,

Daily, and Henderson (1974) provided experimental evidence that in performing psychomotor tasks heavy drinkers were more resistant than moderate drinkers to the effects of alcohol at a given blood alcohol concentration. Their evidence demonstrated that the heavier drinkers were less impaired at any given BAC than the moderate drinkers. This difference in resistance to impairment was equivalent to roughly 0.03 percent BAC for these two groups, depending on the behavioral response measure involved. One difficulty with the sparse literature is that it is not clear to what degree these comments are a function of different behavioral mechanisms. But clearly, within a range of non-abusers of alcohol, the more frequent user is likely to be more resistant to the impairing effect of acute dosages. However, long term, serious chronic abuse, such as is typical of many alcoholics, appears to lead to chronic impairment of many behavioral functions. There is some disagreement in the literature as to the reversibility of some of these effects, but there appears to be strong evidence that when not under the influence of alcohol, heavy chronic alcoholic abusers show impairment compared with normal subjects. It is not clear how these alcoholic abusers who show impairment when not under alcohol would compare when under alcohol with normal individuals under alcohol with regard to some of these same faculties. The following is a summary review of some of the findings of chronic behavioral impairment as a result of heavy chronic use.

Brain dysfunction as a product of the prolonged misuse of alcohol has been inferred from psychological measures of deficit in spatial abstraction and set persistence. These deficits exist despite global indications of relatively intact verbal intelligence (Goldstone et al., 1977). Little work has been done on temporal cognition and alcohol, but Goldstone et al. (1977) did find impairment in alcoholics on time discrimination tests using visual and auditory stimuli. The ability of alcoholics to process short term memory also appears to be specifically impaired, as indicated by difficulties in recognizing meaningful drawings and in recalling words within minutes after learning (Riege & Miklusak, 1976). The short term memory for lists of random words and the free recall of related words have been found to be significantly impaired in alcoholic patients (Weingartner & Faillace, 1971; Weingartner et al., 1976). Evidence suggests, therefore, that alcoholics may be deficient in the short term holding of verbal or semantic content of to-be-remembered information and show greater loss of material verbally coded than of items that defy verbalization (Riege & Miklusak, 1976). Visual-spatial task impairments have been reported for alcoholics, implicating right-hemisphere functions (Jones, 1971). Riege and Miklusak (1976) found significant impairment among alcoholics in the ability to remember nonverbal visual or tactual patterns. One consistent finding was a specific visual-spatial abstracting deficit in alcoholics.

Studying memory impairments, Riege and Miklusak (1976) sought to determine if nonverbal information registered through one sensory modality would be comparatively less well retained by chronic alcoholics than nonverbal information registered through another sensory modality. Story recall and continuous recognition (visual, auditory, and tactual) of nonverbal items relying on imagery code were used to measure within minutes what alcoholics remembered; 18 chronic alcoholics and two control groups were tested. Riege and Miklusak found that the ability to remember is weakened in chronic alcoholics. Persons with extended histories of alcoholism had considerable difficulty with the tasks that required them to remember immediately story content to unfamiliar designs by sight or by touch. These memory impairments were not restricted only to verbal materials but also affected recognition of visual or tactual patterns that defied verbal coding. In these tests, chronic alcoholics without detectable brain impairment remembered far less than controls.

Nelson and Schwartz (1971) studied the performance of 30 outpatient alcoholics on a visual recognition experiment. As did normals, the alcoholics found negatives more difficult to recognize (i.e., required a longer exposure to produce recognition) than positives; this difference increases as a function of difficulty or object complexity. The data also suggest, however, that alcoholics are absolutely and relatively less able than normals to process conflicting visual information. The latter finding led to the hypothesis that alcohol serves to relieve sensory discordance for the alcoholic. It appeared that alcoholics manifested difficulty in processing information relating to surface properties of objects in general and that this problem was exacerbated when the stimulus confronted was in respect to such properties in conflict with the observer's habitual assumptions about the visual world.

Jones (1971) studied 30 chronic alcoholics and 30 hospital controls on a verbal and spatial intelligence test and found that chronic alcoholics performed significantly more poorly than controls on the spatial, but not on the verbal, intelligence test. Alcoholic history was demonstrated to be related to cognitive ability, with long term alcoholics performing more poorly than short term alcoholics. Correlations between verbal and spatial intelligence tests were significant for long term alcoholics, suggesting differential hemisphere sensitivity to the effects of chronic alcoholism with a consequent dissociation in factors related to intellectual functioning. The results of this investigation confirmed previous findings that chronic alcoholics are not impaired on verbal intelligence. The study further made evident that when drinking history is controlled, it is alcoholic history that is related to cognitive performance, although it is unclear whether the age of onset of alcoholism or the number of years of alcoholism is the most important variable.

Vivian (1973) tested 16 chronic alcoholics and 16 non-alcoholics for a possible discrepancy between performance on motor speed and complex perceptual-motor tasks. Utilizing a tapping test as a measure of motor speed, and reaction time and tracing tasks as measures of perceptual-motor coordination, the researcher found that alcoholics did not differ from normals on tapping but did differ from them on the perceptual-motor tasks. The author suggested that the impairment of motor function frequently associated with alcoholism may not consist of a loss of primary motor abilities but rather is a disability in coordinating sensory stimulation with movement.

In a study of intellectual impairment and recovery rates in heavy drinkers, Clarke and Haughton (1975) sought to assess whether heavy drinkers showed significant impairments in visual-spatial and visual-motor reasoning and visual reproduction, and whether these impairments are semipermanent or whether they recover when a person stops drinking. Fifty-five patients diagnosed as "primary excessive drinking" were compared with 55 controls on two verbal tests and two performance tests. Results indicated that the sample of heavy drinkers did significantly more poorly on tests of visual-spatial and visual-motor coordination, visual reproduction, and abstract reasoning even when they had not been drinking for 10 weeks. The heavy drinkers, therefore, exhibited the two general areas of deficit described by Kleinknecht and Goldstein (1972)--perceptual-motor coordination and abstract reasoning. The findings on the severity and length of time the impairment lasts after heavy drinking raise serious implications for fitness to return to work and fitness to drive.

Similarly, in time discrimination tests using visual and auditory stimuli, Goldstone et al. (1977) found that more information was transmitted by social drinkers than by alcoholics and that cognitively unimpaired alcoholics transmitted more information than did cognitively impaired alcoholics. These experiments revealed obvious deficits in temporal information processing by nondeteriorated, detoxicated alcoholics of above-average intelligence. Similar to the findings of Riege and Miklusak (1976), all groups revealed the most transmitted information with audition and the least with vision.

FIELD DEPENDENCE

An association between alcoholism and field-dependent perceptual performance has been observed in several studies. Although there is evidence that alcoholics are markedly field dependent in their perception and tend to have a global concept of their bodies, it is not known whether this limited level of differentiation is a predisposing factor or a consequence of alcoholism.

Research results to date have been contradictory, and at present the implications of these differing interpretations remain speculative.

Karp, Witkin, and Goodenough (1965) found evidence supporting the predisposing theory in a study of the stability of perceptual field dependence (taken as an indicator of level of differentiation) during the alcoholic cycle. Because evidence from nonalcoholic subjects suggests that measures reflecting relative levels of differentiation are highly stable over time, the authors explored the extent of perceptual field dependence under acute intoxication, continuous alcoholism over many years, and prolonged sobriety after an extended history of alcoholism. They hypothesized that if field dependence, or, more broadly, limited differentiation, is a consequence of alcoholism, field dependence might be greater in the intoxicated state than in the sober state, and greater among alcoholics with a long history of alcoholism than among those with a short history. Findings indicated that the extent of field dependence was not altered by alcohol. Although this finding does not provide direct support for the view that marked field dependence associated with alcoholism antedates the onset of drinking behavior, the authors concluded that it does increase the plausibility.

On the other hand, Kristofferson (1968), studying nonalcoholic subjects divided into alcohol and nonalcohol groups, found evidence in support of the consequence hypothesis. Forty-eight males, none of whom were heavy drinkers, were randomly assigned to experimental and control groups and classified for field dependency before testing. No significant difference was found between groups on pretest scores. After alcohol was administered to an average BAC of 0.08 percent, the alcohol group showed a significant increase in perceptual field dependence on the posttest; the control group showed no change. The increase in field dependence did not differentially affect subjects classified prior to the administration of alcohol as high or low in field dependence.

Allen et al. (1971) and Weingartner and Faillace (1971) studied the relationship of STM, state dependence, and memory recovery. In a cross-sectional study, Weingartner and Faillace (1971) found that alcoholics who had been without alcohol for less than 1 week exhibited inferior memory functioning compared with those who had been without alcohol for 3 or more weeks; this suggests that memory functioning in the latter group was recovering during the first 3 weeks after withdrawal. Allen et al. (1971) investigated this same phenomenon in a group of alcoholics in a longitudinal followup through withdrawal. Free-recall measures indicated improvement in memory after 2 weeks; the data also suggested that it was primarily short term memory that was recovering. It would appear that short term and long term memory are independent or that at least it is possible for

an impaired STM to remain adequate for encoding long term memory.

Tarter and Jones (1971) investigated three related questions on motor impairment in chronic alcoholics. Because previous research had indicated that alcoholics are deficient in finger and manual dexterity as well as motor coordination, they sought to determine if alcoholics manifest an impairment of motor abilities when measured by standardized neuropsychological tests. Second, they sought to establish the extent to which the severity of the behavioral deficits is related to the duration of alcoholism. Third, they sought to resolve the question of the permanence or reversibility of the impairments. Twenty-six chronic male alcoholics from an inpatient treatment program served as subjects; 34 controls were selected from the other wards of the hospital. Both groups were given two series of tests over a 2-month period. Results indicated that alcoholics exhibited deficits in muscle strength and motor speed but not perceptual-motor coordination. When the sample of alcoholics was divided into two subgroups on the basis of alcoholism history, it was found that in the short term alcoholics muscle strength and motor speed were initially impaired but improved enough during a 2-month sobriety period so as not to be significantly different from the controls upon retesting. On the other hand, the performance of long term alcoholics was inferior to the controls on both the first and second testing, indicating that no significant improvement occurred during the sobriety interval. These results confirm earlier findings of a progressive decrease in muscle strength with increasing duration of alcoholism history and demonstrated that the shorter the duration of alcoholism, the greater the potential for recovery. The research also supported the previously reported findings of a deficit in motor speed among alcoholics and extended this basic finding to show that the degree of impairment and prognosis for recovery are associated with the duration of alcoholism history. On the first test perceptual-motor coordination was impaired in both the short and long term alcoholics. However, both groups improved from test to retest; the retest performance level of alcoholics also was not significantly different from that of the controls. This suggests that perceptual-motor coordination is intact in chronic alcoholics who are detoxified. These findings are consistent with research on reaction times which indicates that perceptual-motor speed as well as coordination is intact in alcoholics.

TIME-COURSE EFFECTS

In general, the impairing effects of alcohol on skills performance closely follows the blood alcohol concentration. In most situations the rate of consumption of alcohol is such that the rate of rise of blood alcohol concentration is more rapid

than its fall. For nearly all individuals blood alcohol concentration falls at a rate somewhere between 0.012 percent and 0.026 percent. The higher rates are associated with the more experienced drinkers whose chronic use of alcohol stimulates the production of enzymes that metabolize the alcohol more rapidly. With one exception, there is a high correlation between the actual level of alcohol at any given time and the degree of impairment of performance. However, it has been recognized since 1919, when reported by an English investigator, Mellanby, that the impairing effect of alcohol is greater during the period when the alcohol is rising in the blood than when it is decreasing. This is due to the presence of an acute tolerance, that is, a change in tolerance to alcohol produced within a single drug treatment episode. Evidence for this effect is well established in the literature, having been reported by Goldberg (1943), among others. The previously noted study by Moskowitz et al. (1974) examined the differential effect on performance of the acute tolerance between the blood-rising and the blood-falling stages of alcohol consumption; they reported that the difference here, too, was equivalent to 0.02 to 0.04 percent BAC. It is of interest to note that the acute tolerance effect is superimposed on the chronic tolerance effect, so that the acute tolerance effect was shown in both moderate and heavy drinkers. Outside of this effect, which is not of major consequence, it is unimportant what stage of the pharmacokinetic process alcohol is in. A good index to the impairing effect can be found by examining the blood alcohol concentration at the time that performance is to be measured.

It should be noted that Goldberg and some others have suggested that impairing effects occur after the disappearance of alcohol from the blood system. Clearly, such effects occur in individuals subject to alcohol withdrawal symptoms, as in delirium tremors exhibited by alcoholics. However, Goldberg has produced evidence for a unique type of alcohol positional nystagmus which occurs after complete metabolism of alcohol from the body. There is really no good experimental evidence other than the work on positional alcohol nystagmus to identify the effects on performance in the postmetabolism period. It is an area clearly needing further experimental work.

WITHDRAWAL AND TERMINATION EFFECTS

None of the papers submitted for review dealt with this issue. It is well known that chronic heavy abusers of alcohol suffer serious withdrawal symptoms, as reported extensively in the literature of the last few centuries, but the last decade has seen no major contributions to this issue. It is clear from at least one physiological measure, positional alcohol nystagmus, that after clearance of alcohol there still remain changes in body state as a result of the alcohol experience which can

produce changes in behavior. This is a woefully inadequately explored area.

INTERACTION WITH PHYSIOLOGICAL AND PSYCHOLOGICAL STRESS

Little relevant literature during the last decade has dealt with this issue, except as reported in the section on aggression.

ALCOHOL-DRUG INTERACTIONS

The last 3 decades have witnessed a massive increase in the use of pharmaceuticals--self-prescribed, over-the-counter, and illicit drugs, as well as physician-prescribed drugs. It is likely that alcohol will frequently be found in combination with other drugs since alcohol is consumed at least once a month by 60 percent of the adult population. While it is clear that combined alcohol-drug use is prevalent, the consequences of the combined use are unclear, and laboratory studies evaluating the potential danger are scarce. Unfortunately, only a few studies examine one or two drugs at a single or small number of dose levels. Moreover, many studies have employed behavioral measures that are not sensitive and are of questionable relevance. It is important to insure that a wide range of skills are examined systematically before assuming that combined drug-alcohol use has no detrimental results. One cannot simply generalize from one behavioral area to another or predict failure to affect one behavioral variable on the basis of failure to affect another one. It is essential to examine those specific behavioral variables important to safe performance of specific skills.

The experimental literature falls into two broad categories: those studies that have examined predominantly physiologic side effects that are potentially undesirable and those studies that have demonstrated behavioral changes implying decreases in performance of skills.

The relationship of alcohol to barbiturate-involved deaths in Glasgow, Scotland, illustrates the first type of study (Bogan & Smith, 1967). In 36 of the 85 cases investigated, both barbiturates and alcohol were present. The lethal dose of barbiturates was nearly 50 percent lower in the presence of alcohol than when used alone, so that the combined presence of alcohol and barbiturates increased the potential for a fatal overdose.

The second type of study arises from the increased probaability of injury or accident due to heightened behavioral impairments arising from the combined action of the two drugs. Bø and colleagues compared diazepam and alcohol blood levels in 74 drivers hospitalized after driving accidents with

corresponding blood levels in 204 control group drivers. Of the accident group, 41.8 percent had only alcohol present compared with 1.5 percent of the control group; 9.5 percent of the accident group had only diazepam present compared with 2 percent of the control group; and 10.8 percent of the accident group had both drugs present compared with 0 percent of the control group. The results suggest behavior impairment by alcohol and diazepam and increased effects when the two substances are combined (Bø, Haffner, Langard, Trumpy, Bredesen, & Lunde, 1975).

The concurrent presence of two drugs can alter the effects of either or both by several mechanisms, including absorption, distribution, metabolism, excretion, direct chemical interaction, or competition between the drugs for common sites of action in the body. Unfortunately, determining the nature of the interaction of two drugs is far more complex than ascertaining if there is, in fact, an interaction. In most cases, the manner of the interaction cannot currently be specified.

It should be noted that experiments typically compared the effects of four treatments: placebo alone, drug alone, alcohol alone, and drug and alcohol combined with placebo. Yet an extensive set of experiments with meprobamate and alcohol (Carpenter, 1975) illustrates the problems in attempting to predict the effect of one set of dose levels on behavior from the known effects of other dose levels, unless a wide range of levels has been tested in combination. In some cases, an increased dose produced less impairment of behavior than lower dose levels did. The many possibilities for interactions affecting various processes and sites in the body as a function of dose level make predictions difficult. For example, it is not known at what dose level central nervous system mechanisms affecting various behaviors are triggered or suppressed. So if the effects of a drug with alcohol have been examined only as one level, failure to find an interaction does not preclude the possibility of discovering one at other drug or alcohol levels. Nor does the failure to find an interaction with one behavioral measure preclude finding it with another.

When two drugs are combined, the results can be described as producing effects similar to or opposite from those of either drug presented separately. Opposite effects are called antagonistic. Similar effects are described as intra-additive if the combined effect is less than the sum of the two single effects; as additive if the effect is the sum of the two separate effects; or as supra-additive or potentiating if the effect is more than the sum of the two single effects. Judgments regarding the degree of effect are frequently a matter of which dose levels of alcohol and of the drug are used. In the following studies, the terms used by the authors have been followed, although frequently it was not clear what evidence existed for statements that the results indicated potentiation. Kissin (1974)

suggested a reason for avoiding judgment on the degree of effect: effects may occur that are qualitatively different from the responses to either drug or alcohol.

THE ANTIANXIETY (MINOR) TRANQUILIZERS

This class of psychotropic drugs is the most likely to be found in combination with alcohol among the general population. Users generally are unaware that these drugs are CNS depressants with considerable possibilities for increasing the effects of alcohol on performance skills and alertness. This misunderstanding appears to be the most frequent negative consequence of joint use. There is also evidence that alcohol increases benzodiazepine blood levels (Hayes, Pablo, Radomski, & Palmer, 1977).

MEPROBAMATE

Meprobamate, in combination with alcohol, has been examined extensively for possible effects on driving-related skills. Goldberg (1963) reported decreases in oculomotor control and body steadiness, as well as subjective reports of drowsiness and fatigue, after combined alcohol-meprobamate use. Loomis (1963), using a driving simulator, confirmed these findings with tracking and reaction time measures.

Zirkle, McAtee, King, and VanDyke (1960) examined the effects of combined meprobamate-alcohol use in eight tests ranging from simple arithmetic to changes in perceptions on visual illusions. Statistically significant performance losses were found on six of the tests, while increased impairment trends were seen on the other two.

Forney and Hughes (1964) examined the effects of meprobamate and alcohol on subjects' performance on arithmetic and verbal mental tests while the subjects were also responding in a delayed auditory feedback device. Impairment was greater than under either the drug or alcohol alone. An extensive battery of tasks given to subjects using the meprobamate-alcohol combination (Reisby & Theilgaard, 1969) revealed increased impairments in time estimation, attention, reaction time, body steadiness, and oculomotor control and alertness. These effects on humans are corroborated by similar evidence of enhanced behavioral disruption of a variety of behaviors in animals (Wallgren & Barry, 1970). Rubin, Gang, Misra, and Lieber (1970) speculated that these results come from an alcohol-induced decrease in meprobamate metabolism rates.

BENZODIAZEPINES

The most frequently used antianxiety tranquilizers are the benzodiazepines, such as diazepam and chlordiazepoxide. There is evidence that diazepam by itself or in combination with alcohol is overrepresented in driving accidents. There is, however, little evidence of increased behavioral deterioration when alcohol and chlordiazepoxide are combined. Although Goldberg (1963) found losses in oculomotor control and standing steadiness for alcohol-chlordiazepoxide combinations, Hughes, Forney, and Richards (1965) failed to find increased impairment on pursuit tracking tasks or in subjective evaluation of symptoms. Nor did Miller, D'Agostino, and Minsky (1963) find impairment on either physiologic measures or a digit symbol test. Reports by Bowes (1960) on clinical experience also do not suggest behavioral impairments from combined alcohol-chlordiazepoxide consumption.

Evidence for performance impairment under diazepam appears more certain. Burford, French, and LeBlanc (1975) found that combined alcohol-diazepam treatments produced greater impairment of reaction time on a step pursuit tracking task than did alcohol alone. A subjective judgment scale administered simultaneously showed little evidence that subjects were aware of the greater degree of impairment under the combined dose treatments.

Smiley, LeBlanc, French, and Burford (1975), examining the effects of diazepam and alcohol in subjects driving an instrumented car, reported decreased ability to stop accurately and a changed power spectrum for steering wheel angle movements. Other researchers examined chlordiazepoxide and diazepam with a battery of sensory, perceptual, and motor tasks. Although there were no significant increased deficits for chlordiazepoxide with alcohol, there were enhanced deficits for the diazepam treatment (Franks, Starmer, Chesher, Jackson, Hensley, & Hensley, 1975).

Molander and Duvhok (1976) examined the effects of diazepam, oxazepam, and methylperone on critical flicker fusion frequency, physical coordination, and mood. Diazepam in combination with alcohol produced increased deficits in critical flicker fusion frequencies and coordination ability, but not in mood. This finding strengthens the evidence that subjective judgments may be inadequate to suggest degree of impairment. The other drugs had fewer effects on the response variables. Other researchers reported that combined administration of diazepam and alcohol increased impairment of coordination and attention (Linnoila, Saario, & Maki, 1974; Morland, Setekliev, Haffner, Stromsaetner, Danielsen, & Wethe, 1974).

Linnoila and Mattila (1973) examined diazepam-alcohol interaction in a driving simulator. Subjects collided more frequently, ignored instructions, and made more steering errors under the combination. Linnoila and Hakkinen (1974) in a similar

experiment using professional drivers of considerable experience, reported similar results. The diazepam-alcohol combination produced greater impairment of driving skills than either diazepam or alcohol alone.

Although a few of the earlier studies, such as those of Lawton and Cahn (1963), failed to find greater deficits with diazepam and alcohol combined, the overwhelming evidence from recent research has pointed to increased impairment from combined alcohol and diazepam. The increasing evidence of impairments suggests that more sensitive and relevant behavior variables are being examined.

THE ANTIPSYCHOTIC (MAJOR) TRANQUILIZERS

The antipsychotic or major tranquilizers are typically more potent than the antianxiety tranquilizers and are used for more seriously emotionally disturbed patients. The most prominent of these drugs are the phenothiazines such as chlorpromazine and the alkaloids of rauwolfia including reserpine.

The effects of chlorpromazine and alcohol on a battery of human performance skills were examined by Zirkle, King, McAtee, and VanDyke (1959). Tests of mental arithmetic, correctness of visual perceptions in illusions, and digit symbols were significantly more impaired by joint drug-alcohol treatments; other tests were affected less strongly. Goldberg (1961) and Loomis (1963) presented evidence of mechanical impairment. Milner and Landauer (1971) compared the interaction of alcohol with chlorpromazine and thioridazine, another phenothiazine, using three motor skills performance tasks. Both drugs produced increased reaction response times; chlorpromazine produced the greater effect. However, Saario (1976) failed to find any interaction between thioridazine and alcohol on complex reaction time, coordination, or attention tests.

Kissin (1974) noted that, in contrast to the less conclusive evidence for alcohol-chlorpromazine interaction in humans, there are ample animal studies indicating supra-additive effects. Studies indicate that chlorpromazine increased alcohol effects on respiration, motor activity, sleeping time, and the ability to perform avoidance and escape responses. Moreover, there is evidence that chlorpromazine may retard alcohol metabolism.

Few human studies evaluate resorpine interactions with alcohol, although Burger (1961) and Feldmann (1962) reported increased reaction time. The evidence from animal studies, however, appears more conclusive in reporting increased impairment under combined drug-alcohol treatments, disruption of choice discrimination and shock avoidance responses, and increased duration of anesthesia.

The differences in degree of effect between animal and human studies, combined with the wide variability of differences in effects on different behaviors among the antipsychotic tranquilizers, make generalization difficult. Clearly some evidence exists for increased impairment in performance skills, which suggests the need for advising caution in using alcohol in combination with any of the antipsychotic tranquilizers.

MORPHINE AND ITS DERIVATIVES

Forney and Hughes (1968) described a series of experiments on animals measuring motor activity levels after combinations of alcohol with codeine or morphine were administered. Increased impairment was found for morphine, but not for codeine. Support for the synergistic effects of morphine with alcohol also was offered in animal studies by Eerola (1961). Kissin (1974) summarized several epidemiologic studies suggesting that combined use of morphine and alcohol increases the probability of death. While the nature of the interaction is unknown, it appears that repeated exposure to morphine derivatives sensitizes the patient to alcohol.

MARIHUANA

Considerable evidence now points to the use of marihuana alone as a danger in human-machine interactions such as driving (Moskowitz, 1976). Recent studies offer evidence that combined alcohol-marihuana use increases performance impairment.

Both mental arithmetic scores and pursuit tracking ability evidenced increased impairment with combined alcohol-marihuana use (Manno et al., 1971). When a subject's attention was divided, researchers found decreased ability to monitor visual signals in central and peripheral vision (Macavoy and Marks, 1975). A marihuana-alcohol combination produced greater deficits on tests of standing steadiness, manual dexterity, and psychomotor skill (Chesher, Franks, Hensley, Hensley, Jackson, Starmer, & Teo, 1976). Vigilance, information processing, and oculomotor control showed increased impairment as well (Moskowitz, 1977). Also, combining the two drugs in rats made their remaining on a moving belt more difficult (Kalant & LeBlanc, 1974).

All studies agree that skills performance impairment increases in humans under the combined use of marihuana and alcohol.

BARBITURATES

The well-known danger to human life from combined use of alcohol and barbiturates has stimulated work on the behavioral effects of sublethal doses. Researchers examined the interaction

of alcohol and phenobarbital--a long-acting barbiturate--and found that complex reaction times were sufficiently increased to describe the effects as supra-additive (Joyce, Edgecombe, Kennard, Weatherall, & Woods, 1959).

Doenicke and Kugler (1965) and Doenicke, Kugler, Spann, Liebhardt, and Kleinert (1966) examined the effects of alcohol consumption at intervals up to 24 hours after the administration of various medium- and short-acting barbiturates. Subjects showed a markedly increased tendency to fall asleep, accompanied by impaired motor performance, even at delayed intervals.

Loomis (1963) examined the effects of secobarbital on subjects tested in a driving simulator where tracking and reaction times were measured. Again, results demonstrated markedly increased impairment of performance under the combined dose compared with either the drug or alcohol alone.

A series of studies by Osterhaus (1964) demonstrated signs of severe intoxication when barbital was taken by persons with blood alcohol concentrations in the 0.06 to 0.16 percent range. Symptoms included unconsciousness and extended sleep, vomiting, and severe motor impairment.

These results in humans are supported by extensive animal studies (Wallgren & Barry, 1970); combined effects on sleep, mortality rates, respiratory failure, and avoidance behavior were noted in many species. In all cases, the effects of the two drugs were greater than that of either drug alone, and frequently were described as supra-additive.

Alcohol abusers who have developed tolerance to alcohol exhibit a similar cross-tolerance to barbiturates. Anesthesiologists report that alcoholics require increased doses of barbiturates; Devenyi and Wilson (1971) and Kissin (1974) reported that alcoholics have used barbiturates to alleviate alcohol withdrawal symptoms. Given the low threshold for fatalities in the combined use of these substances, such practices are extremely hazardous.

Similarly, chloral hydrate frequently is used as a hypnotic to induce sleep. Unfortunately, it also accentuates the CNS depression produced by alcohol and can lead to respiratory arrest and death (Koppanyi, 1957). Other researchers examined the effects of chloral hydrate and alcohol on simple and complex choice reaction times, on a rotary pursuit task, on a vigilance task, and on a variety of physiological measures. The combined administration produced heart rate increases and pulse pressure decreases. The combined use also decreased performance on the two tasks (Sellers, Carr, Bernstein, Sellers, and Koch-Weser, 1965).

STIMULANTS

Theoretically, stimulants might antagonize the effects of alcohol, a CNS depressant. Several studies have examined use of the combination for various behaviors assumed important to driving. In general, some of the effects of alcohol were opposed, although the results are rather variable and appear quite dependent on the dose levels and behaviors examined.

Newman and Newman (1956) examined the ability of 15 mg of dextroamphetamine and 300 mg of caffeine to counteract the influence of alcohol on measures of hand steadiness, flicker fusion, and body balance. Only body balance was slightly less impaired when caffeine was administered to the subjects.

Hughes and Forney (1964b) administered dextroamphetamine and alcohol to subjects performing a battery of mental tests while in a stressful delayed auditory feedback situation. Performance on verbal and arithmetic tests did not improve. Forney and Hughes (1965) used the same technique to examine mental performance of subjects under the stress of auditory feedback while under the influence of caffeine and alcohol. Of the nine mental tasks, caffeine mitigated the effect of alcohol on the performance of two simple arithmetic tests and on a color discrimination task.

Brown, Hughes, Forney, and Richards (1966) examined the effect of d-amphetamine on pursuit tracking tasks for 3.5 hours. The tracking task was administered at four levels of difficulty, and the ability of the stimulant to counteract some of the effects of the alcohol was a function of the difficulty level of the task. The amphetamine improved performance at some levels but not at others. Similar interactions with the response measures were exhibited in a study on amphetamine-alcohol combinations (Wilson, Taylor, Nash, & Camerson, 1966). Although antagonism was found in three tests of mental performance, none was found in measures of intellectual or psychomotor performance.

Nash (1966) reviewed the work on the possible antagonism between caffeine and alcohol and noted the great variability in results. Although researchers have reported that caffeine antagonizes, or adds to, the behavioral deficits produced by alcohol, generally the effects reported have been quite small. The conflict in conclusions may be related to the choice of behavioral variables examined. If, as Kissin (1974) suggested, alcohol is acting to reduce inhibition of behavior, caffeine may increase performance disturbance. If alcohol is acting as a depressant, caffeine may perform its anticipated antagonistic role. Overall, the anticipated antagonism between alcohol and stimulants occurs only sporadically on some selected behaviors and not on others.

Some subjective effects suggest an antagonism between stimulants and alcohol in individuals who abuse the alcohol-amphetamine combination (Kipperman & Fine, 1974). Researchers report combined use as a means of extending an alcoholic binge or of modulating the effects of high-dose levels of amphetamines. The subjects reported various side effects ranging from gastrointestinal upset to heart palpitations.

ANTIDEPRESSANT DRUGS

Few behavioral studies in humans have examined the combined effect of alcohol and antidepressant drugs. Landauer et al. (1969) examined alcohol-amitriptyline effects on a step pursuit tracking task, the pursuit rotor, and a dot tracking task. All three measures showed significant response loss for the drug and alcohol combination. In examining the combination of amitriptyline and other drugs with alcohol (Seppala, Linnoila, Elonem, Mattila, & Maki, 1975), researchers found that alcohol and amitriptyline increased deficits of motor coordination and reaction time. However, Hughes and Forney (1963) reported a minor tendency, albeit insignificant, toward antagonism between the effects of alcohol and nortriptyline on mental tasks performed under auditory delayed feedback. This finding was supported in animal studies involving drugs in this class.

ANTIHISTAMINES

Antihistamines are drugs used to control symptoms of allergy and motion sickness. Despite their very prominent side effect of sedation and their use as a major constituent of over-the-counter sedative drugs, there are comparatively few studies of the behavioral consequences of combining antihistamines and alcohol.

Hughes and Forney (1964a) examined the effects of clemizole, diphenhydramine, and tripelennamine on subjects taking a battery of nine mental tasks performed under the stress of delayed auditory feedback and a pursuit tracking task. Although there was no additional performance loss under the combined dosages for the mental tests, the pursuit tracking task was impaired significantly by the diphenhydramine-alcohol combination, and a nonstatistically significant trend was noted with the other antihistamines. A symptom checklist produced increased evaluations of the diphenhydramine-alcohol combination as a depressant.

Landauer and Milner (1971) examined the effects of pheniramine, cyproheptadine, and clemastine in a series of psychomotor experiments and found no evidence of impairment due to one of the drugs alone or to the drugs in combination with alcohol. However, it is questionable that the response variables were sufficiently sensitive to demonstrate potential deficits.

Linnoila (1973) examined the effects of diphenhydramine and meclastine on performance skills. Subjects receiving the combined alcohol-drug treatments reported subjectively greater feelings of impairment. Only the diphenhydramine-alcohol combination, however, produced statistically significant impairment on the objective tests, notably one test involving coordination.

Moskowitz and Burns (1973, 1976) examined diphenhydramine-alcohol using two tracking tasks, a division of attention task, and a measure of information-processing rate. Diphenhydramine increased the impairment produced by alcohol on all behavioral measures.

Although behavioral research appears to suggest that antihistamines enhance an alcoholic impairment of skills performance, only future research can determine the degree and nature of the impairment for specific drugs.

DRUGS PRODUCING ALCOHOL INTOLERANCE

Kissin (1974) noted a class of drugs that produces marked reactions when combined with alcohol consumption. The best known example is disulfiram (Antabuse), used to induce abstinence in alcohol abusers. These chemicals apparently interfere with some aspect of the metabolism of alcohol, either the transformation of alcohol to acetaldehyde or its further subsequent metabolism. In the case of disulfiram, the enzyme aldehydra-dehydrogenase is inhibited, leading to an increase in blood levels of acetaldehyde. The degree of reaction varies with alcohol and disulfiram levels, producing symptoms of headaches, flushing, vomiting, nausea, and respiratory difficulties. Calcium carbimide and sulfonylurea produce similar results.

Several drugs are reported to mildly inhibit liver alcohol dehydrogenase and thereby slow the conversion of alcohol into acetaldehyde. Alcohol-associated symptoms of impairment then become more severe. Drugs in this category include pyrazola, phenylbutazone, pheniprazine, and metronidazola.

GENERAL SUMMARY

Alcohol is the most frequently used drug in our society. It is used most frequently and in greatest quantitites by young males, those most likely to be involved in military performance tasks.

As with other drugs, the effects of alcohol are dependent on the dose administered, the degree of experience with the drug, the rate of consumption of the drug, and the contents of the gastrointestinal tract. While there is strong evidence for chronic tolerance developing to alcohol, the tolerance is relatively minor, being equivalent to roughly 1 ounce of pure alcohol. Moreover, it is not clear whether the chronic tolerance effect has as large an effect on cognitive performance or decisionmaking, the most important elements of skills performance, as it has on more overtly conspicuous motor skills.

In addition to chronic tolerance, which is a function of drinking experience, there is an acute tolerance which occurs during a single drinking session. This is reflected in a decreased degree of impairment for a given blood alcohol concentration as a function of the duration of drinking. The slower the consumption rate, the lesser the degree of impairment. Because alcohol is absorbed through the gastrointestinal tract, primarily the small intestines, substances in the tract, such as food, which slow the rate of absorption lead to a considerably decreased blood alcohol concentration for a given dosage.

Although the above factors are significant in the variability of degree of impairment, the prime source of variability of impairment among individuals is the difference in blood alcohol concentration, as a function of intake. The differences in consumption rates between individuals are as great as 20 to 1 within a day, and more so when examined over an extended duration. With some variation, blood alcohol concentration is an excellent index of the degree of impairment found in individuals.

At higher dosages nearly all functions are impaired, with individuals becoming comatose or unconscious, even dying. The literature on the areas of impairment by alcohol indicates that impairment of peripheral functions, both motor output and sensory input, occurs at a slower rate and higher dose levels than impairment of more central phenomena such as perception, information processing, cognition, and division of attention. These latter functions are of greater significance for skills performance demands in modern society than the gross motor performance or physical strength which might have been more important in military performance in the past.

The emphasis of research on skills performance has centered on central processing and tracking performance. Tracking performance, of course, is a key element in many complex skills situations. Tracking is a rather complex function with components from many

stages of behavioral processing. Alcohol is more likely to affect some forms of tracking, such as pursuit tracking (which involves monitoring more than one input) than others, such as compensatory tracking.

A major element of alcohol's effect on central processing is reflected in the deterioration of visual performance. Many eye movement studies have shown that visual search behavior is strongly affected by alcohol due to increased duration of fixations and pursuits requiring, in turn, modification of strategies for observing the environment.

Division of attention is characteristic of many complex military and civilian higher order skills performance situations. It is uniquely sensitive to the effects of alcohol, showing deficits after an intake of 0.5 ounce of alcohol.

Alcohol not only impairs performance but also impairs awareness of the decrease in performance, so that corrective or compensating behavior is less likely to be adopted. Memory is frequently an important function in complex skills performance. There is considerable literature suggesting impairment by alcohol, especially of short term memory. However, there is considerable debate about the nature of memory mechanisms and functions. Lacking this knowledge, researchers cannot evaluate whether a particular task would be detrimentally affected.

Whether alcohol produces a significant state-dependent learning, and to what degree this is important in skills performance, remains an open question. Examination of complex skills performance situations such as driving indicates that alcohol, even at the lowest measurable blood alcohol concentration, produces an increased impairment of a serious nature. In the analysis of driving and flying, particular note was made of the importance of the effect of alcohol on division of attention, which is a major component of these complex tasks and makes these tasks uniquely sensitive to impairment.

In many situations in the military, individuals have to perform as members of a group, for example, as a crew monitoring and controlling various tasks. In these situations, the emotional state of the individuals and their susceptibility to performance failure under stress are extremely important. The presence of alcohol appears to increase antagonistic or aggressive expressions by individuals. There is extensive debate as to the underlying nature of the increased aggression. Does alcohol stimulate the aggressive behavior as such or serve as a disinhibitor releasing already existing trends? Or is the aggressive response elicited by alcohol due to expectations or social set? Research has not as yet been definitive and it remains an area requiring investigation.

One result of chronic use can be the appearance of central brain dysfunction with, in the extreme, psychotic states. This brain dysfunction may or may not clear up after some considerable

period of withdrawal from use of the beverage. Field dependence, which appears to reflect distorted perceptual functioning, frequently has been noted as a concomitant of excessive chronic drug use.

The time curve of alcohol impairment closely follows the blood alcohol curve over time. In general, the rate of disappearance of alcohol from the blood is comparatively rapid and linear with respect to time, when compared with many other psychoactive drugs which disappear from the blood in a negatively exponential curve over a much longer time.

One question which should be explored in greater depth is whether impairment exists after the blood alcohol curve has reached zero. Continued performance decrements might be found as metabolic byproducts of alcohol which are themselves impairing, such as acetaldehyde, or as a function of a cellular withdrawal reaction. This area has been insufficiently researched and should be examined with greater care, since there are indications of a post-blood-alcohol effect.

A matter of considerable importance is the interaction between alcohol and other drugs. Since alcohol is so universally used, it is often present in combination with other drugs, both legal prescription or over-the-counter drugs and illegal drugs of abuse. This is of increasing importance, given the drug habits of individuals in the age range of the military. With few exceptions, the combination of alcohol with other drugs leads to increased impairment, usually of an additive nature, although claims have been made for some drugs' producing more than an additive effect. In some cases, such as caffeine and amphetamine, claims have been made for antagonistic effects. The literature is sparse in view of the many interactions that can occur. This is an important area for future research. In undertaking such research, investigators should note that quite often the drugs and alcohol not only interact in terms of behavioral changes due to direct CNS effects but also interact indirectly as the two drugs affect the absorption, distribution, and metabolism of each other.

Another inadequately examined area is that of alcohol's effects when individuals are fatigued, sleep deprived, or required to perform at different times in the diurnal cycle.

In conclusion, despite the fact that more research has been done on alcohol than on any other drug in history, many areas remain to be explored regarding the behavioral effects of alcohol, as well as the physiological and central nervous system mechanisms that underlie its behavioral effects. Previous research tended to center on psychiatric consequences of alcohol abuse, and only in recent years has the importance of examining behavioral consequences of acute and chronic alcohol use been realized. As our society makes more complex demands on the individual, exploration of these areas becomes increasingly important.

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3. A CRITICAL REVIEW OF THE DRUG/PERFORMANCE LITERATURE ON OPIATES

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PREFACE

Results from approximately half the articles reviewed are not included in this paper because of flaws in experimental design and execution, inappropriate statistics, lack of statistical analysis, or other deficiencies. However, in some areas so little work exists that results from papers whose soundness could be questioned have been included, accompanied by a brief statement of the weakness of the data. Where data are presented without such comment, the results as discussed are considered sound. Because there are large qualitative as well as quantitative species differences in response to opiates, especially among subprimate species, no animal data are included in this review.

HUMAN STUDIES

SENSORIMOTOR FUNCTION

General Activity and Wake-Rest Cycles

Self-reports and reports by observers are consistent in noting increased relaxation, nodding, coasting, and physical and mental inactivity in nontolerant persons following single injections of morphine and heroin (Kay et al., 1967; Martin & Fraser, 1961; Smith & Beecher, 1959, 1962). Although clinical reports of inactivity of persons addicted to opiates are common (Kay, 1975), objective measurement, such as numbers of hours spent in bed, fails to reveal statistically significant effects (Fraser & Isbell, 1952).

Sleep disturbances have been reported after single doses of heroin and morphine in nontolerant persons. Delay to sleep onset increased from 15 min without drug to 1 hr with drug. Number of awakenings increased 50 percent and total awake time in the first 6 hours of the night increased up to 25 percent after single doses of opiates. There is some indication that pattern of sleep is also disturbed as measured by electroencephalographic (EEG) changes. Total proportion of rapid-eye-movement (REM) sleep, a stage during which much dreaming is thought to occur, decreased after single doses of opiates (Kay et al., 1969; Lewis et al., 1970). The ultimate behavioral consequences of EEG changes during sleep are not clear, however. Repetition of these studies with double-blind drug administration will place these results on a firm foundation.

No significant changes in behavioral sleep patterns have been observed during chronic, as opposed to acute, opiate administration. Specifically, no changes in proportion of time awake, number of awakenings during the night, or time needed to fall

asleep occurred during chronic opiate use (Kay, 1975; Orr & Stahl, 1978). Changes in EEG sleep stages during chronic opiate administration have been observed, but their behavioral significance is unclear. Failure to find such changes in sleep patterns may reflect deficiencies in control conditions against which these effects have been evaluated. Confirmation of these results requires further research.

Investigators frequently report large individual differences in changes of sleep measures in response to both acute and chronic opiate administration (Kay et al., 1976; Lewis et al., 1970; Orr & Stahl, 1978).

Total night sleep time can be increased by about 40 to 50 min for as long as 18 weeks after sudden withdrawal from chronic methadone. Increases in amount of REM sleep, also noted during withdrawal, may simply reflect the increase in total sleep time (Kay, 1975; Martin et al., 1973). The extent and reliability of changes in sleep after withdrawal are compromised by irregularities in procedures during control periods. Confirmation of these results also requires further research.

Work Capacity and Endurance

A single dose of intravenous morphine had no effect on performance decrements normally observed in nontolerant subjects on the "USAF SAM multidimensional pursuit test" over a 4-hr testing period. The test requires simultaneous centering of the positions of four separate pointers with rudder, stick, and throttle controls (Bauer & Pearson, 1956). While this test is clearly sensitive to the effects of fatigue over time, testing in this study allowed frequent rest periods during the 4-hr session. Information is lacking on the effects of opiates on tasks requiring continuous and uninterrupted attention, and/or vigorous or sustained physical output over periods of several hours.

Sensorimotor Coordination

Single doses of morphine and methadone in nontolerant subjects produce a 10 to 80 ms slowing in simple visual reaction time tasks, such as pressing a button to an irregularly occurring light flash (Hill et al., 1952; Rothenberg et al., 1977). Large individual differences on this task in response to opiates were noted (Rothenberg et al., 1977).

In contrast, chronic methadone users show faster simple visual reaction times by 40 to 70 ms (15 to 25 percent) than non-drug-using control subjects (Gordon, 1970; Rothenberg et al., 1977). A similar result has been noted when the task required a single response to multiple visual stimuli. However, when different buttons were pressed to different lights, no differences were

found between chronic methadone users and control subjects (Gordon, 1970). Ex-methadone-addicts (drug-free for 2 weeks) also were faster than non-drug-using controls on the simple visual manual reaction time test (Gordon, 1970). In one ex-addict, the fast simple visual reaction time measure during chronic methadone use was maintained out to 11 months after detoxification (Rothenberg et al., 1977).

While changes in simple visual reaction time after single doses of opiates are clearly drug-produced, performance differences between chronic users and control subjects cannot necessarily be attributed to chronic use of the drug. See later section on chronic use for a discussion of this issue.

Slowing of simple visual reaction time by acute opiates may reflect opiate reduction of visual sensitivity. Single doses of methadone in nontolerant subjects reduced the ability to detect a brief flicker on a bright field. The maximum decrement and duration of the decrement were dose-related up to 10 mg (Rothenberg et al., 1979). Again, large individual differences in magnitude and duration of the effect were observed.

In a visual-manual task (placing balls of various sizes into moving holes under time constraint), a single dose of meperidine reduced performance in nontolerant subjects. Not enough information was provided to determine whether primarily speed or accuracy was affected (Lass, 1969). In other visual-manual pursuit tracking tasks no significant effects of single-dose opiates were observed (Bauer & Pearson, 1956; Kornetsky et al., 1957).

On the other hand, measures of visually guided oculomotor control show changes after both acute and chronic opiates. Single doses of methadone in nontolerant persons retard by up to 40 ms (20 percent increase in time from nondrug performance) time to start a rapid eye movement (saccade) to refixate a rapidly displaced target. The slowing of saccade latency after opiates parallels the increase in visual-manual reaction time reported above. Accuracy in refixating the displaced target also decreased, the eye undershooting the new target location by up to 9^{o} (25 percent undershoot) instead of the usual nondrug 1^{o} to 4^{o} under these stimulus conditions. Horizontal smooth pursuit eye following of slowly moving visual targets in predictable trajectories was poorer after single-dose methadone, the eye failing to match target amplitude (Rothenberg et al., in press-a, in press-b). Although all of these effects were statistically significant, subjects showed large individual variability in degree of response to drug.

There is a report of increase in duration of nystagmic eye movements induced by cold water irrigation of the ear after single-dose morphine, meperidine, and methadone (Gutner et al., 1952). The effectiveness of caloric stimulation is quite variable among individuals, and duration of nystagmus has been criticized as a

poor measure. Failure to report whether the eyes of subjects were closed, open but occluded, or open and fixated, as well as what instructions were given subjects, compromises this study. Accurate information on possible vestibular actions of opiates, both with and without visual influence, is needed, especially in view of persistent clinical reports of lightheadedness and dizziness after acute opiate use.

When current methadone addicts were tested just before and 2 hours after their daily methadone, latency to saccade onset to a peripheral target was faster in current addicts before their dose than in a similar group of drug-free ex-addicts. This result is similar to the faster visual-manual reaction times reported for addicts above. After the methadone addicts received their dose, however, time to start the saccade increased, maximum velocity of the eye movement decreased, and there was a trend toward decreased accuracy (Moskowitz & Sharma, 1979). These authors also report reduction in slow-phase velocity of the optokinetic response (eye following of slowly moving stripes across the entire visual field) in methadone addicts after their usual daily dose. All these results parallel the effects of methadone in nontolerant individuals, suggesting that tolerance to the acute effects of opiates on eye movements does not develop fully during chronic methadone use.

Methadone addicts more accurately matched eye velocity to target velocity in a smooth pursuit tracking task than did ex-addicts and nonaddict controls, but were no different from ex-addicts in ability to position a visual marker continuously over a moving target with a hand control. Premethadone and postmethadone performance on this task was the same for the methadone addicts (Moskowitz & Sharma, 1979). Ex-addicts were the control group for many of the studies of eye movements of current addicts, and comparisons of current addict performance against non-drug-using nonaddicts are still lacking.

As in the visual-manual reaction time experiments, the difference between chronic methadone users and ex-addicts and nonaddicts may not necessarily be attributable to chronic opiate use. However, the oculomotor deficits seen after single-dose methadone in nontolerant people and after daily methadone in current addicts appear directly related to the drug.

In summary, opiates appear to decrease some, but not all, aspects of visual function directly. Other sense modalities have been insufficiently tested to conclude that opiate action on sensory capacity is restricted to some modes of visual function.

COGNITIVE FUNCTIONS

Attention

Single doses of heroin in ex-addicts had no effect on number of missed stimuli on an auditory continuous performance task (CPT) over a 30-min period postdrug (Volavka, 1974). The CPT is a vigilance-type attention test in which stimuli are presented at high rates (up to 1/sec), and a critical stimulus or sequence of stimuli, presented less often, must be detected. These tests have been found to be sensitive to effects of such drugs as barbiturates and certain classes of tranquilizers. Single doses of methadone similarly were without effect on nontolerant subjects on a 10-min visual CPT when measured at peak subjective drug effect (Rothenberg et al., 1977). In both the auditory and the visual studies large individual differences in response to drug were noted, although the mean effects over the entire group were not significant.

No differences appeared between methadone addicts and non-drug-using controls in the visual CPT. The performance of methadone addicts did not change with additional doses of methadone given after the usual daily dose (Rothenberg et al., 1977).

Failure to find significant acute or chronic opiate effects on the attention measures reported here does not necessarily indicate a lack of opiate effect on attention. The large individual variability indicates that some subjects did indeed show performance decrements on both auditory and visual CPT. Insufficient test sensitivity could contribute to the insignificant group findings. Furthermore, short-term vigilance-type tests have been the only ones used to date. Opiate effects have not been measured with tests of selective attention, attention switching, and susceptibility of attention to distraction, although some of the psychomotor tests discussed above may contain elements of these factors.

Problem Solving

Despite the subjective reports of "mental slowing" reported after single-dose opiate in nontolerant persons, there have been no objective measurements on opiate effect on problem solving, aside from a slowing of oral and written addition after single-dose heroin and morphine (Smith et al., 1962).

Information Processing

No reported studies explore the effects of opiates on tasks in which the rate or quantity of information presented to the subject has been systematically manipulated. The following tests reported in the literature, however, can be loosely described as

measures of "information processing." Single-dose heroin and morphine in nontolerant persons reduced performance on oral and written addition problems, on a coding test requiring marking a random series of letters according to a changing set of instructions, on recall of auditory number sequences, and on detection of hidden figures in pictures. Most performance decrements were in speed rather than accuracy measures, with fewer items completed in a given time or more time taken to complete a test. Median performance changes on tests after drug ranged up to 7.2 percent of postplacebo scores (Smith et al., 1962).

Current methadone addicts and nonaddicted controls did not differ in performance on a digit-symbol substitution task (Appel & Gordon, 1976).

Decisionmaking

While decisionmaking per se has not been the prime focus of opiate studies reported in the literature, data collected in several studies can be interpreted within a decisionmaking framework. In a visual signal detection study, up to 10 mg of methadone in nontolerant persons had no systematic effect on decision criteria used to evaluate visual information on each trial. This task used a yes-no response, and subject bias toward making positive or negative responses on the whole was not altered by methadone (Rothenberg et al., 1979).

In contrast, single-dose heroin in nontolerant addicts increased choice reaction time over a 30-min vigilance-type auditory attention task. Accuracy of response, however, was not altered by heroin (Volavka, 1974). But there were no differences in choice reaction time in a multiple-visual-stimulus, multiple-response task among nonaddicts, current methadone addicts, and ex-opiate-addicts (Gordon, 1970).

Since decisionmaking effects of opiates have not been directly addressed by researchers, conclusions drawn from existing data are tentative. Possible opiate effects on decisionmaking should be studied through experiments in which speed and accuracy trade-offs can be directly manipulated by weighting procedures and in more naturalistic, multiple-option settings.

Communication Skills

No experimental studies have examined the effects of opiates on communication skills. One clinical study (Tozman & Kramer, 1977) reported marked transient stuttering in patients addicted to both alcohol and methadone. Two patients were being withdrawn from both drugs, and one patient was being withdrawn from alcohol only. Duration of impairment was 2 to 3 weeks from start of withdrawal. The association of stuttering with concurrent addiction to and subsequent withdrawal from methadone and alcohol is implicit in this study, but no definite conclusions can be drawn.

Possible opiate action on speech fluency, receptive language comprehension (e.g., speech reception under noisy conditions), operation of mechanical and electronic communication devices, and reception and production of nonverbal communication are unexplored.

COMPLEX SIMULATION ENVIRONMENTS

Driving

The effects of opiates on driving are as yet unknown. Investigations of this question have been undertaken, but they do not warrant any firm conclusion, as they suffer from one or more methodological problems.

The effects of chronic opiates on driving performance have been studied by interviewing methadone maintenance patients using a questionnaire to elicit information regarding number of accidents, traffic violations, miles driven, and so on during periods when the patient was drug-free or using methadone or heroin (e.g., Blomberg & Preusser, 1972). As participation in such a study is voluntary, the sample obtained is likely to be biased in favor of better drivers with "good" records. Indeed, Blomberg and Preusser found that methadone maintenance patients were no worse drivers than a group of non-opiate-users. Results obtained on the basis of a nonrepresentative sample cannot be generalized to methadone patients as a group, or to the even broader group of opiate users. Another problem with retrospective interviewing is reliance on patients' estimates of their own driving statistics, which are likely to be inaccurately recalled (e.g., "How many miles per year did you drive 9 years ago before you began using opiates?"). Even if retrospective interviews are combined with data obtained from department of motor vehicles records, whatever measure is taken from these records must be evaluated relative to the total number of miles driven during a given period, a value that must be obtained from patients' own estimates (e.g., Maddux et al., 1977).

A second method for investigating the effects of opiates on driving is to study either chronic or single-dose opiate administration on performance in a simulated driving situation. Single doses of codeine and of alcohol have been reported to increase frequency of "collisions" in a simulated driving test. In combination, codeine and alcohol have further increased the number of "collisions" (Linnoila & Mattila, 1973). However, insufficient information about the methods used to simulate driving makes these data hard to evaluate. The major difficulty with driving simulators is generalizability. Until it has been shown that simulated driving performance is correlated with some aspect of actual driving, there is no way to determine the usefulness of these studies in predicting the effects of a drug on driving itself. Similarly, in order to predict effects of opiates on actual driving by using performance measures such as reaction

time, attention, tracking, and so on, such measures in total must be highly correlated with driving skills and be comprehensive enough to encompass all the significant variables connected with driving.

The effects of opiates on actual driving performance over a prescribed course have not been reported in the literature reviewed. The development of actual "road tests" that take into account variables such as poor weather, fatigue, traffic congestion, and reactions to unexpected events would make possible the evaluation of drug effects on driving.

Other

The literature reviewed contains no evaluations of effects of opiates in other simulated environments.

DRUG STATES

ACUTE DRUG EFFECTS

Subjective effects of acute opiates are important because they may lead to suboptimal performance in many situations and may provide leads to hitherto unstudied phenomena.

In pain-free nontolerant persons, acute opiates can produce somatic symptoms of nausea, dizziness, itchiness, warmth, headache, sweatiness, and visual difficulties. Vomiting occurs in up to 40 percent of nontolerant persons receiving opiates. Nonsomatic effects include physical and mental inactivity, mental clouding, dejection, anxiety, and dysphoria. While most nontolerant nonaddicts report unpleasant physical and emotional effects, a small percentage reports pleasant effects such as euphoria. The incidence and severity of subjective effects appear to be dose-related. Incidence of subjective effects is lower in nontolerant persons with pain and in nonambulatory persons, the latter suggesting vestibular-ocular involvement (Fraser & Isbell, 1952; Goodman & Gilman, 1975; Gravenstein et al., 1956; Smith & Beecher, 1959, 1962).

Some physiological changes induced by opiates may be expected to have direct effects on certain performance measures. Single-dose opiate constricts the pupil of the eye (miosis) in nontolerant persons. Miotic effects are present in darkness as well as in light. Pupil diameter may be reduced after opiates by as much as 50 percent under moderate light conditions, thereby decreasing to one-fourth of predrug values the amount of light entering the eye. The extent of miosis is dose-related and varies with the specific opiate used and with route of administration. Significant miotic effects of single-dose opiates can be measured.

out to 24 hours postdrug (Fraser & Isbell, 1952; Fraser et al., 1954; Gorodetzky & Martin, 1965; Kay et al., 1967; Martin & Fraser, 1961; McCrea et al., 1942). Methadone addicts showed significant increase in miosis after their daily dose of methadone, indicating incomplete tolerance to miotic effects of opiates (Bigelow et al., 1979). Miotic effects of opiates may well affect performance of visual tasks. Further data are needed on miotic effects under a wide range of steady-state lighting conditions and on the effects of opiates on dynamic pupillary response to sudden changes in illumination.

Acute opiates in nontolerant persons also depress respiratory function (Gravenstein et al., 1956; Martin et al., 1968) and body temperature (Fraser & Isbell, 1952). The significance of these physiological changes under extreme environmental conditions and with strenuous physical activity are unknown.

Sleep of nontolerant persons is disrupted after single doses of opiates. Total waking time during the night and time required for sleep onset are both increased. The effects are dose-related, and variability across individuals in response to opiates is high (Kay et al., 1969; Lewis et al., 1970). Without double-blind techniques, however, these results can be considered only tentative.

Simple reaction time to visual stimuli slowed in a dose-related fashion after single-dose methadone. The slowing of visual reaction time produced by anticipation of shock, however, was abolished by morphine. The altered response times after morphine with anticipation of shock were the same as after morphine with no shock and in both conditions the response times were slower than without morphine. An increase in choice reaction time in an auditory task after heroin has been demonstrated. Large variability in response to drug across subjects was noted (Hill et al., 1952; Rothenberg et al., 1977; Volavka, 1974).

Detection of a transient flicker in a bright visual field was reduced after methadone. Maximum effect and duration of effect were dose-related. Large quantitative variability in response to drug was noted (Rothenberg et al., 1979).

Accuracy of quick eye movements (saccades) to targets off the center of vision decreased after methadone in nontolerant persons. The magnitude of the undershoot error increased with increased horizontal target displacement. Also, time to onset of saccade increased after methadone. Accuracy of smooth pursuit eye movements to targets slowly moving in predictable paths decreased after methadone (Rothenberg et al, in press-a, in press-b). When saccades were measured in current methadone addicts before and after their usual daily dose, maximum saccade velocity decreased and time to saccade onset increased postdrug. Slow phase eye movement velocity to moving stripes (optokinetic nystagmus) decreased after methadone in the addicts. A trend toward decreased saccade accuracy was noted postdrug. Thus

tolerance to the acute effects of opiates on eye movements is not complete in chronic users (Moskowitz & Sharma, 1979).

While present research indicates clear visual performance decrements in some measures following single-dose opiates, there is insufficient information to determine the possible effects of acute opiates on other sensory modalities and sensorimotor systems.

The only report of opiate-induced decrements in visual-manual performance showed that maximal performance of well-trained subjects decreased on a task requiring placement of various-sized balls in moving holes under time constraint after meperidine (Lass, 1969). Large individual differences in response to drug were noted (40 percent had no performance decrement).

Oral and written addition, circling elements of strings of letters according to a changing set of instructions, recognition of hidden figures in pictures, and recall of an auditory sequence of numbers were all poorer after heroin and morphine. Speed of response appeared to be more affected than did accuracy (Smith et al., 1962).

A brief report notes increased collision frequency after codeine and codeine and alcohol combined in an unspecified simulated driving task (Linnoila & Mattila, 1973).

In summary, single doses of opiates produce generally unpleasant subjective effects, including nausea and vomiting; decrease in pupil size, respiration, and body temperature; slowing in visual-manual reaction time; and decreases in more complex functions, including decreased sensitivity to transient change in illumination not related to pupil size, retarded and inaccurate saccadic eye movements, and inaccurate smooth pursuit eye movements.

CHRONIC USE

Studies reported in this section have relied on two basic designs for assessing chronic effects of opiates, neither of which is adequate to determine causal connections between chronic drug use and possible altered performance. Results from designs using comparison of nonaddict control groups and addict groups could be due to factors correlated with but not caused by chronic drug use, such as predisposing factors to addiction and sample selection biases. Results from designs using preaddiction and postaddiction measures in experimentally readdicted ex-addicts require that drug-free ex-addicts be similar to never-addicted drug-free controls, a pattern specifically contradicted in some areas (see above and withdrawal/termination section below). The connection between performance changes and chronic opiate use is best tested by designs using preaddiction and postaddiction comparisons in drug-naive subjects, ethically unjustified with human subjects. However, most of the simple measures discussed in this section can be readily tested in nonhuman primates.

Chronic use of opiates is clinically associated with decrease or even qualitative change of acute drug effects. Alterations of physiological parameters likely to affect behavior have been noted. During periods of addiction lasting up to 34 weeks, reports have noted significant increases over predrug levels in body temperature and decreases in respiratory rate, systolic blood pressure, pulse rate, and pupil diameter (Fraser & Isbell, 1952; Martin & Jasinski, 1969; Martin et al., 1973). These physiological changes may alter performance in extreme environmental conditions and under vigorous physical activity, although no studies have examined this area.

Whereas acute opiates produce sleep disturbances (see above), available studies of chronic opiate effects on sleep document no behavioral changes (Kay, 1975; Orr & Stahl, 1978). Inadequate control conditions and questionable statistical evaluation make interpretation of these data difficult.

Sexual dysfunction, including impotence and retarded ejaculation, has been reported by chronic opiate users (Cushman, 1972; Hanbury et al., 1977; Mintz et al., 1974). Problems associated with interviews, self-report questionnaires of current function, retrospective reports of predrug function, biased sampling, and inadequate statistical analysis should be corrected to document these findings. Female sexual, as opposed to reproductive, function with chronic opiate use has not been adequately examined.

Current methadone addicts and recently detoxified ex-addicts were faster on a simple visual-manual reaction time task than nonaddict controls, although there were no differences between groups on a choice visual-manual reaction time test (Gordon, 1970; Rothenberg et al., 1977).

Current methadone addicts needed less time to initiate a rapid eye movement to a target in the peripheral visual field than did drug-free ex-opiate-addicts. In addition, eye velocity matching to a slowly moving target was better in the current methadone group than in either drug-free ex-addicts or nonaddict groups (Moskowitz & Sharma, 1979).

The retrospective driving studies all report no differences between opiate addicts and nonaddicts on measures such as frequency of collisions and number of traffic violations (Blomberg & Preusser, 1972; Maddux et al., 1977). However, relying on voluntary participation and self-reports of current and past driving patterns and mileage estimates can lead to systematic errors in data obtained.

In summary, few decrements in performance have been noted with chronic opiate use. In fact, in some areas current addicts appear superior to nonaddicts or ex-addicts. However, few measures have been reported. Null results frequently do not reach the literature, and the interpretation of positive results is clouded by the design difficulties noted at the beginning of this section.

TIME-COURSE EFFECTS

Peak constriction of pupillary diameter (miosis) after single-dose opiates in nontolerant persons occurs from 1 to 4 hr postdrug, depending on the specific opiate and the route of administration. Opiate-induced miosis is significant out to 12 hr postdrug and evidence indicates considerable miosis when measured 24 hr after methadone and morphine. Codeine had the least miotic effect of a wide range of natural and synthetic opiates but was significant when measured 24 hr postdrug. While the time course of subjective opiate symptoms (e.g., sickness, sleepiness, itchiness) paralleled the time course of miotic effect during the first several hours postdrug, subjective symptoms had largely returned to predrug levels by 24 hr (Fraser et al., 1954; Gorodetzky & Martin, 1965; Kay et al., 1967; Martin et al., 1973). Miotic response to the daily methadone dose in methadone addicts was significant when measured between 2 and 6 hr postdrug (Bigelow et al., 1979).

Since these studies on pupillary constriction used varying light conditions, it is presently not clear whether the time course of opiate-induced miosis differs in dark- and light-adapted eyes. This variable may account for slightly different results across studies.

Significant reductions on performance measures (such as addition, recognition of embedded figures in pictures, recall of auditory strings of numbers, and visually guided placement of various-sized balls in moving holes) were found between 40 min and 3 hr postdrug. By 5 to 7 hr some performance decrements were still evident, but were less. Morphine projects from the disrupting effects of shock on visual-manual reaction time from 1 to 2 hr postdrug (Hill et al, 1952; Lass, 1969; Smith et al., 1962).

WITHDRAWAL/TERMINATION

Immediate withdrawal symptoms, largely observations of autonomic nervous system activity, included yawning, tearing, sweating, pupillary dilation, tremor, gooseflesh, vomiting, fever, increased respiratory rate, and increased systolic blood pressure. Severity of withdrawal signs is an exponential function of size of maintenance dose, asymptoting at about 400 mg/day. Time onset of withdrawal signs varies between several hours and several days after the last dose, depending on the specific opiate used. Duration of immediate withdrawal varies from several days to several weeks depending on the specific opiate used and on dose level (Andrews & Himmelsbach, 1944; Martin & Fraser, 1961; Martin et al., 1973). Sensitivity of respiratory response to CO_2 was elevated immediately after withdrawal from 60 mg/day morphine above preaddiction levels. Within 7 weeks after withdrawal, response to CO_2 returned to preaddiction levels. From 11 to 30 weeks postwithdrawal, respiratory sensitivity to CO_2 decreased below preaddiction levels.

At the end of the first week of withdrawal from 240 mg daily morphine, an increase of 9 mm systolic and 5 mm diastolic

blood pressure over preaddiction levels has been noted. Similarly, pulse rate was up 10 beats/min, temperature up 0.5°C., and respiration rate up 3 respirations/min, while caloric intake dropped by 40 percent. In contrast, 11 weeks after withdrawal, systolic blood pressure was decreased by 4.5 mm; temperature was lowered 0.1°C.; respiration rate was increased by 1 respiration/min; and caloric intake was no longer different from preaddiction levels (Martin & Jasinski, 1969; Martin et al., 1968). The significance of these short and long term physiological withdrawal symptoms for performance under physically demanding or extreme environmental conditions is not yet known.

There may be some increase in total sleep time for as long as 13 weeks after withdrawal from chronic methadone. EEG measure of REM sleep may increase for as long as 13 weeks after withdrawal from opiates (Kay, 1975; Lewis et al., 1970). Occassional drugs administered during control periods, and the non-double-blind design, make reliability of these data suspect.

Simple visual-manual reaction times of methadone ex-addicts 7 and 12 days after last drug use were faster than those of non-drug-using nonaddict controls, although not quite as fast as current methadone addicts. In one subject studied during methadone addiction and for 11 months after withdrawal, visual-manual reaction time remained unchanged and was faster than nearly all nonaddict control subjects (Gordon, 1970; Rothenberg et al., 1977).

One clinical report notes transient but severe stuttering in three patients simultaneously addicted to methadone and alcohol, two of whom were being withdrawn from alcohol and methadone, one from alcohol alone. The stuttering largely cleared within 2 to 3 weeks from start of withdrawal (Tozman & Kramer, 1977).

While the physical symptoms occurring shortly after withdrawal can be disabling, the unresolved issue is the nature and extent of protracted withdrawal. Although some of the st dies reported in previous sections used ex-addicts, either for preaddiction baseline prior to experimental addiction or for comparison with nonaddict or current addict groups, no studies have systematically explored possible changes in various performance measures known to be affected by either acute or chronic opiates as a function of time from withdrawal from opiates.

To explain why former addicts report recurrence of withdrawal symptoms when they return to the places associated with drug use, Wikler has suggested a conditioning explanation. An experiment using naltrexone to precipitate withdrawal in methadone addicts had provided some support for the idea. After 12 conditioning trials in which naltrexone injections were paired with various external stimuli, significant changes in skin temperature and respiration in the same direction as those observed after naltrexone injections were observed after saline injections. There was no conditioned pupillary response, however, and heart rate changes did not reach statistical significance (O'Brien et al., 1977).

INTERACTIONS WITH PHYSIOLOGICAL AND PSYCHOLOGICAL STRESSORS

Aside from the clinical observations that incidence and magnitude of side effects of acute opiates are lower in persons with pain than in pain-free individuals, only one experimental study has addressed the interaction of opiates with stressors. Shock administered after response will slow subsequent simple visual reaction times. Single-dose morphine abolished the disruption in performance caused by shock, although reaction times in conditions of morphine with shock and with morphine alone were still slower than reactions with neither morphine nor shock (Hill et al., 1952).

Information is lacking on the interactions of acute and chronic opiate effects on performance with stressors such as sleep deprivation, physical fatigue, short term strenuous physical activity, short and long term vestibular stimulation, extremes of temperatures, and conflict-producing situations.

DRUG-DRUG INTERACTIONS

Two reports have shown effects of opiates in combination with alcohol. In a driving simulation study the combined effect of codeine and alcohol in single doses increased the frequency of "collisions" observed over that of alcohol alone (Linnoila & Mattila, 1973). As this report includes no description of measures or statistics used, these data are hard to evaluate.

There is a clinical report of marked transient stuttering in three patients following concurrent methadone and alcohol use. The stuttering developed during alcohol withdrawal for all patients, and concurrent methadone withdrawal for 2 of the 3 patients. Stuttering cleared within 2 to 3 weeks after the start of detoxification from both drugs (Tozman & Kramer, 1977).

Finally, there is a case report of severe amblyopia (visual loss) in one eye of a patient who had ingested large quantities of heroin mixed with quinine (about 5 to 7 g/day of quinine). Three months after cessation of quinine, vision was still deficient. Although this case probably does not represent a real drug-drug interaction effect, it may be worth noting, as heroin and quinine are frequently combined in street use (Brust, 1970).

POSTSCRIPT

Although specific gaps in knowledge have been discussed at appropriate places in the review, one finding, noted by many investigators, deserves additional comment. There is considerable variability among subjects in response to single doses of opiates across a wide variety of measures. The immediate implication of this result is that opiates may fail to produce

significant drug-related changes in measures across a group, yet may significantly and strongly alter performance of some subjects within that group. The causes of such variability are as yet unknown and, except for some studies correlating personality variables with atypical euphoric responses to opiates, the problem seems to have attracted little investigative attention. Opiates change behavioral performance through physiological alterations of the central nervous system. Binding sites for opiates on cell membranes have already been well mapped in the mammalian central nervous system, and detailed maps of binding sites in the primate brain are under preparation. Some evidence already exists for correlating the function of sites binding opiates in the visual nervous system with opiate alteration of visual performance. Other binding site locations are likely candidates for opiate-induced changes in respiration and in producing nausea. Studies of binding site variability and of subject differences in neurochemicals found at binding site locations may provide markers accounting for and thus predicting subject variability in response. The finding of great between-subject variability in response to opiates remains a perplexing and unexplored problem and one that, regardless of the methods used, deserves intensive investigation.

GENERAL SUMMARY

ESTABLISHED FINDINGS

Time course and magnitude of opiate effects depend on dose (Fraser et al., 1954; Gorodetsky and Martin, 1965; Kay et al., 1967; Rothenberg et al., 1977, 1979), specific opiate used (Kay et al., 1967; Gorodetsky and Martin, 1965; Fraser et al., 1954), and route of administration (Fraser et al., 1954). Effects of injected opiates peak within 15 minutes to 2 hours after administration, whereas peak effects after oral opiates may occur within 1 to 4 hours. Behavioral changes produced by single-dose opiates usually cannot be measured 24 hours postdrug, although some physiological reactions (e.g., miosis) are still evident.

Single-dose effects of opiates in nontolerant individuals usually produce such unpleasant subjective effects as nausea, vomiting, and dysphoria, although a small percentage of non-opiate users report euphoria (Smith and Beecher, 1959, 1962; Fraser and Isbell, 1952). Other physiological effects that may impair performance include pupillary constriction (Fraser and Isbell, 1952; Gorodetsky and Martin, 1965), a respiratory depression (Gravenstein et al., 1956; Martin et al., 1968), and decreased body temperature (Fraser and Isbell, 1952). Visual-manual reaction time is slowed by opiates (Lass, 1969; Rothenberg, et al., 1977), transient visual flicker detection impaired (Rothenberg et al., 1979), and latency and accuracy of saccadic eye movements and accuracy of smooth pursuit eye movements decreased (Rothenberg et al., in press, a and b). Opiates also impair performance on cognitive tasks such as oral and written addition, recognition of hidden figures in pictures, and recall of auditory number sequences (Smith et al., 1962). However, stress-induced slowing of simple visual-manual reaction time by shock is reduced by single doses of morphine in nontolerant subjects (Hill et al., 1952).

Repeated users develop tolerance to many of the effects of opiates. Degree of tolerance, however, depends on the specific effect measured. For example, chronic methadone users show pupillary constriction for several hours after their daily dose of methadone (Bigelow et al., 1979). Similarly, saccade latency and slow phase eye velocity to moving targets are also retarded after methadone in current addicts (Moskowitz and Sharma, 1979). In contrast, additional methadone does not increase visual-manual reaction time in current addicts as it does in nonaddicts (Rothenberg et al., 1977).

Significant increases in body temperature and decreases in respiratory rate, systolic blood pressure, pulse rate, and pupil diameter have been noted during chronic opiate use (Fraser and Isbell, 1960; Martin and Jasinski, 1969; Martin et al., 1973). In contrast to these specific performance deficits after acute opiates, chronic opiate users sometimes show superior performance when compared with nonaddict control subjects. Thus, addicts

responded more quickly than nonaddicts on a visual-manual reaction time task (Gordon, 1970; Rothenberg et al., 1977) and were superior in matching eye velocity to a moving target (Moskowitz and Sharma, 1979). Current methadone addicts also needed less time to initiate a saccadic eye movement than did drug-free former addicts (Moskowitz and Sharma, 1979).

When opiates are suddenly withheld from a chronic user, a typical pattern of physiological signs ensues, including yawning, tearing, sweating, pupillary dilation, tremor, gooseflesh, vomiting, fever, increased respiratory rate, and increased systolic blood pressure. The time of onset of these immediate withdrawal signs varies from several hours to several days after the last dose, and their duration varies from several days to several weeks, all depending on the specific opiate and on the maintenance dose (Andrews and Himmelsbach, 1944; Martin and Fraser, 1961; Martin et al., 1973).

Some of the physiological signs noted immediately after withdrawal change direction between 11 and 30 weeks after withdrawal. These include a reduction in systolic blood pressure and body temperature below levels measured before experimental addiction (Martin et al., 1968; Martin and Jasinski, 1969). Beyond the period of immediate withdrawal there is little evidence of performance decrement. Ex-addicts tested up to 12 days after termination of drug performed a simple visual-manual reaction time task faster than nonaddict controls, although not quite as fast as current methadone addicts (Gordon, 1970).

RESEARCH NEEDS AND ISSUES

Although the effects of opiates on general activity, sleep and wake-rest cycles, driving, and sexual function have been investigated, problems of experimental design or of statistical analysis indicate a need for more work to confirm reported findings. Available evidence suggests possible sleep disturbance after acute opiates and during withdrawal from chronic use, and male sexual dysfunction and lack of driving impairment among chronic opiate users.

Additional information would be useful in several areas where established findings exist. Acute opiates clearly produce deficits in some visual and visual-motor functions. Opiate action on other visual functions should be studied, especially because tests of other performance functions such as attention and problem solving often use visual stimuli as test probes. Further work is needed to determine if other sensory and sensorimotor abilities also are altered by opiates. Certain of the visual-motor deficits produced by opiates correspond to the known functions of sites where opiates bind in visual parts of the central nervous system. It should be noted therefore that opiates also bind in at least two auditory areas of the central nervous system. On the basis of reported opiate side effects (dizziness, light headedness, nausea, and vomiting), further study is recommended of opiate action on

vestibular function and on visual-vestibular and kinesthetic-vestibular interactions.

Although tests of attention reported in the literature fail to show significant change with acute and chronic opiates (Volavka, 1974; Rothenberg et al., 1977), it is premature to conclude that opiates do not alter attention. Tests used to date have explored only a narrow range of attention phenomena; studies of measures of selective attention and of distractibility would then be particularly useful.

So little work has been done on opiate action on problem solving and information processing that such projects should receive high pri rity. Several reports have pointed to opiate action on speed rather than on accuracy of response; studies of performance that manipulate speed and accuracy tradeoffs would therefore be a good starting point. Because performance of complex communication skills depends critically on intact sensory and motor function, demonstrated opiate-induced deficits in these functions suggest that opiates might alter communication skills.

Opiate action on driving behavior can be studied most validly under road test conditions. Existing results drawn from retrospective surveys and driving simulation studies are inadequate to assess this problem. Effects of opiates on behavior in other complex environments are valuable to the extent that performance on the simulated task predicts performance in the complex environment, a precondition not often met in simulated tests.

Study of opiates and stress in combination is especially indicated because both opiates and stress produce changes in the same measures of the autonomic nervous system and because initial evidence demonstrates that morphine may ameliorate the disruptive effects of stress on simple sensorimotor performance (Hill et al., 1952). Drug-drug interaction involving opiates should be studied in all areas of performance discussed here.

Three research issues are important for any new work in this area. The first concerns tests of higher functions such as attention, information processing, or problem solving that use sensory or sensorimotor capacities previously shown to be altered by the drug under investigation. These alterations must be accounted for before attributing a drug-induced deficit in performance to these higher functions. When a test of higher function uses sensory or sensorimotor components not already studied with the drug under investigation, description of such effects or testing sufficiently precise to rule out such effects should be the first order of business.

The second research issue pertains to studies of the effects of chronic use of opiates on humans, which generally rely on comparing measures collected before, during, and after experimental addiction in drug-free ex-addicts. Prior addiction to the drug under study may result in altered before-drug measures, producing

a change in the baseline against which chronic drug effects are measured. In addition, comparing performance of presently addicted subjects with that of nonaddicted controls may not give a valid measure of chronic drug use because observed differences in the two groups may be due to non-drug-related differences. In lieu of experimental addiction of drug-naive humans, addiction of naive primates may yield useful data, especially for simpler measures of performance.

Finally, individual response to opiates is highly variable across subjects. Thus, the functions of some individuals may be substantially altered by opiates even when there are no statistically significant group effects. Although this factor is widely recognized, virtually no experimental investigation of the issue has taken place. The most valuable immediate contribution would be the development of indices for predicting individual response to opiates. The similarity of opiate side effects to motion sickness suggests a possible starting point for this research.

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4. EFFECTS OF CENTRAL NERVOUS SYSTEM STIMULANTS ON HUMAN PERFORMANCE

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INTRODUCTION

OVERVIEW

In their concluding remarks in what continues to be a definitive review of the early work on the effects of caffeine and amphetamine on human performance, Weiss and Laties (1962) posed two questions. First, how do amphetamine and caffeine enhance performance; do they produce superior performance or do they merely restore performance degraded by fatigue, boredom, or other influences? Second, is the "benefit" of the enhancement outweighed by the cost of obtaining the enhancement in terms of side effects of these drugs? In the 17 years since these questions were posed, no conclusive answer has been found for the first question. Evidence that these drugs actually improve performance has been tempered by evidence that these drugs may only restore fatigue-induced decrements. As for the second question, Weiss and Laties (1962), referring only to the drugs' acute effects, concluded that caffeine and amphetamine were rather benign agents.

Interest concerning the effects of central nervous system (CNS) stimulants on human performance has shifted in recent years. During World War II and the period that followed, interest was generated by the possibility that stimulants could not only maintain alertness for prolonged periods of time but also might actually improve physical performance. Seashore and Ivy (1953), in one study of an extensive series, examined these effects of stimulants (caffeine, amphetamine or methamphetamine) under a variety of military conditions. In general, these compounds were found to be superior to placebo in increasing alertness and improving some types of muscle coordination. Although these studies suffered from certain procedural problems and were concerned with a rather unique category of human performance conditions, the results of Seashore and Ivy (1953) generated a tremendous research interest in the performance-enhancing effects of these drugs on numerous other physical and intellectual measures. The results of a majority of the studies of this nature were the subject of the review by Weiss and Laties (1962). In recent years, however, the emphasis of research in this field has taken on an additional dimension. The high incidence of nonmedical use of the stimulants by certain segments of the population has caused researchers to question whether these drugs could adversely affect certain types of performance. In addition, accumulating evidence suggests that long term use of these compounds may produce physiological and psychological disturbances of a nature and severity quite different from the acute administration condition. These two factors have generated research aimed at determining if there are specific types of performance or conditions that could be adversely affected by the drugs or if their susceptibility to adverse effects changes during prolonged periods of drug intake.

In the following review of CNS stimulants and human performance, an attempt is made to examine the evidence that has accumulated since the paper by Weiss and Laties (1962). The CNS stimulants reviewed are not limited to caffeine and amphetamine, but also include cocaine, methylphenidate, and nicotine. Human studies involving sensorimotor functions, cognitive functions, or simulated performance are included. In those situations where human studies are not conclusive or are incomplete, available studies on the relevant effects of CNS stimulants on animal performance and behavior are discussed.

This review aims to provide the reader with a feeling for the experimental findings concerning the effects of CNS stimulants on human performance. Because the individual research areas investigating either the actions of the stimulant drugs or the nature of human performance encompass such broad interests, definitions, and methods, reports from studies combining the two areas have often failed to convey purpose and results in a manner that is meaningful to those with interests in either area. In reviewing the numerous and varied studies, the author hopes this paper's format provides some consistency of thought.

A thorough review of either the physiological and pharmacological actions of the stimulants or the measurement of human performance is beyond the scope of this paper. However, since a minimal level of knowledge concerning the drugs and tests would greatly aid the interpretation and understanding of the experimental results reported in this paper, brief explanations and descriptions are provided where appropriate.

CENTRAL NERVOUS SYSTEM STIMULANTS

The CNS stimulant compounds, shown in table 1, are considered to be drugs that improve mental and physical performance. This review attempts to provide evidence that will aid the reader in determining if this reputation is based on sound experimental findings. The stimulants can be divided into several broad categories according to a number of classifications. This review deals with the individual drugs and avoids any categorization. The amphetamines, probably the best known representatives, are the drugs most discussed in this review. Methylphenidate is a compound with actions and therapeutic indications very similar to those of amphetamines. Cocaine is a short-acting stimulant that is having a resurgence of popularity. The xanthines, of which the best known is caffeine, may be the most widely used of the stimulants. Nicotine, the active ingredient of the tobacco plant, continues to have widespread popularity.

TABLE 1

CENTRAL NERVOUS SYSTEM STIMULANTS

I.	Amphetamine
	a. d-Amphetamine (Dexedrine)
	b. dl-Amphetamine (Benzedrine)
	c. Methamphetamine (Methedrine, Desoxyn)
II.	Cocaine
III.	Methylphenidate (Ritalin)
IV.	Caffeine
V.	Nicotine
VI.	Diethylpropion (Tenuate)
VII.	Phenmetrazine (Preludin)
VIII.	Mephentermine (Wyamine)

EXPERIMENTAL PROCEDURE AND DESIGN

The experimental procedures used to study CNS stimulant effects on performance are, for the most part, methods developed in experimental psychology. Each is more fully described later. These procedures were designed to examine a specific aspect of human performance. Questions concerning the actions of drugs demand certain types of tests. Some examples (tests): (1) Are movements slowed (tapping rate)? (2) Are movements less accurate (dotting accuracy)? (3) Is the time to respond to a stimulus impaired (simple reaction time)? (4) Are decisions made more slowly (choice reaction time)? (5) Are mental processes impaired (simple arithmetic, digit-symbol substitution)? (6) Is memory impaired (digit-span)? These represent only a small number of the tests that have been used to investigate the effects of drugs on human performance.

In many of the studies reviewed, the lack of consistency concerning doses, routes of administration, and time of administration makes a detailed comparison between otherwise similar studies extremely difficult. This review attempts therefore to compare studies as completely as possible, pointing out when the

above factors might account for differences in results, or, more important, where caution should be exercised in the interpretation of results.

Experimental design is another area where caution should be exercised in directly comparing studies. In general, three designs were most often encountered in the studies reviewed. The first is the repeated-measures or within-subject design in which each subject receives all treatments, with the order of treatment being randomized. Sufficient time between tests must be allowed in order to prevent carryover effects from one session to the next. A second design is the between-subjects design in which subjects are randomly assigned to either treatment or control groups. Given the wide intersubject variability on most tests, this design requires using greater numbers of subjects to insure equal performance by the two groups prior to drug testing. The third design involves the use of pretest-posttest comparisons for which subjects are trained to a plateau level of performance prior to drug testing.

The review of the laboratory tests is divided into categories according to sensory function, psychomotor skills, and cognitive skills. In certain examples, the classification of a particular task has been somewhat arbitrary. Certain of the tasks employed in the various studies require sensory, motor, and cognitive contributions. The relative contribution of each of these systems was a factor that was not considered in many of the studies. For example, the degree of contribution of cognitive skills to a task may be a function of familiarity with the task, with fewer cognitive skills required for a well-learned task. In addition, a simple tapping test used to measure sensorimotor coordination becomes a measure of physical endurance if performance is required for long periods. In situations such as these, the interpretation of drug effects could be more difficult.

SENSORIMOTOR STUDIES

WAKE-REST CYCLES

Because of their widespread use by people to stay awake, the effects of stimulants on normal sleep patterns have been studied in recent years. Amphetamine has been shown to prevent the impairment of psychomotor performance following sleep deprivation (Kornetsky, Mirsky, Kessler, & Dorff, 1959). A similar effect for cocaine was demonstrated by Fischman and Schuster (in press). Rechtschaffen and Maron (1964), using EEG and eye movement recordings, studied the effects of d-amphetamine (15 mg) on the stage of sleep in subjects. The drug reduced total sleep and increased the delay to the first period of rapid eye movement (REM) or dream sleep. In addition to these effects, body movements also increased following intake of d-amphetamine. In an attempt to control for the possible confounding effects of body movements,

the researchers gave a second group of subjects 15 mg of d-amphetamine plus 100 mg of pentobarbital. The combination caused a greater reduction of REM sleep than pentobarbital alone. These results were later confirmed by Backeland (1966).

Oswald et al. (1968) studied the sleep pattern of six subjects who took d-amphetamine or phenmetrazine regularly. Subjects' sleep duration and sleep patterns were normal. However, when the drug was withdrawn, both the duration of sleep and the amount of REM sleep increased. Sleep did not return to normal in these patients for 2 to 8 weeks after drug termination.

Other stimulants have also been shown to have similar effects on sleep. Backeland (1966) showed these effects for methylphenidate, and Oswald et al. (1968) for diethylpropion. Lewis (1970) studied the effects of four stimulants on sleep in eight male subjects. Amphetamine (7.5 mg), fenfluramine (40 mg), diethylpropion (25 mg), chlorphentermine (50 mg), and a combination of amphetamine (7.5 mg) and fenfluramine (40 mg) were tested at 1-week intervals in all subjects in a double-blind manner. Two placebo sessions were also run. Measures of intervening wakefulness, number of shifts from one stage to another, and subjective ratings of quality and duration of sleep were measured. Fenfluramine did not affect the proportion of REM sleep. Diethylpropion reduced the amount of REM sleep in the first 3 hours, but not for the entire night. Amphetamine, chlorphentermine, and the drug combination reduced REM sleep for the whole night. Chlorphentermine administration produced a greater reduction in REM sleep than the other drugs. The combination of amphetamine and fenfluramine was associated with ratings of the poorest quality of sleep. When all of the measures were taken into account, the order of increasing disruption of sleep for the first 3 hours of the night was placebo, fenfluramine, diethylpropion, chlorphentermine, amphetamine, and the combination. For the entire night, the order was the same except that fenfluramine and diethylpropion reversed positions.

Kornetsky et al. (1959) deprived subjects of sleep for 72 hours during 2 consecutive weeks (Sunday through Wednesday of each week). During the first week, a placebo was given 44 and 68 hours after the start of sleep deprivation. For the second week, subjects received 10 mg of d-amphetamine at 44 hours and 15 mg of d-amphetamine at 68 hours after the start of sleep deprivation. Subjects were tested 90 minutes after the oral drug administration in a series of three reaction time procedures (simple reaction time, choice reaction time, and simple learning) and a continuous performance task. Administration of the 15-mg dose of amphetamine after 68 hours restored performance on the simple and choice reaction time tests to nonsleep levels. The scores on the continuous performance test were improved after amphetamine, but not to non-sleep-loss levels. The authors suggested that there was a strong relationship between the amount of impairment produced by sleep loss and the amount of impairment still present after amphetamine. Those performance measures

least affected by sleep loss (reaction time) returned to non-sleep-loss levels after amphetamine, while performance most affected by sleep loss was less improved by amphetamine.

WORK CAPACITY-ENDURANCE

In a widely cited series of experiments, Smith and Beecher (1959, 1960a, 1960b) studied the effects of amphetamine on athletic performance. In the first experiment (1959), which was possibly the best controlled of the six studies, the effects of amphetamine (14 mg/70 kg), secobarbital (100 mg/70 kg), or placebo on the swimming times of 15 collegiate swimmers were measured. Each subject was tested in his preferred event. During the 12 consecutive days of the experiment, each subject swam two heats, separated by a 15-minute rest period. Each day the subjects were given one of the three drugs. Amphetamine was given 2-3 hours prior to the test and secobarbital was given 55 minutes prior. On 6 of the 12 days the swimmers competed with each other, and on the remaining 6 days each swimmer was tested individually. The results between the first and second swims were somewhat different. On the first swim, regardless of the distance (either 100 or 200 yards), 14 of the 15 swimmers performed significantly better following amphetamine compared with placebo. For the second swim, only the shorter distances showed improvement after amphetamine. The results also indicated that swim times generally improved more during individual tests than during competitive tests. Secobarbital produced performance decrements in all tests.

In a second experiment also involving swimmers, Smith and Beecher (1960a) attempted to increase the motivational level of the subjects. The 16 subjects were tested individually (in their preferred event) but were promised a steak dinner if they could equal or top the median time of their three previous college competitions. In addition, all subjects cheered and encouraged each other during testing, much like they do at a meet. Each subject swam six times, three times after amphetamine (same dose and time as the previous study) and three times after placebo. All swimmers earned the steak dinner; however, 11 of the 16 performed better following amphetamine compared with placebo. When the 100- and 200-yard events were combined, the time difference was significant.

In another series of experiments, Smith and Beecher (1960b) also tested the effects of amphetamine on the performance of track-and-field athletes. Significant improvements in performance by runners, weight lifters, and shot-putters were reported following amphetamine administration. Weiss and Laties (1962) suggested that these results argue against the idea that amphetamines only improve performance that has been degraded by boredom or fatigue.

Other experiments on the effects of amphetamine on athletic performance have failed to find any enhancement of performance. However, significant differences in dose, time of administration, and experience of the subjects do not allow for a fair comparison with the studies by Smith and Beecher.

Ikai and Steinhaus (1961) measured the effects of amphetamine on the tension of the forearm muscles during maximal effort. Ten subjects were given 30 mg of amphetamine orally and tested 25 minutes later. A significant increase in maximal tension was reported after amphetamine. Lack of proper placebo controls, however, leaves these data open to question. Adamson and Finlay (1965) tested 10 mg of amphetamine on grip strength and bar chinning. Subjects were tested 2 hours after receiving either the drug or the placebo. In six experimental sessions, each subject received drug or placebo capsules on two occasions and no medication on two other occasions, allocated at random in a double-blind manner. Grip strength was significantly improved by amphetamine, but chinning was not. These results suggest that amphetamine improves static strength tests but has no effect on endurance.

Andean Indians believe that chewing coca leaves increases work capacity. The leaves contain cocaine and other alkaloids which could possibly produce this effect. However, few controlled studies have examined this question. In two separate studies, Hanna (1970, 1971) studied the effects of coca leaf chewing on Quechua Indians of Peru. In the first study, six regular coca leaf chewers were compared with six nonusers on the basis of physiological responses to submaximal exercise on a step test. Coca chewers showed lower exercise and recovery heart rates accompanied by higher blood pressure. In the second and better controlled study, five regular users and seven nonusers were compared on a bicycle ergometer test. Each subject was tested under chewing and nonchewing (24 hour) conditions. Oxygen intake, ventilation rate, and blood pressure were unaffected by coca leaf chewing.

Seppanen (1977) measured the effects on physical work capacity of smoking tobacco or breathing carbon monoxide (1,100 ppm) or air. All subjects were smokers who did not smoke for 12 hours prior to the session. Each was tested under all conditions. Heart rate and blood pressure were measured at rest, during exercise, and at physical work capacity on a bicycle ergometer. Breathing carbon monoxide caused no change in heart rate at rest; smoking cigarettes increased the heart rate. Blood pressure at rest or during exercise was not affected by either carbon monoxide or cigarettes. Physical work capacity was decreased by both. When maximal work capacity was calculated, carbon monoxide caused the greatest decrease. Unfortunately, this study did not include a group of nonsmokers. Including nonsmokers would have provided a better idea of whether differences existed between physical work capacity groups or whether the groups were differentially affected.

Lovingood, Blyth, and Peacock (1966) studied the effects of d-amphetamine (15 mg), caffeine citrate (500 mg), and high temperature (125.6° F) on the performance of 24 male subjects on strength, mental, and psychomotor tests. Although a significant improvement was claimed for d-amphetamine and caffeine, poor presentation of data and low levels of significance do not allow conclusions to be drawn.

Franks, Hagedorn, Hensley, and Starmer (1975) measured the effects of caffeine (300 mg) alone and in combination with ethanol (75 mg/kg) on 68 students (both sexes) performing a number of tests, including cognitive, perceptual, and motor functions. The test battery consisted of standing steadiness, simple and choice reaction time, manual dexterity, simple arithmetic, and verbal fluency. Placebo control sessions were run. Caffeine in combination with ethanol did not alter plasma ethanol concentrations. With the exception of the choice reaction time test, caffeine did not antagonize ethanol-induced performance decrements. These data argue against the popular concept that a cup of coffee will antagonize any overindulgence in alcohol.

SENSORIMOTOR COORDINATION

The ability to make adjustments in muscle activity based on sensory input is termed coordination. The integration of the sensory and motor systems is extremely complex. Perturbations to either system can result in severe impairment to the overall efficiency of coordination. One problem in designing specific tasks to measure deficits in sensorimotor coordination is that, while changes from normal may be readily observed, it is not always clear at what point the system has been affected. This problem is especially acute when the effects of various drugs on sensorimotor coordination are measured. The objective of this area of research has not been to determine a specific site of action for a given drug, but to determine if the drug has an effect.

The tasks designed to measure sensorimotor coordination vary in complexity with the type of coordination required. Among the simple tasks, tapping is considered to be a basic test of muscle coordination. The speed at which one can perform a movement involving rapid changes in direction involves motor and proprioceptive integration. The tasks used to measure tapping may simply require a finger tapping a switch or a telegraphy key. The number of taps in a given period provides an easily quantifiable measure. As was previously pointed out, the lack of consistency in the type of test used in the various studies makes interpretation of results difficult. In some studies that measured tapping for long periods, the test becomes more one of endurance than of coordination. Differences in procedural administration such as informing the subjects of the results may have significant effects on subsequent performance. In addition, impaired performance may be easier to observe than improved

performance, which may only occur under special conditions (Weiss & Laties, 1962). In general, tests of tapping have failed to demonstrate significant differences between placebo and amphetamine conditions (Brown, McAllister, & Turek, 1974; Dickins, Lader, & Steinberg, 1965; Ideström & Schalling, 1970; Legge & Steinberg, 1962).

Tracking is a more complex measure of coordinated movement. Although differences in the specific measurement techniques are numerous, the subject is generally required to follow a moving target with a stylus. One form of this test is the pursuit rotor where the subject attempts to keep a stylus in contact with a small target on a moving turntable. Total time on target is the dependent variable. Unfortunately, details such as size of the target or speed of the turntable are rarely included in procedural descriptions, making a comparison of results difficult.

Vigilance is a type of performance that is not dependent on muscle strength or coordination. Vigilance, sometimes termed monitoring, is the process of maintaining attention to small stimulus changes in the environment. When these changes occur, some form of response is required. In an early series of studies on the effects of amphetamines on vigilance, Mackworth (1964) found that 10 mg of amphetamine, given orally 1 hour before the task, significantly reduced the number of missed signals, while not affecting the initial level of performance. Mackworth and Taylor (1963) found that the detectability of the signal declined during the course of a session. Mackworth (1964, 1965) found that amphetamine (10 mg, 1 hour before the session) decreased the rate of decline in signal detectability; it had no effect on the initial level but caused significant improvement 2 hours after drug ingestion.

In a study examining the effects of d-amphetamine (10 mg) and fenfluramine (30 mg) alone and in combination, Brown et al. (1974) reported that amphetamine significantly improved performance on such psychomotor tasks as tapping, reaction time, and card sorting, while fenfluramine had no effect on these tasks. The effect of the combination of the two drugs was not significantly different from the effect of amphetamine alone. This is one of the few studies to report that amphetamine usage resulted in significant improvement in reaction time. However, the results of the various measures were recorded as the mean scores of four testing sessions at 46, 90, 150, and 210 minutes after oral ingestion of the drugs. Although graphs of the results across time indicated some possibly interesting effects, the authors failed to discuss these effects, choosing instead to average all scores.

Tests of the effects of tobacco smoking on performance have also yielded conflicting results. In some studies, there are marked differences between deprived smokers and nonsmokers tested after smoking. Other studies have shown that performance differences between smokers and nonsmokers are unrelated to the

cigarette factor. Myrsten, Post, Frankenhauser, and Johansson (1972) reported that smoking facilitated performance when compared with nonsmoking levels in both a simple reaction time task and a stressful reaction time task. Facilitated learning of the pursuit rotor was reported by Frith (1968). In general, however, the majority of studies either have failed to find significant effects (Frankenhauser, Myrsten, Post, & Johanssen, 1971; Leigh, Tong, & Campbell, 1977; Smith, Tong, & Leigh, 1977; Tong, Knott, McGraw, & Leigh, 1974; Tong, Leigh, Campbell, & Smith, 1977) or have suffered from poor experimental design (Gale et al., 1972; Johnston, 1966).

In one of the few studies to test more than a single dose of a drug, Evans, Martz, Rodda, Lemberger, and Forney (1976) tested 5, 10, and 15 mg/70 kg of d-amphetamine on stance stability, motor function, and mental performance. Twelve subjects were tested in once-a-week sessions. Two practice sessions were given to eliminate learning effects. To insure more uniform drug absorption, subjects fasted 3.5 hours before taking the capsule. To prevent the presence of alcohol, each subject was tested with a Breathalyzer before drug administration. Blood pressure and heart rate were measured before drug ingestion and at three successive 30-minute intervals after the drug. Following this period, subjects were tested on the other procedures. Standing steadiness was measured on a Wobble Board. Subjects were given three 30-second tests involving eyes open, eyes closed, and eyes open with vibratory input. Sensorimotor coordination was tested with the pursuit meter, with three 100-second tests (7, 2, and 5 cycles per second) being given. Mental performance was evaluated using the technique of delayed auditory feedback. In addition, the subjects were asked to indicate if they had received an active drug. The results showed a dose-related increase in blood pressure with no change in heart rate. These results agree with the results of Martin, Sloan, Sapira, and Jasinski (1971). Stability of stance was improved by amphetamine only if the eyes were closed. With the pursuit meter, only the 7-cycle-per-second task showed a significant dose-related improvement. Delayed auditory feedback performance was unaffected by any dose tested. The subjects' abilities to discriminate amphetamine from placebo increased with dose. At 5, 10, and 15 mg there was no difference from placebo. At 10 and 15 mg 83 percent of the subjects were able to recognize the drug.

Analysis of the results found by Evans et al. (1976) perhaps offers the best indication to date of the effects of amphetamine on psychomotor skills. The design of the study controlled for such variables as dose of drug, placebo effect, fatigue, and practice effects. The results showed that enhancement of motor performance by amphetamine was limited to a test measuring a relatively rapid response; amphetamine did not result in an overall improvement, as has been suggested. In contrast to other studies, performance on cognitive tests was unaffected by amphetamine (see next section).

Morselli (1976) studied the relationship of blood levels of amphetamine with performance on a number of tasks involving motor function and attention. Amphetamine was administered to six subjects at a dose of 20 mg (free base) as either phosphate salt or cationic resin formulation. Each subject received each formulation in experimental sessions separated by 7 days. Blood was collected at 0, 30, 45, 60, 90, 102, 140, 240, 360, and 720 minutes after drug. All four tests of performance were administered before drug intake and 1, 2, and 4 hours after. The tests used were (a) a comparison of numbers for sameness (modified choice reaction time), (b) an O'Connor test--metal pins introduced into small holes using each hand, (c) a clerical test--match letters and numbers, and (d) the Wechsler Memory scales. The results showed that performance on all four tests was significantly improved by either amphetamine formulation (no difference between formulations). No relationship was found between amphetamine peak blood levels and the various performance measures.

COGNITIVE STUDIES

INFORMATION PROCESSING

The question of whether the stimulant drugs can actually improve intellectual performance above normal levels has been the subject of numerous studies. While a number of these studies have shown improvement in performance on simple tasks such as arithmetic or verbal learning, the problem of boredom or fatigue influencing the results has not been adequately controlled. Indeed, the results of these studies tend to suggest that regardless of other factors, improved performance is only observed on simple, not more complex, tasks. Smith et al. (1963) reported that amphetamine (14 mg/70 kg) improved performance on a simple coding task. Weitzner (1963) compared the effects of the same dose of amphetamine on the same task used by Smith et al. (1963) and on a more complex task. Significantly improved performance was reported on the simple, but not the difficult, procedure. Other investigators have also reported no effects of amphetamine on solving complex arithmetic problems (Hurst et al., 1969; Smith & Beecher, 1964).

Evans and Smith (1963) measured performances of normal subjects on a variety of mental tasks after giving the subjects 10 mg d-amphetamine, 16 mg morphine, or a combination, versus a lactose placebo. Tasks were designed to test various mental operations such as evaluation, memory, and cognition. Subjective effects were examined using the Nowlis Adjective Checklist. The McClelland Need Achievement Scale was also administered. A somewhat surprising finding was that morphine improved performance on all tests based on logical judgment and in which the answer was selected from several choices. Amphetamine did not produce significant effects on the mental tests but did increase subjects' activation level and need for achievement.

Hurst and Weidner (1966) examined the influence of task-induced stress on cognitive performance and its interaction with drugs. The suggestion was made that enhancement of cognitive performance by drugs is primarily a motivational phenomenon, obtained only when there are intrinsic or extrinsic task factors that tend to degrade performance from that of the optimally motivated subject. Repetitious aspects would induce boredom or fatigue, which should be relieved by stimulants. Stressful aspects involve interfering emotional responses, which could be relieved by a variety of compounds. Hurst and Weidner (1966) believed that cognitive performance may be facilitated or hampered by any given drug depending on the motivational aspects of the task involved. Subjects were 63 student volunteers administered either d-amphetamine (10 mg), methylphenidate (10 mg), chlordiazepoxide (10 mg), or no drug. Half of each group received a capsule (placebo) and half did not. In all cases, the drug was disguised in decaffeinated coffee given under the cover of a "taste perception test." Self-ratings of mood were obtained with the Nowlis Adjective Checklist. Performance was measured by administration of the Paced Sequential Memory Task. Motivation was measured by requiring half of each group to work for a fixed payoff and half for an incentive payoff based on performance on the second test. Results showed that d-amphetamine significantly improved performance on the first test but not on the second test given 2 hours later. These results contradict previously cited reports that performance enhancement by the amphetamines is dependent on the prior existence of fatigue. No other drug effects on performance were found. The motivation and placebo manipulations also did not show any effects. Amphetamine was the only drug to register a significant mood effect, showing higher scores for "vigor" and lower scores for "fatigue." In spite of the lack of significant amphetamine effects on the second test, the authors still considered amphetamine to have an enhancing effect on cognitive performance in nonfatigued subjects. However, in a later study (Hurst, Weidner, & Radlow, 1967), using essentially identical task conditions, d-amphetamine (14 mg/70 kg) not only failed to enhance performance but actually showed a detrimental effect.

The code-tracking apparatus, one method used for measuring complex learning, presents the subject with a series of choice points with three alternatives, only one of which leads to the next choice point. In order to choose the correct alternative, the subject must attend to successive directional cues delivered in the form of four short colored light signals. These signals must be learned for each trial, which consists of 30 choice points. Task difficulty can be manipulated by increasing the time between light signals and choice points.

Dureman (1962) tested the effects of caffeine (200 mg) and amphetamine (20 mg) on the code-tracking performance of 12 subjects. Performance was measured 30 minutes prior to, and 3 and 6 hours after, oral administration of one of the two drugs or placebo. Each subject received all treatments in a balanced

design. Though not to a significant degree, both amphetamine and caffeine reduced errors at 3 hours and amphetamine also reduced errors at 6 hours.

Repeated acquisition of a sequence of responses is another method used to study learning in humans. Walker (1978) used this procedure to determine the effects of d-amphetamine (5, 10, and 15 mg orally) on four male subjects. Within a given session, each of 10 stimulus lamps was associated with pressing one of three switches. The task required the subject to learn the switch that illuminated each lamp. The same sequence was correct throughout a 15-minute session but changed across sessions. Each completion of a sequence counted as a trial. The completion of five trials incremented a point counter. An incorrect response turned off the stimulus lamp for 2 seconds. Subjects were allowed a 5-minute rest period between the two 15-minute sessions. All subjects were given 12 practice sessions prior to the initiation of drug administration sessions. The following 12 sessions were placebo only sessions, followed by drug or placebo sessions. The results showed that subjects' overall accuracy, as measured by total errors, decreased, while the rate of responding increased. However, possibly due to the small number of subjects, these results were not statistically significant.

A similar procedure has been used to study drug effects on learning in animals. In the repeated acquisition procedure (Thompson, 1974) pigeons were trained to make four responses on three keys in a specified sequence in order to gain access to grain. Under the learning condition, the four-response sequence changed from session to session. Under the performance condition, the sequence remained the same over sessions. Incorrect responses (pecking a key not in the response sequence) produced a 5-second timeout. Four doses of d-amphetamine (0.5, 1, 2, and 4 mg/kg) were tested under both conditions; all doses were injected 30 minutes prior to the session. Control performance on noninjection days indicated that the number of errors in the learning condition tended to decrease across trials within a session, while the error rate tended to be lower and constant across trials in the performance condition. Amphetamine was found to impair overall accuracy under both conditions in a dose-related manner. With amphetamine, the error rate still decreased across trials in the learning condition, but at a slower rate. In contrast, in the performance condition, the error rate remained constant but was higher than during the drug session. These latter effects were detected at lower doses under the performance condition. The results of these studies suggest several areas of concern for researchers designing learning or performance procedures for human testing. The study by Thompson nicely emphasizes how subtle differences in procedure can yield wide differences in behavior. More important, the study demonstrates how the behavior of subjects in separate, though similar, procedures may show different sensitivities to the effects of drugs.

DECISIONMAKING

The relation of amphetamine-induced mood changes to behavior in situations involving value judgments has been examined by several authors. Smith and Beecher (1960a, 1960b) observed the effects of 14 mg of dl-amphetamine, 100 mg of secobarbital, and placebo on the swimming performance of trained athletes competing individually or in groups. The subjects were asked to estimate their performance time. When tested with amphetamine, subjects demonstrated improved performance. Secobarbital significantly impaired performance. The subjective data showed that after secobarbital, swimmers tended to overrate their performances (i.e., lower time). The effects of amphetamine on judgment were not conclusive. Distortions in judgment with either drug were more pronounced when subjects swam individually. These data may possibly be confounded by the specific effects of these drugs on time perception.

Smith and Beecher (1964) tested the effects of amphetamine on the judgment of students solving 25 calculus problems. The subjects were given either dl-amphetamine (14 mg/70 kg) or placebo 2 hours before the test. Both groups significantly overestimated the number of correctly solved problems, with the amount of overestimation by the amphetamine group being greater. Of particular importance was the fact that performance (number of correctly solved problems) was unaffected by the drug. Smith and Beecher suggested that amphetamines do not enhance performance on complex intellectual tasks, at least when the subjects are not sleep deprived.

Hurst et al. (1972), in a similar series of studies, examined the effects of amphetamines on judgment and decisionmaking. The subjects, 93 student volunteers, were divided into three groups and given 14 mg/70 kg of d-amphetamine, dl-amphetamine, or placebo. The effects of the drugs on math reasoning and self-appraisal were measured. The results were in agreement with those of Smith and Beecher (1964). Although performance itself was unaffected, subjects given d- or dl-amphetamine significantly overappraised their performance compared with subjects given placebo.

Laboratory studies of time judgment effects of drugs have yielded inconsistent results. Goldstone, Boardman, and Lhamon (1958) tested the ability of subjects to judge whether the duration of an auditory tone was more or less than 1 second. Amphetamine was reported to decrease the estimate when compared with placebo. In a second experiment, Goldstone and Kirkham (1968) again found that amphetamine decreased the estimate while secobarbital increased the estimate.

Hurst (1962) studied the effects of d-amphetamine on the risk-taking behavior of 29 penitentiary inmates in gambling for cigarettes. Subjects had a series of choices between alternative gambles associated with different amounts of risk and

payoff. Each subject received d-amphetamine (10 mg orally) and placebo. With amphetamine, subjects made significantly more choices for the high-risk alternative.

COMMUNICATION SKILLS

Until recently, reports of increased talkativeness following ingestion of amphetamine or other stimulants have, for the most part, only been found in the anecdotal literature. A 1967 review of the effects of drugs on speech found relatively few well-controlled studies (Waskow, 1967). Jaffe, Dahlberg, Luria, Breskin, Chorosh, and Lorick (1972) studied the effects of d-amphetamine on the sound-silence pattern of speech monologues. Their findings suggested that the average pause duration was shortened by d-amphetamine, while the mean vocalization duration was unaffected.

Gottschalk et al. (1971) measured speech for short periods in subjects who had taken d-amphetamine (15 mg) or placebo. Two hours later, the average number of words spoken was greater following drug than placebo. There were no differences after 4 hours. In an indirect measure of speech, Hurst, Radlow, Chubb, and Bagley (1969) measured the number of words written by college students assigned to write an essay for 20 minutes. The average number of words written by students given d-amphetamine (14 mg/70 kg) was 10 percent greater than when they were given placebo. Using two procedures, Stitzer et al. (1978) studied the effects of d-amphetamine (5-20 mg) on speech monologues in isolated human subjects. Drug effects were studied under double-blind conditions using a repeated-measures design. In one procedure, four subjects were instructed to talk some of the time during the 40-minute experimental session. In the second procedure, four subjects were also instructed to talk, but earned points under a fixed-interval 5-minute schedule of reinforcement (i.e., points accumulated with the first word spoken at the end of the 5-minute interval). In both procedures, d-amphetamine produced reliable increases in the amount of talking by the subjects. Thus, under both isolation and social conditions, d-amphetamine has been shown to affect the rate of human speech.

In humans, changes in social behavior have been observed following high doses of amphetamine (Ellinwood, 1972; Griffith et al., 1977; Rylander, 1972). Griffith et al. (1972) studied the effects of d-amphetamine on the social behavior of human subjects in a residential research ward. In the first study, using a time-sampling observational technique, researchers measured the effects of the drug (5-30 mg oral) on the amount of time subjects spent standing and socializing over 6-hour periods. In all three subjects tested, d-amphetamine increased the amount of time spent socializing or standing. In a second study, verbal behavior was measured in isolated pairs of subjects during 1-hour sessions. Timers, actuated by throat microphones, allowed the measurement of total time spent talking by each subject. Adjective checklists

were administered before and after the session. Using a dose-range similar to the first study, the authors reported a dose-related increase in total speaking time in five of the seven subjects. The adjective checklists proved to be as reliable and sensitive to the drug effects as the speaking time measure. Of interest was the observation that speaking time of one partner given placebo increased when the other partner was given amphetamine, although the adjective checklist showed responses appropriate to the administered drug. This is an example of a socially mediated indirect drug effect. The results of Jaffe, Dahlberg, Luria, and Chorosh (1973) also support this finding.

Observations of animals have also indicated a disruption of social behavior following amphetamine. Kjellberg and Randrup (1973) rated the social behavior of six pairs of monkeys given d-amphetamine (0.5, 0.15, or 0.37 mg/kg, R.C.). The results showed that most aspects of social behavior were reduced by amphetamine while a few were increased. The net effect of the drug was a disruption of normal social patterns.

The results of these studies suggest that the amphetamines in the clinical dose range may cause fundamental changes in normal human behavior. In addition, there may be indirect drug effects on individuals who have not taken a drug when they are in a social situation with a person who has taken an amphetamine.

DRIVING PERFORMANCE STUDIES

Adequately designed studies investigating the effects of CNS stimulants on skills related to driving a motor vehicle are rare. Although driving is a skill often taken for granted, it requires complex integration and normal functioning of sensorimotor systems. Several problems in measuring driving skills and their sensitivity to drugs can be defined. Drivers differ in their abilities prior to taking drugs. Little effort has been directed toward establishing baseline standards so that better conclusions can be drawn relating drug effects to changes in driving performance. Without actually testing drugs on performance while driving, one must resort to driving simulators or a battery of psychomotor tests to evaluate a number of different skills. At present, there is little agreement on which tests adequately measure driving ability. A more comprehensive review of drug effects on driving performance can be found in a recent monograph published by the National Institute on Drug Abuse (Willette, 1977).

In an early study, Rutenfranz and Jansen (1959) studied the interactions of ethanol (0.5 or 1.0 g/kg) with either caffeine (200 mg) or methamphetamine (10 mg) in a driving simulator. Two subjects were given ethanol alone or in combination with caffeine or methamphetamine. Both doses of ethanol caused a deterioration in driving performance. Both methamphetamine and caffeine

reversed the effect of the low dose and partially reversed the effect of the high dose. The authors stated that caffeine was less potent than methamphetamine, although this statement is based on an arbitrarily chosen single dose of both drugs. In addition, the design of the study did not test the effects of placebo administration or the effects of caffeine or methamphetamine alone. More subjects should have been tested.

Caffeine's prevalent use is probably to increase a person's alertness upon awakening or when driving or studying. However, there have been few well-designed studies that have directly examined these effects of caffeine on complex performance related to vehicle operation. Hauty and Payne (1955) and Payne and Hauty (1954) showed that caffeine enhances monitoring performance in an aviation trainer. Regina, Smith, Keiper, and McKelvey (1973) evaluated the effects of caffeine on four indices related to performance in an automobile simulator. Thirty minutes after ingestion of 200 mg of caffeine or placebo, each subject drove an automobile simulator for 90 minutes. According to the authors, caffeine was found to enhance performance on those indices related to gradually appearing signals (changes in car speed) or discrete signals (on-off high-beam signals). However, examination of separate 30-minute intervals failed to show time-related drug effects for the four measures.

Clayton (1976) speculated on the relevance of laboratory studies to the driving situation. He concluded that, in terms of sensory process and perceptual skills, the most valid predictor of accident rate is dynamic visual acuity, the ability to perceive a moving object transversing the visual field in a horizontal plane at a constant angular velocity. No studies directly relating drug effects on this ability to driving have been carried out. However, ongoing studies (Schuster, unpublished observations) are testing the effects of methamphetamine on smooth pursuit eye movements of rhesus monkeys. These animals are trained to follow a 1-inch-diameter spot of light which transverses a field of 20° of visual angle on a screen 1 meter from the eyes. The center of the spot dims slightly for 400 milliseconds under a random interval of 20 seconds. If the animal presses a lever during this time, it is rewarded with 1.5 milliliters of water. If the animal presses the lever at any other time, the spot of light is extinguished and the animal must wait 30 seconds for another trial. Results to date have shown that the animals can quickly learn this task and perform it with high accuracy. Recordings of eye muscles have shown the smooth pursuit eye movements of the monkeys to be very similar to eye movements of humans performing an identical task (Holzman, Levy, Uhlenhuth, Proctor, & Freedman, 1975). Methamphetamine has been found to produce a decrement in smooth tracking at low doses (0.125 mg/kg). This decrement is manifested behaviorally by the animals' failing to respond to the light dimming as quickly or accurately compared with their performance on control days. Although the behavioral deficit produced by the low doses may not be dramatic, if even small increases in latency are translated

into practical terms of driving, a possibly hazardous situation could be envisioned. The task may be more relevant to the driving situation than measures such as simple or choice reaction time, where requirements on the subject are much less. Also, as previously discussed, tests of stimulant effects on reaction time have not yielded consistent effects.

Wilde (1975) proposed that the causation of accidents was related to a process in which drivers try to match the amount of perceived risk to the degree of risk they are willing to tolerate. Previously discussed data suggest that amphetamine may improve mood and lessen fatigue. Increased risk taking as a reflection of these drug effects was studied in situations unrelated to driving (Hurst, 1962); however, there may be reason to further examine these effects.

DRUG STATES

CHRONIC DRUG EFFECTS

To this point, the discussion of the actions of the CNS stimulants on human performance has been limited mainly to the acute effects of these drugs. Growing evidence from experimental and clinical studies indicates that the acute and chronic administration of these drugs produces widely different effects. In discussing directions for future research, Weiss and Laties (1962) noted that there were no experimental data on the effects of chronically administered amphetamine on human performance. This section discusses the available data concerning the physical and psychological effects of repeated stimulant administration. Where appropriate, studies involving the long term effects of stimulants on animal performance are included.

In the therapeutic dose range, the amphetamines are not thought to be toxic. However, when these drugs are taken in high doses over an extended time, medical and behavioral complications occur. Some clinical and experimental evidence suggests that irreversible morphological and behavioral toxicity may result from chronic high-dose usage (Citron, Halpern, & McCarron, 1970; Escalante & Ellinwood, 1972; Kasirsky, Zaidi, & Tansy, 1972; Rumbaugh et al., 1971). Citron et al. (1970) reported a necrotizing angiitus in human drug abusers. Although methamphetamine was the suspected causative agent, all patients had a history of polydrug abuse. There have been laboratory studies in which better controlled methods were used. Rumbaugh et al. (1971) gave 1.5 mg/kg methamphetamine intravenously to rhesus monkeys every other day for 2 weeks. Extensive neurological effects marked by petechial hemorrhages and cerebral edema were reported. Shybut et al. (1976) were unable to replicate these results. Seiden, Fischman, and Schuster (1977) maintained rhesus monkeys on high doses of methamphetamine for 3 to 6 months. Following a 1- to 3-month drug-free period, no

gross neurological changes were found. These contradictory results could have been due to numerous procedural differences. However, biochemical analysis of specific brain regions of these monkeys showed a 70 percent reduction in caudate dopamine levels, which was apparently irreversible.

In contrast to the effects of acutely administered low doses of stimulants, high doses of virtually all the amphetamine-like compounds have been shown to induce psychotic symptoms in presumably nonschizophrenic individuals (Angrist & Gershon, 1970; Bell, 1965, 1973; Connell, 1958; Griffith et al., 1972; Rylander, 1972). The most common psychotic reaction resulting from these high doses is a state which so closely resembles paranoid schizophrenia that misdiagnosis has often resulted (Bell, 1973). This psychosis, which may develop slowly or may have a sudden onset, is characterized by a variety of symptoms including delusions of persecution, visual and auditory hallucinations, changes in body image, hyperactivity, and excitation (Angrist & Gershon, 1970; Ellinwood, 1967, 1972; Griffith et al., 1972; Kramer, Fischman, & Littlefield, 1967). Griffith et al. (1972) administered increasingly high doses of d-amphetamine to six amphetamine abusers, five of whom developed paranoid psychosis. Angrist and Gershon (1970) gave higher doses of d- and l-amphetamine to former abusers over a shorter period than in the Griffith study. In addition to finding a progression of symptoms quite similar to the former study, Angrist and Gershon (1970) also reported visual, olfactory, and auditory hallucinations. During the middle stages of these studies the authors noted a complex stereotyped behavior pattern manifested as repetitive grooming or manipulation of mechanical objects (Angrist & Gershon, 1970; Ellinwood, 1967, 1972; Griffith et al., 1972). Following the termination of drug administration, the psychotic symptoms waned, often in the reverse order of appearance. Abrupt discontinuation of the use of amphetamine does not lead to a physiologically disruptive state. Withdrawal of the drug does not constitute a life-threatening situation as is the case for physical dependence of the barbiturate type. Upon abrupt withdrawal of amphetamine, there may be a prolonged period of sleep, lethargy, or a depressive reaction. Similar symptoms appear when the use of cocaine is abruptly terminated.

Given the residual effects following high-dose stimulant administration in animals, the possibility remains that similar effects may be found in humans. Although clinical observations and tests may indicate this to be true, numerous predisposing factors unrelated to drug intake could be the cause. In addition, the lack of behavioral data before the drug episode makes definitive answers impossible. Several authors have suggested that once an individual has developed an amphetamine psychosis, it is readily reinitiated, even following long drug-free periods (Ellinwood, 1969; Kramer et al., 1967). Utena (1974) suggested that there may even be an increased potential for psychotic reactions precipitated not only by amphetamine but also by physical and

psychological stress. Facial tics and mouthing movements have been noted to increase with psychological stress in abstinent amphetamine abusers (Utena, 1974).

The effect of repeated cocaine administration has been an issue in question for several years. In an early review of the literature, Tatum and Seevers (1929) concluded that there was no evidence of tolerance to cocaine's effects after periods of sustained intake; in fact, their own data suggested that monkeys, dogs, and rabbits became supersensitive to the behavioral and physiological effects. Subsequent research by others has supported this idea (Downs & Eddy, 1932a, 1932b; Post, 1977; Stripling & Ellinwood, 1976). However, several reports have also demonstrated tolerance to certain effects following repeated cocaine administration. Matsuzaki, Spingler, Misra, and Mule (1976) showed tolerance to the cardiovascular, respiratory, and convulsive effects of cocaine in rhesus monkeys following 2 days of once-a-day intravenous injections of a minimal convulsive dose.

One aspect of stimulant abuse in humans which has not been adequately assessed is the development of motor dyskinesias (Ellinwood, 1972; Kramer et al., 1967). Experimental observations of monkeys administered high doses of stimulants indicate that these dyskinesias also develop (Ellinwood, 1971a, 1971b; Post, 1977). Evidence presented by Eibergen and Carlson (1975) demonstrated that monkeys maintained on chronic methadone treatment showed exaggerated dyskinetic response to methamphetamine for as long as 17 months after the end of the methadone treatment. Studies by other investigators have also indicated increased sensitivity to stimulants following an extended period of narcotic administration. Schuster et al. (unpublished observations), using a procedure originated by Falk (1969), studied the effects of methamphetamine before and after chronic methadone on tremor in rhesus monkeys trained to press a lever with a specified amount of force. The results indicated that, following a 45-day treatment with methadone, tolerance developed to the effects of methamphetamine at doses which totally disrupted responding prior to methadone. The tolerance was accompanied, however, by an increased tremor when the animals attempted to press the lever.

SUBJECTIVE DRUG EFFECTS

The relationship between the subjective effects of a drug and subsequent task performance is an extremely complicated and poorly understood interaction. The effects of the psychomotor stimulant drugs on subjective ratings of mood changes have been remarkably consistent between studies, despite the wide variety of measures used. These drugs consistently increase stimulation and euphoric mood while decreasing fatigue and boredom. Since it is difficult, if not impossible, to compare different individuals on the basis of their verbal reports of subjective drug effects, most investigators have relied on checklists of adjectives

that describe mood. Typically, subjects are asked to check true or false or to give a numerical value to their current mood state. For example, Hurst (1962) used the Nowlis Adjective Checklist (Nowlis & Nowlis, 1956) which includes 33 or, in a later study (Hurst et al., 1969) 58 adjectives to measure subjective effects following amphetamine administration. The subjects were required to assign a numerical value between -3 and +3 to their mood state. These values were analyzed in terms of three mood clusters from the scale--anxiety, fatigue, and surgency (undefined by the author, but probably vigor). Hurst el al. (1969) observed that d-amphetamine (14 mg/70 kg) produced decreased fatigue and increased surgency.

Frankenhauser and Post (1966) gave 15 mg of d-amphetamine (orally) to subjects and measured mood changes using a checklist consisting of the following adjectives: alert, tired, vigilant, sleepy, tense, interested, and bored. The results were plotted as percentage of placebo value versus time after drug administration. Subjective measures were already affected 35 minutes following drug ingestion, the time of the first measurement, peaking at 2-3 hours.

Hollister and Gillespi (1970) used a different adjective checklist mood scale consisting of 50 adjectives with a 4-point scale ranging from "not a bit" to "extremely." Three factors were measured--active, stimulated, and drowsy. A dose of 0.2 mg/kg of d-amphetamine (average dose 15 mg) administered orally to 12 normal volunteers was shown to decrease drowsiness and to increase stimulation and activity 1 and 3.5 hours later.

In another study (Dickins, Lader, & Steinberg, 1965), a checklist of 26 adjectives describing mood was divided into categories of desirable (e.g., clearheaded, sociable, efficient) and undesirable (e.g., drowsy, confused, dizzy). Amphetamine sulfate (15 mg orally) increased desirable adjectives to a greater extent than a mixture of amobarbital plus amphetamine, which increased desirable adjectives more than the barbiturate alone. However, comparisons between amphetamine and placebo control did not produce statistically significant results.

The failure to include more than a single dose of a drug is a major factor to consider in evaluating these studies. The effect of a drug on mood, as with any other parameter, cannot be assumed to be an all-or-none threshold phenomenon unless a wider range of drug doses is evaluated. For example, what may be reported as increased stimulation and pleasant feelings at a lower dose could become increased anxiety at a higher dose of the same drug. This criticism is especially relevant to the report by Dickins et al. (1965), in which the adjectives were divided into desirable and undesirable. What is desirable at one level may become undesirable at another level. While there are obvious limitations on the number and range of drug doses that can be tested in human subjects, lower doses than those commonly used

could certainly be tested, as could somewhat higher doses with appropriate monitoring.

The importance of testing more than one dose of a drug has been recognized in several recent studies on the effects of psychomotor stimulants on mood. For example, Stitzer et al. (1978) reported that d-amphetamine, in the dose range of 5-20 mg, affected the rate of speaking in isolated humans in a manner that corresponded with subjective reports measured by a 48-item adjective checklist. This checklist, which was in part derived from the Profile of Mood States (POMS) checklist (McNair & Lorr, 1964), requires subjects to rate their current mood on a scale of 0 (not at all), 1 (a little), 2 (quite a bit), and 3 (extremely). In two of the four subjects tested, a 5-mg dose of d-amphetamine was behaviorally active (i.e., an increase in rate of speech) and was also associated with higher scores on the subjective checklist. For the remaining two subjects, in whom the 5-mg dose did not produce an increase in speech, there was not an increased score on the checklist either. One subject had a lower subjective score after 15 mg than after 5 mg. When the checklist was further broken down, this subject's score was noted to be decreased for adjectives such as lively, vigorous, carefree, alert, friendly, and cheerful, with increases for adjectives indicating tension and anxiety.

Decreased euphoric mood as measured by six POMS scales (anxiety, vigor, fatigue, confusion, anger, and dejection) following doses of 10 and 20 mg of d-amphetamine has been observed in some individuals (Smith & Davis, 1977). These authors labeled the subjects with decreased euphoria as paradoxical responders. It is questionable whether these individuals are truly paradoxical responders or whether they are more sensitive to the effects of the drug which at higher doses would have the same effects in other individuals.

The Addiction Research Center Inventory (ARCI) has been used extensively to characterize the effects of various drugs in humans (Haertzen, 1966), including the psychomotor stimulants. The scales of the ARCI, developed using a prisoner population with long histories of drug use, are drug specific. These scales include the morphine-Benzedrine group (MBG), a general measure of euphoric drug effects; the Benzedrine group (BG), a more specific indication of amphetamine-induced euphoria; the pentobarbital-chlorpromazine-alcohol group (PCAG), a measure of sedation; and the lysergic acid diethylamide group (LSD), a measure of dysphoric and psychotomimetic effects. Martin (1970) has also developed an amphetamine (A) scale that is drug specific. A variety of orally administered drugs have been tested using these scales, including amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate. All of these drugs have been shown to decrease PCAG scale scores below placebo while increasing the A and BG scores in a dose-related fashion. At high doses (20-25 mg/70 kg) of amphetamine, increases in the LSD scale scores have been observed. Low and intermediate doses

(5-10 mg/70 kg) have resulted in increased feelings of well-being and contentment, while high doses have produced increased feelings of nervousness and tension (LSD scale).

The ARCI and POMS questionnaires have also been used to evaluate subjective stimulant drug effects in human subjects given intravenous cocaine. Fischman, Schuster, Resnekov, Schick, Krasnegor, Fennel, and Freedman (1976) administered intravenous cocaine in doses ranging from 4 to 32 mg to nine male volunteers. In addition, d-amphetamine (10 mg) or saline was administered as a control injection. The subjects never received more than one injection each day. Prior to each session and 1 hour after drug or saline administration, the subjects filled out the subjective effects questionnaires. The subjects were also asked to identify the drug and compare it with illegally acquired stimulants they were accustomed to self-inject (on a scale of 0 to 10: 0 = placebo, 5 = the same, 10 = the highest ever taken). The results showed that the subjects were capable of accurately discriminating all doses of cocaine above 4 mg as well as discriminating 10 mg of d-amphetamine from placebo. They were less capable of discriminating between cocaine and amphetamine. Doses of 16 or 32 mg of cocaine were identified as amphetamine on several occasions, while d-amphetamine was correctly identified twice. The results of asking the subjects to rate their drug effects showed that a dose of 16 mg of cocaine was most similar to an average street dose. In general, there was a dose-related increase in ratings, with 10 mg of d-amphetamine rated as having a subjective effect of approximately 12 to 16 mg of cocaine. Comparison of predrug and postdrug scores for the ARCI showed no differences for saline injections. The A, MGB, and BG scores after cocaine injections all showed increases that were consistently related to dose. The LSD scale was relatively unchanged, while the PCAG score decreased following all cocaine doses except 4 mg. The scores following d-amphetamine were changed in a manner similar, though not identical, to cocaine. These results are interesting in several respects. They add valid evidence to support the widely held notion that the effects of cocaine are similar to those of d-amphetamine. Although only one dose of d-amphetamine was tested, the results of asking subjects to identify the drug they had received showed that they could readily discriminate between drug and placebo, but they were less able to tell d-amphetamine from cocaine. This was true at 1 hour following an intravenous injection, when one might assume the cocaine effects would be dissipating.

A later study by the same group of investigators (Javaid, Fischman, Schuster, Dekirmenjion, & Davies, 1978) was designed to correlate physiological and subjective effects with plasma concentrations following intravenous (16 or 32 mg) and intranasal (16, 64, or 96 mg) cocaine. In general, there was a good correlation between changes in cardiovascular and subjective effects and the peak plasma cocaine concentrations after both routes of administration.

Another interesting observation was that plasma levels of cocaine were still fairly elevated at 60 minutes after drug administration when the cardiovascular and subjective effects had returned to baseline. This effect may bear on the results of the previous study in which subjects could not distinguish between cocaine and d-amphetamine at 60 minutes. Determining the cues that people use in discriminating drug effects is an area for future research.

An observation on the plasma levels of cocaine in these subjects strengthens the criticism, which has been repeatedly stated throughout this review, that more than one dose should be tested. An individual's sensitivity to a drug's effects surely varies. Plasma levels of cocaine in this later study (Javaid et al., 1978) were found to vary more between subjects, ranging from 86 to 309 mg/ml 5 minutes after the intravenous administration. The half-life of cocaine (time needed for concentrations to decrease to half of initial levels) varied from 16 to 87 minutes. Possible explanations for the variability are many. The correlation of plasma levels to physiological or subjective effects in individual subjects was not reported by Javaid et al. (1978).

The results from the various studies on the subjective effects of the CNS stimulants agree on the finding of increased feelings of euphoria and well-being. The question of how these feelings affect a person in a social situation has been investigated in a number of studies.

Smith and Davis (1977) compared the effects of d-amphetamine, l-amphetamine, and methylphenidate on mood in a group of 16 subjects made up of psychiatrists, psychologists, and graduate students. This group was chosen because the members were expected to be good observers of their own behavior. There were nine sessions, each separated by at least 3 days. The first session was always placebo followed by two additional placebo tests randomly spaced between a single test of 10 and 20 mg for the three drugs. The mood scales (Profile of Mood (POMS) and a Linear Mood Scale) were rated before the drug (8:30 a.m.), 1 hour post, 3.5 hours post, 4 hours post, and at the end of the day (10 p.m.). Subjects were instructed to indicate changes in mood from their predrug level. The results for euphoria measures suggested that d-amphetamine had approximately 2 to 3 times the potency of l-amphetamine and methylphenidate.

DRUG-DRUG INTERACTIONS

As Ellinwood, Eibergen, and Kilbey (1976) discussed in an excellent review, several common patterns of drug abuse involve stimulant use along with other drugs. Two major patterns of abuse of drug combinations with stimulants are (1) the use of amphetamine to maintain alertness for 24- to 48-hour periods followed by sedatives or alcohol to come down; (2) intravenous

injection of high doses of amphetamine at short intervals for several days, ending with alcohol or sedatives (Kramer et al., 1967). These two patterns represent abuse of one drug (in this case a stimulant) on a chronic basis followed with a second (maybe even a third) drug. Before considering the possible results of interactions in this situation, the acute effects of a stimulant combined with other drugs should be examined. Again, many of the studies suffer from poor design.

Investigators who have studied the effects of amphetamine-barbiturate combinations on performance in humans have reported predominantly antagonistic effects (Dickins et al., 1965; Dureman, 1962) or predominantly amphetamine effects (Laties, 1961; Legge & Steinberg, 1962; Nash, 1962). Unfortunately, differences in compounds, dose ratios, and test procedures do not allow for a critical comparison of results. Lack of placebo controls in most studies was especially evident.

Legge and Steinberg (1962) studied the effects of amphetamine (15 mg) on cyclobarbitone (300 mg) alone and in combination on performance of simple mental and motor tasks and on subjective reports. The authors concluded that the mixture produced a pattern of effects different from that of either drug alone in that greater euphoria, elation, and excitement were found. Although a double-blind drug administration procedure and placebo controls were used, the study had several procedural problems that do not entirely allow these conclusions. The number of subjects was not clearly stated nor was the method used to divide the subjects into the four groups (amphetamine, cyclobarbitone, mixture and control). Students worked in pairs, but no mention was made as to whether both members received the same drug. Subjective measures consisted of subjects' describing in their own words their feelings and emotions and the times they occurred. Performance tests were administered at 40, 60, 80, and 100 minutes after taking the drugs. Twenty minutes after drug ingestion, the subjects ate a light lunch, the authors assuming that drug absorption was complete. These problems are representative of the poor design used in numerous other studies.

Wilson, Taylor, Nash, and Camerson (1966) studied the combined effects of ethanol (1.2 g/kg) and amphetamine (15 mg/kg) on the psychomotor performance of 32 student volunteers. No differences were shown between ethanol-amphetamine and ethanol-lactose on balance, skipping, Purdue Peg Board, pursuit rotor, or digit span. Breathalyzer analysis during testing showed blood alcohol levels from 0.06 to 0.06 percent, levels capable of producing observable behavior effects. Unfortunately, the choice of test procedures and the failure to include proper placebo controls make these results of little value.

The combination of stimulants and narcotics has a long history among heroin addicts (Green & DuPont, 1973; Langrod, 1970). The "speedball" is a combination of heroin and cocaine injected at the same time. Amphetamine is also used this way, the

proposed reason for the combination being an increased rush of the heroin injection. Narcotics, barbiturates, and cocaine have the common effect of depressing the respiratory center (Goodman & Gilman, 1975). In the case of the heroin addict where tolerance to this effect would develop, the combination of narcotic and cocaine may not be as likely to cause a toxic effect as for an occasional user of either drug.

Experimental studies on animals have shown that ethanol may prolong and intensify certain behavioral effects of amphetamine such as stereotyped behavior or startle responses (Todzy & Becker, 1974). This potentiation may be due to an altered liver metabolism of amphetamine which results in a higher blood level of the stimulant (Creaven et al., 1970). Although the routes of amphetamine metabolism differ in rats and humans, these results still should be considered as possibly relevant to the human situation.

The use of amphetamine with marihuana has been widely reported. Brill, Crupton, Frank, Hackman, Lomax, McGlothlin, and West (1970) reported that 100 percent of a sample of college students who used marihuana regularly also used other drugs including amphetamines. Carlin and Post (1971) surveyed 107 marihuana users and found that 60 percent had taken amphetamines in combination. Studies on the effects of combinations of CNS stimulants and marihuana or its active constituent Δ^9-tetrahydrocannabinol (THC) have shown few significant effects when compared with the impairment produced by marihuana alone (Evans et al., 1976; Forney, Martz, Lemberger, & Rodda, 1976; Gagnon & Elie, 1975; Zaleman et al., 1973).

GENERAL SUMMARY

ESTABLISHED FINDINGS

Single doses of the amphetamines or related stimulants produce a number of effects which are quite similar. These effects include: (1) decreased sense of fatigue (e.g., Kornetsky et al., 1959; Seashore & Ivy, 1953); (2) elevated mood (e.g., Fischman & Schuster, 1976; Martin et al., 1971); (3) decreased appetite (Cox & Maickel, 1972; Harris, Ivy, & Searle, 1947; Maickel & Zabik, 1977); (4) increased heart rate and blood pressure (e.g., Byck et al., 1977; Fischman & Schuster, 1976; Martin et al., 1971); (5) increased talkativeness (e.g., Stitzer, 1978). The magnitude of these effects varies according to (1) the specific drug, (2) the dose administered, (3) the route of administration, and (4) the extent of previous exposure to the drug.

Cocaine is an effective local anesthetic which blocks the conduction of action potentials down axons. When cocaine is sniffed, the compound anesthetizes the nerve endings in the nose. While many of the behavioral and toxic effects of cocaine are

similar to amphetamine, one important difference is the short duration of action of cocaine. Depending on dose, the effects of amphetamines may last for hours, whereas the effects of cocaine may persist for only a few minutes before metabolism by liver and plasma enzymes terminates its action.

The effects of a single administration of cocaine in humans were described by Freud (1974) as including euphoria, vigor, anorexia, insomnia, and increased pulse rate and body temperature. Only recently have well-controlled studies measuring physiological and subjective effects in humans been conducted (Byck, 1974; Fischman et al., 1976; Freud, 1974; Resnick & Kestenbaum, 1976). These studies have generally found dose-related increases in heart rate and in systolic and diastolic blood pressure. Subjective effects included euphoria occasionally followed by dysphoria.

In humans, the subjective effects of amphetamine and cocaine are quite similar (Fischman et al., 1976; Kramer et al., 1967). In animals, both d-amphetamine and cocaine induce stereotyped behaviors, increase locomotor activity, and decrease food intake (Rogers & Nahorski, 1973; Scheel-Kruger, 1972; Van Rossum & Simons, 1969). Both drugs have been shown to have rate-dependent effects on operant behavior in animals; that is, low rates of lever pressing are increased and high rates are decreased (Barrett, 1976; Kelleher & Morse, 1968; Sanger & Blackman, 1976). Most of the available data regarding the repeated administration of cocaine come from drug self-administration studies in rhesus monkeys. Deneau, Yanagita, and Seevers (1969) demonstrated that monkeys will initiate intravenous self-administration of cocaine when the infusion is made contingent upon a lever press response. Johanson, Balster, and Bonese (1976) made an infusion of 0.2 mg/kg of cocaine contingent upon a single lever press for 23 hours a day. All monkeys initiated self-administration and continued at high intake rates until death ensued in less than 5 days. The same authors also reported similar results for amphetamine.

Caffeine, the most commonly consumed stimulant today, is a naturally occurring compound capable of producing CNS excitation, particularly in the cortex. The mechanisms involved are still poorly understood. Following oral administration, peak effects usually occur within 30 minutes. These effects may include increased respiratory rate or peripheral vasodilation. Toxic effects may range from mild tremors, tachycardia, or vomiting to convulsions and cardiac arrest.

Nicotine is the principal alkaloid of the tobacco plant. In addition to the well-known and preferred route of administration via tobacco smoke, nicotine can also be administered either orally or parenterally. In low to moderate doses nicotine causes peripheral vasoconstriction with an associated rise in blood pressure and heart rate. Central stimulation may follow after administration of these doses, although tolerance to this

effect develops in a short time. Toxicity following high doses (60 mg) of nicotine is marked by convulsions and cardiovascular or respiratory arrest. Nicotine is primarily metabolized by deactivation in the liver. In animals, low doses of nicotine increase motor activity.

DIRECTIONS FOR FUTURE RESEARCH

Further research is needed to more fully understand the nature of the effects of the CNS stimulants on human performance. The goals for future work in this area can be broadly divided into two major categories. The concerns of the first category should be to design and carry out well-controlled studies that will not only yield additional data but will also clarify the results of many of the earlier studies in this area. This systematic replication method of approaching the problem should attempt to develop, at least in principle, a standardized testing procedure. This procedure should include the use of those performance testing methods that would be most likely to yield consistent results regardless of the laboratory. Until these procedures can be identified, the interpretation of drug effects will be open to procedural qualifications. The design and application of these procedures should consider the results from experiments with animal subjects, namely, that the behavioral effects of stimulant administration depend on the rate of responding and the complexity of the task. Although possibly more difficult to design, procedures that would control or allow measurement of the subjects' expectations would be valuable.

The second category of future research needs involves the investigation of the effects produced by an extended administration regimen of the CNS stimulants. Evidence to date demonstrating the emergence of psychotic behavior patterns in subjects given high doses of amphetamine has been quite convincing. Obviously, because of the nature of these effects, future research will be forced to rely heavily on animal experimentation methods. However, these methods are capable of providing answers to several vital questions regarding the consequences of long term stimulant administration. For example, the relationship between task performance and tolerance development during chronic stimulant administration remains an intriguing question. Also, how does withdrawal of the stimulant affect subsequent task performance? An equally important application of animal experimentation methods should be the further investigation of the behaviorally and physiologically toxic effects associated with prolonged stimulant use. These studies are vital not only as a method of characterizing the symptomatology of excessive stimulant use but also as a means for finding effective approaches to treatment.

Additional recommendations for future research relate specifically to the individual stimulant drugs. Trends and patterns of stimulant use would suggest that the popularity of cocaine is increasing sharply. Much of the knowledge concerning the effects

of cocaine, more so than for the other stimulants, is based on anecdotal reports. Although recently conducted studies are adding to the knowledge base, the need for an expanded research effort remains.

Numerous questions also remain about the interactions of stimulants and other drugs of abuse. Perhaps the greatest usage of stimulants with other drugs in today's society would involve a stimulant (caffeine or nicotine) and a depressant (ethanol). The increasing recreational use of cocaine and the continued anorectic use of amphetamine would also suggest that more attention should be directed toward the study of their interactions with ethanol or other depressants such as the barbiturates.

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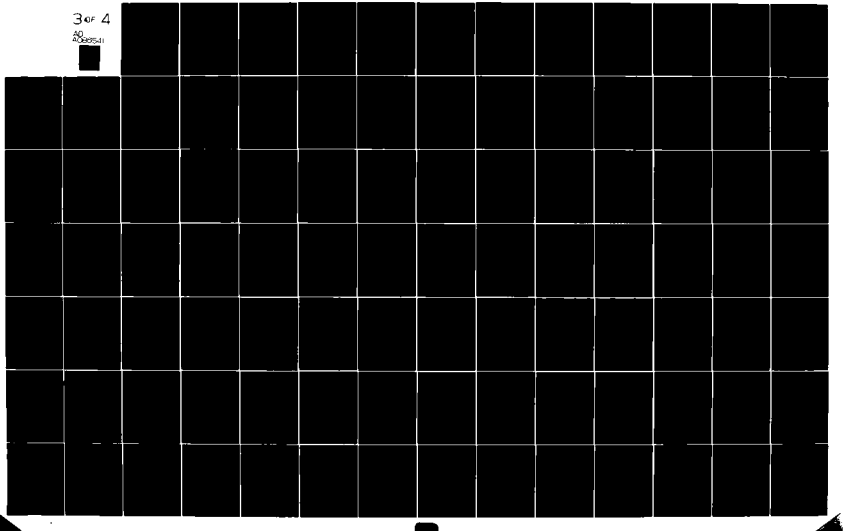

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5. EFFECTS ON PERFORMANCE OF DEPRESSANTS USED RECREATIONALLY

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INTRODUCTION

Certain guidelines must be formulated to discuss the effects on performance of depressants used recreationally. The literature abounds with studies of the effects of depressant drugs on performance, but many of the drugs are not used recreationally. Thus, the first task is to define the types and characteristics of the depressants that are abused.

The most commonly known are the narcotic and nonnarcotic sedatives and hypnotics. Examples of narcotic "downers" are the barbiturates, secobarbital (Seconal), pentobarbital (Nembutal), and amobarbital (Amytal). They are all Schedule II substances highly subject to abuse as listed in the Controlled Substances Inventory List.

Nonnarcotic hypnotics include glutethimide (Doriden), flurazepam (Dalmane), methaqualone (Quaalude), ethclorvynol (Placidyl), and methyprylon (Nodular). Glutethimide and methyprylon are listed as Schedule III substances, less subject to abuse, and flurazepam and ethclorvynol are Schedule IV substances, still less subject to abuse.

Second are the antianxiety drugs or minor tranquilizers. Included in this category are the benzodiazepines (Valium, Serax, Tranxene), meprobamate (Equanil, Miltown), and chlordiazepoxide (Librium). All these are Schedule IV substances.

Third is a miscellaneous category of antihistamines, nonopiate analgesics, antimotion agents, and antihypertensive drugs. These are represented by chlorpheniramine (Codamol) and dimenhydrinate (Dramamine), both Schedule IV substances.

Major tranquilers, including the phenothiazines (e.g., Thorazine), thiothexenes (Navane), and butyrophenomes (Haldol), evidently are not abused.

Beyond these categories, interactions occur between these drugs and alcohol as well as between drugs taken in combination. Drug-drug interactions will be evaluated, but drug-alcohol interactions will be discussed by Moskowitz in his paper prepared for this project.

Guidelines for evaluation of dose levels also are required to pursue the analysis undertaken here. With rare exceptions, dose levels reported in the literature studies are not equivalent to the dosages used by abusers. For example, the bulk of studies of diazepam used doses of 10 or 20 mg, whereas the abused doses commonly appear to be 50 mg or more. The data must be considered in the light of such gross differentials, which confound direct comparability.

The route of administration also must be considered. The bulk of the studies appraised in this report are based on oral administration furnished in single doses. Abusers sometimes rely on intravenous procedures and take drugs chronically and at intervals of their choice. Experimental studies clearly cannot use dose levels equivalent to abuse levels.

Abusers frequently pay little attention to dose levels and instead concern themselves with color or mix drugs indiscriminately, with cost serving as the ultimate basis for their selection.

For all these reasons, the discussion to follow provides no more than an indication of the effects on performance of drugs when used recreationally.

In addition, a thorough discussion of the tests, test situations, and populations employed in the studies is in order. McNair (1973) has categorized measures used in studying antianxiety drugs by their degree of sensitivity. In part on the basis of his methods, the tests utilized in the studies covered in this report may be broadly categorized as follows (the tests vary from the standard psychological tests of intelligence to complicated electrophysiological and neurophysiological measures):

A. Psychological Tests

1. Reflex Speed. These are primarily involved with motor coordination and involve few complicated decisions.

   a. Tapping speed. A clear motor test; average sensitivity.
   b. Simple reaction time, visual and auditory. Average sensitivity.
   c. Symbol copying. A test of motor-eye coordination; average sensitivity.

2. CFF-AFF. This is the frequency at which perception of an intermittent flashing light or an auditory source changes to a steady state. It is related to the excitability of the nervous system.

   a. CFF. Average sensitivity.
   b. AFF. High sensitivity.

3. Tasks Involving Decisionmaking

   a. Sorting tasks. These tasks usually involve sorting cards or other objects according to a set of rules. The rules may even be changed during the test depending on the subjects' performance. A classic example is the Wisconsin Card Sorting Test, a sensitive measure of brain damage.

b. Choice reaction time. In this type of test subjects are required to respond to one or more stimuli in a special order or as part of a series; average sensitivity.

4. Learning and Memory. Tasks in this category require the subject to memorize lists, pairs of words, groups of symbols, etc.

   a. Proactive and retroactive inhibition. This involves the learning of at least one list and its effect on recall of another; low sensitivity.
   b. Digit span. The required task is to repeat after the experimenter digits either forward or backward; low sensitivity.
   c. Scanning. Scanning involves short term memory for the presence of a number in an array of numbers presented for a short period; intermediate sensitivity.

5. Concentration and Vigilance Tasks. These tasks require continuous attention or performance of a specific attention task under a specified time limit.

   a. Continuous performance test (CPT). The subject is required to respond to a critical stimulus in a series of similar stimuli, auditory or visual; high sensitivity.
   b. Digit symbol substitution test (DSST). This is a subtest of the WAIS. The subject is required to write beneath a number a symbol from a symbol matching code; high sensitivity.

6. Perceptual Motor Performances. These require responding to a visual stimulus that may vary or move.

   a. Tracing. Mirror tracing requires considerable hand-eye coordination; also included are maze tracings; indeterminate sensitivity.
   b. Motor skills tasks. Many of these were designed to be comparable to driving skills and flying skills.
      (1) Pursuit rotor test. Low sensitivity.
      (2) Driving simulators. High sensitivity.
      (3) Saccadic eye movements during reading.

7. Time Estimations and Awareness of Risks and Deficits. In these tests the subjects are to judge time durations between stimuli or to rate their performance at various tasks; indeterminate sensitivity.

B. Electrophysiological and Neurophysiological Tests

1. Galvanic skin response (GSR). This is a measure of skin resistance taken by measuring the change in electric potential between two points on the skin. Closely allied is palmar sweating; both high sensitivity.

2. Contingent negative variation (CNV). This is a very sophisticated measure of electric potential shifts in the brain that occur during a reaction time task; intermediate sensitivity.

3. Evoked potential--visual (VEP), auditory (AEP), and somatic (SEP). These are measures of electric potential during stimulation; indeterminate sensitivity.

Tests listed as indeterminate were not used enough in the test batteries to be rated.

The subjects used were primarily young and were students or other captive populations. Very few studies used a neurotic population (for whom the drugs were originally designed). Further, few studies of hypnotics investigated the effect on performance the day after sleep was induced.

The discussion and tables in the body of the report should be read with the following in mind.

Many of the studies are concerned with more than one drug, and the results may be presented for single drugs. If the design, for example, is a comparative one testing the effects of secobarbital and d-amphetamine separately, then, since the purview of this report is depressant effects, only these are cited. If, however, secobarbital and d-amphetamine are studied separately and mixed, then all these results are included. Generally, then, the name of the table indicates which drug effects are cited. Some studies are included in more than one table.

Abbreviations used in these tables are p.o. (by mouth); A (acute or single dose administration); C (chronic dosage over a period of days); i.v. (intravenously); h.s. (hour of sleep); tid (three times a day); and qid (four times a day). For other abbreviations describing the tests, the reader is referred to the test descriptions.

BARBITURATES

The effects of barbiturates on performance have been studied extensively. Although table 1 includes only 21 studies, all dating from 1957 to 1976, it can be considered representative of the many studies for which published articles exist.

The drug most commonly studied is secobarbital, represented by 10 articles. Six studies report on effects of amobarbital; four concern pentobarbital; and both heptabarbitone and cyclobarbitone are represented by one study.

One article compares effects of two barbiturates (Belleville & Fraser, 1957); two compare barbiturates with other nonnarcotic sedatives or hypnotics (Bixler et al., 1973; Saario & Linnoila, 1976). Others compare barbiturates with major and minor tranquilizers (Betts et al., 1972; Hart et al., 1976). Nine studies compare the effects of amphetamines with those of barbiturates (Borg et al., 1972; Bustamente et al., 1970; Frankenhaeuser & Post, 1966; Idestrom and Schalling, 1970; Legge & Steinberg, 1962; McKenzie & Elliott, 1965; Smith & Beecher, 1960a, 1960b; and Talland & Quarton, 1965). Legge and Steinberg (1962) examined the effects of mixing two substances, cyclobarbitone and amphetamine. Dalton et al. (1975) studied the mixture of marihuana and secobarbital.

As in many studies dealing with other substances, male students most frequently were the only population used in these investigations. One group, however (Belleville & Fraser, 1957), relied on postaddicts. This was a special population of addicted prisoners, a group at Lexington frequently selected during the 1950's and 1960's. In another study (Idestrom & Schalling, 1970), normal students were divided into subgroups with low and high psychasthenic scores.

INTELLECTUAL FUNCTIONING

The most sensitive variables appear to be those concerned with intellectual functioning. For example, the digit symbol substitution test is consistently impaired (Bixler et al., 1973; Evans & Davis, 1969; Hart et al., 1976; Idestrom & Schalling, 1970; Kornetsky & Orzack, 1964). Doses as low as 100 mg secobarbital, 50 mg amobarbital, and 300 mg cyclobarbitone had significant effects in terms of this measure.

Coordination of one or more tasks was quite sensitive to barbiturates. Such measures as pursuit rotor, driving simulator tests (hand-eye coordination, adaptive tracking tests, and visual auditory tracking) are significantly impaired (Belleville & Fraser, 1957; Bixler et al., 1973; Borland & Nicholson, 1974; Dalton et al., 1975; McKenzie & Elliott, 1965; and Saario & Linnoila, 1975). These tasks are designed to tap variables considered to be involved in such complex events as vehicle driving and airplane flying.

ATTENTION TASKS

Attention tasks, visual and auditory, are inconsistently affected. The continuous performance test was affected by 200 mg

secobarbital (Evans & Davis, 1969; Kornetsky & Orzack, 1964). The latter authors point out, however, that the effect on this task is much less than that associated with 200 mg chlorpromazine.

Visual search time and auditory vigilance are attention tests that are not consistently affected. Hart et al. (1976) showed that auditory vigilance was significantly impaired by 50 mg amylobarbitone, but when visual search time was utilized as the variable a significant finding did not result. Belleville and Fraser (1957) demonstrated significant slowing in visual reaction time of subjects under intoxication. Idestrom and Schalling (1970) reported a significant effect of 300 mg amobarbital, but a significant finding was not yielded for choice reaction time with a dosage of 150 mg amobarbital. Similarly, Frankenhaeuser and Post (1966) found that 200 mg pentobarbitone increased both simple and complex auditory reaction time. In contrast, Hart et al. (1976) found impairment of auditory reaction time with dose levels of 100 mg amylobarbitone only when presented against white noise. This lack of effect was also found by Saario and Linnoila (1975) in their driving test paradigm with 100 mg amylobarbital.

PERFORMANCE VARIABLES

Performance variables with large motor components such as tapping, athletic performance, mirror drawing, counterpressing, cycling strength, symbol copying, and vehicle handling had inconsistent effects in the reports covered.

Tapping was significantly affected by 30 mg cyclobarbitone, 150 mg secobarbital, 300 mg amylobarbital, and 300 mg pentobarbital, as shown in Legge and Steinberg (1962), Dalton et al. (1975), and Frankenhaeuser and Post (1966). But Hart et al., (1976) found no effect on tapping by 100 mg amylobarbitone, and Potvin et al. (1975) found no effect with 100 mg secobarbital.

Performance on mirror drawing was affected by 300 mg amobarbital only for the highly psychasthenic subjects who were presumably under stress in the test reported by Idestrom and Schalling (1970). Frankenhaeuser and Post (1966) found that 200 mg pentobarbital overcame the practice effect characteristic of the control subjects.

Symbol copying, a purely motor task, showed no effect with 200 mg secobarbital (Kornetsky & Orzack, 1964).

Athletic performance was shown in three studies to be significantly affected. Borg et al. (1972) found that 300 mg amobarbital decreased cycling endurance in contrast to 10 mg amphetamine, which increased it. Smith and Beecher (1960a, 1960b) found not only that athletic performance, such as swimming and running, was depressed by 100 mg secobarbital but also that the athletes' estimation of their own performance level was impaired.

PHYSIOLOGICAL AND NEUROLOGICAL VARIABLES

Physiological and neurological variables such as pulse, blood pressure, heart rate, standing steadiness, and hand steadiness were differentially affected. Pulse rate, for example, was significantly decreased by 200 mg pentobarbitone in Frankenhaeuser and Post (1966). Legge and Steinberg (1962) and Dalton et al. (1975), however, found that 300 mg cyclobarbitone had no effect, and 150 mg secobarbital and marihuana increased pulse rate. Steadiness as measured on a wobble board was increased when marihuana and secobarbital were combined, as reported in Dalton et al. (1975). Both hand steadiness and standing steadiness were significantly impaired by 300 mg amylobarbitone (Idestrom & Schalling, 1970), but 100 mg secobarbital, given at hour of sleep, was associated with improvement in static hold steadiness and no improvement in dynamic hold steadiness when the subjects were awakened during stage 4 sleep.

Memory was also differentially affected. Evans and Davis (1969) provided a systematic analysis of components of memory. They found that tasks requiring the most stressful effort (long lists, serial recall, meaningful word recall, and proactive inhibition on learning a new list) were least affected by 100 mg, 200 mg, and 250 mg secobarbital. Greater effect was evident for measures of a purely rote nature, which depend on memory strategies of a lower order.

SUMMARY

Because the results of these various studies of barbiturates and their effects on performance are counterindicative, it is difficult to formulate a synthesis of the findings.

The disparities among the measures employed, the dosage levels utilized, and the drugs administered contribute to the problem of reaching overall conclusions.

Three tentative conclusions can, however, be offered:

1. It appears that tasks requiring cognitive integration and coordination of multiple skills are most affected by the barbiturates.

2. It appears that both physiological variables and reflex variables are less affected by the barbiturates.

3. It appears that the effects of barbiturates on these variables are dose-related.

DIAZEPAM

Table 2 presents 21 studies using diazepam (Valium), the most commonly prescribed psychotropic drug throughout the world.

In 14 studies, the drug was administered in single doses and, with three exceptions, by mouth. The dosages vary between 5 and 40 mg. The most common dosage is 10 mg. Subjects are preponderantly normal males, usually volunteer students, whose ages and physical conditions as well as other identifying characteristics may thereby confound comparison with abusers. Only Masuda and Bakker (1966) differentiated their normal subjects by high- and low-anxiety categories. All the studies were double-blind and most used control groups.

Seven studies found a significant effect on the physiological measure, critical flicker frequency, with drug administration at either the 10-mg or 20-mg level (Besser & Duncan, 1967; Haffner et al., 1973; Liljequist et al., 1978; Masuda & Bakker, 1966; Molander & Duvhok, 1976; Saario et al., 1976; and Seppala et al., 1976). Kortilla and Linnoila (1975), however, using an intramuscular injection of 10 mg, found no such effect.

Other physiological measures that showed differentials were: (1) pupil dilation, which Kotzan (1978) found was less than placebo after 10-mg dosage; (2) auditory flutter fusion, in which Besser and Duncan (1967) demonstrated a decrease in threshold after 10 mg; (3) galvanic skin response, which decreased when subjects were tested under stress conditions after medication as compared with placebo conditions (Masuda & Bakker, 1966).

Psychological variables that showed differentials were:

1. Attention Tests. When measured by paper-and-pencil tests, attention was impaired in three studies (Lawton & Cahn, 1963; Linnoila & Mattila, 1972; Marjerrison et al., 1973).

2. Reaction Time. Both simple and choice reaction time, pursuit motor tracking are impaired significantly in eight studies (Borland & Nicholson, 1974; Kortilla, 1976; Kortilla & Linnoila, 1975; Liljequist, 1978; Linnoila, 1973; Linnoila & Mattila, 1972; Seppala et al., 1976). Ghoneim et al. (1975) and Milner and Landauer (1973) showed no effect at 10 mg. These measures are very important, as they relate to components of vehicle driving and airplane flying.

3. Intelligence and Achievement Tests. These seem to be quite sensitive. The digit symbol substitution test (DSST), addition and written mathematics tests are all significantly impaired (Jaattela et al., 1970; Lawton & Cahn, 1963; Liljequist et al., 1978; Masuda & Bakker, 1966).

4. Memory and Learning. These are impaired in tests of digit span and visual scanning, learning paired associates, acquisition tasks, and random digit recall (Ghoneim et al., 1975; Jaattela et al., 1977; Jones et al., 1978; Liljequist et al., 1978. Ghoneim's group found the Benton Visual Retention Test unaffected even with 20 mg.

5. Motor Tasks. Studies cited in Table 2, using pegboard tests, dot tracing, picking up matches, and tapping, are not consistently affected.

There are in addition experiments using driving simulators, including studies by Linnoila and his group (1972, 1973); Milner and Landauer (1973); Seppala et al. (1976); Kortilla (1976); and Dureman and Norrman (1975).

In summary, the more complicated tasks--pursuit rotor, motor coordination, and choice reaction time--seem to be more impaired than the simpler tasks. However, changes in the threshold of the c.f.f. demonstrate that this physiological measure is a good indicator of the effects of these drugs on the brain.

BENZODIAZEPINES AND MISCELLANEOUS AGENTS

Table 3 presents the results of studies of the effects on performance of several benzodiazepines compared with each other as well as with other hypnotics, sedatives, and minor tranquilizers.

Substances included in this table are (1) minor tranquilizers, such as ethchlorvynol, oxazepam, nitrazepam, clobazam, flunitrazepam, bromazepam, and flurazepam; (2) hypnotics, specifically glutethimide, secobarbital, and amobarbital; and (3) other substances, including thioridazine, caffeine, methylphenidate, methohexitone, halothane, and nitrous oxide. These studies were chosen to illustrate the actions of minor tranquilizers other than diazepam and meprobamate. This should not be considered a thorough examination of these agents, merely an illustrative one. The reason is that the actions of many of the benzodiazepines are similar to those of diazepam and need not therefore be considered anew.

Glutethimide and ethchlorvynol are both controlled substances, Schedules III and IV respectively, and as a result are included in this review. The actions of meprobamate, one of the earliest minor tranquilizers that was heavily abused, are presented in table 4.

The subjects studied in this group of papers were primarily normal student volunteers who were males except in Peck et al. (1977), which used only females. Two studies distinguished

between good or sound sleepers and poor or light sleepers (Church & Johnson, 1979; Peck et al., 1977). One used surgical patients (Gale, 1976). Seven studies employed single-dose administration of medication provided orally to the subjects (Ashton et al., 1974; Clarke & Nicholson, 1977; Kaplan et al., 1968; Lahtinen et al., 1978; Parrott & Hindmarch, 1978; Peck et al., 1977; Strasser & Muller-Limmroth, 1973). Two studies relied on intravenous injections in single-dose administrations (Holgate, 1973; Gale, 1976). Four studies measured the effects on performance of various substances taken daily (Saario et al., 1976; Hindmarch, 1977; Hindmarch et al., 1977; Church & Johnson, 1979).

Dosages are not comparable in most cases. One study of nitrazepam used doses of 2.5 mg, 5 mg, and 10 mg (Peck et al., 1977), and another used 25 mg (Ashton et al., 1974). Three studies of clobazam used 5 mg, 10 mg, and 20 mg in different paradigms (Hindmarch et al., 1977; Lahtinen et al., 1978; Parrott & Hindmarch, 1978).

Because of these variations in study design, it is difficult to look at the drug effects test by test following the procedures employed in previous sections of this review. Instead, a study-by-study description seems in order.

A comparison of 500 mg glutethimide, 500 mg ethclorvynol, and 500 mg secobarbital indicates that glutethimide has the greatest effect on performance of the three agents. Performance of four separate patterns on measures using a pursuit meter, as well as procedures employing verbal output, reverse reading, and subtraction, are seriously impaired when the subject is awakened 4 hours after ingestion. Ethchlorvynol, however, is more potent in impairing color determination in the Stroop test. The subjective evaluations did not correlate with behavioral effects and were, at best, equivocal (Kaplan et al., 1968).

Human operant performance as demonstrated by pressing various lights in a specified order was measured after 5 mg diazepam, 25 mg amobarbital, and 10 mg methylphenidate. The results were inconsistent except that amobarbital had less "hangover" effect than diazepam (Holgate, 1973).

Strasser (1973) measured pursuit rotor performance after subjects had taken 20 mg of oxazepam and found performance significantly impaired. However, when white noise at the level of 80 dB was added, performance improved. This demonstrates oxazepam's effect as an anxiolytic drug in a stress situation.

Ashton et al. (1974), Hindmarch (1976), and Peck et al. (1977) all studied the effects of nitrazepam. Ashton et al. found that a 25-mg dose caused a decrement in amplitudes of both contingent negative variation (CNV) and visual evoked potential (VEP). Both of these measures indicate decreased arousal. Hindmarch found no effect at 5 mg of nitrazepam on either choice

reaction time or the DSST. However, when Peck et al. (1977) divided subjects into light and sound sleepers, they found that light sleepers improved on 5 mg and 10 mg. This was characteristic for auditory vigilance, tapping, and auditory reaction time, but not short term memory. In general, improvements occur with dull, monotonous tasks. Evidently the drug helps those subjects who have abnormal sleep patterns and are adversely affected by the stress of performance on these tasks.

A comparison of 5 mg nitrazepam, 1 mg flunitrazepam, and 15 mg flurazepam by Hindmarch (1977) was included to show that even very low doses have an effect on performance the next day after ingestion with alcohol.

Three studies of 5 mg, 10 mg, and 20 mg clobazam show no effect on reaction time at any dose level after ingestion at bedtime the night before (Hindmarch et al., 1977; Lahtinen et al., 1978; Parrott & Hindmarch, 1978). Lahtinen et al. did find an impairment of reverse parking after 20 mg were taken. Still more sensitive were manual skills, such as picking up beads, matches, and so on, which were impaired by only 10 mg of clobazam taken the previous evening. Another measure that proved sensitive was reaction time using different levels of reinforcement. Parrott and Hindmarch, using a high- and low-level reinforcement design, found that only performance under low reinforcement was impaired. They also measured personality variables and described a group of highly anxious subjects who performed better under conditions of high reinforcement when treated with clobazam.

Clarke and Nicholson (1977) studied an active metabolite of diazepam (nordiazepam) given orally to determine whether this substance had persistent effects, since residual blood levels remain after the original substance is eliminated. They found impairment of visuomotor coordination by 5 mg nordiazepam at 6.5 hr and by 10 mg diazepam for only 2.5 hr. They concluded that the metabolite has a greater danger potential than the original substance for interaction effects with other drugs.

In a unique experiment, Gale (1976) compared the effects of an average of 1.51 methohexitone mg/kg; short-duration halothane in 70 to 80 percent nitrous oxide in oxygen, duration 3 to 12 min; long-duration halothane in 70 to 80 percent nitrous oxide in oxygen, duration 20 to 60 min; and diazepam i.v. 4 mg/min (mean dose 0.31 mg/kg). The subjects were patients who would be undergoing either dental surgery or minor general surgery. The recovery phase was defined after administration ceased. The investigators found that auditory reaction time was increased by methohexitone and at 1 hr after diazepam. Visual reaction time was not consistently impaired. Static ataxia was markedly impaired by long term halothane at 50 to 70 min, but diazepam caused impairment at 90 min.

Tracking was impaired by both long term halothane and methohexitone, and diazepam if lasted beyond 1 hr. Finally,

arithmetic and the Stroop test showed prolonged impairment up to 1.5 to 2 hr. Evidently diazepam allows the slowest recovery up to 3 hr.

Finally, flurazepam, a frequently prescribed and often abused hypnotic, was found by Church and Johnson (1979) to have a significant effect as long as 24 hr after ingestion on DSST performance and choice reaction time. Subjective effects, however, were not consistent and did not correlate with performance scores.

As noted above, differentials in study design are sufficiently gross to confound any clear generalizations regarding the effects of this category of substances on performance variables in experimental studies. Extrapolation to abusive regimens is also not essayed.

Other substances that deserve special discussion are methaqualone and propoxyphene, both of which are frequently abused but have been specifically omitted from the tabular analysis because minimal information concerning them exists. A nonbarbiturate hypnotic, methaqualone is classified as a Schedule II substance because of its potential for abuse.

Rock and Silsby (1978) describe its use by U.S. troops in Europe. They indicate that it is rarely used abusively in isolation and is commonly combined with hashish or with alcohol. Its effects, even when used alone, are powerful and frequently lethal. In 1972 Schnoll and Fishkin finally established that it can result in dependence levels equal to those of the barbiturates. In view of this, it is surprising to find the small number of investigations of its effects. Saario and Linnoila (1976) completed one of the few behavioral studies of this substance. They combined 250 mg methaqualone with 25 mg diphenhydramine to determine the effect the next morning on driving skills. They found no effect on driving skills as measured in their driving stimulator. However, they did report subjective drowziness. Another study, (Pascarelli, 1973) refers to 35 previously published studies, none of which deal with its behavioral effects.

Among the claims concerning the effects of methaqualone are that it acts as an aphrodisiac, but no behavioral studies substantiate this. Nevertheless, this dangerous substance is widely abused.

Another substance, propoxyphene, has been generally considered non-habit-forming for some time and with little effect greater than that of aspirin. It is, however, currently considered a dangerous analgesic or hypnotic (Eli Lilly and Company, 1979), and it is contended that serious central nervous system effects, amenable to potentiation by alcohol or other depressants, result from its abuse. As with methaqualone, behavioral studies are virtually lacking for propoxyphene. One by Kiplinger et al. (1974) showed virtually no significant effects on auditory feedback performance, pursuit meter, and steadiness after ingestion of 65 mg propoxyphene.

Norpropoxyphene has fewer central nervous system effects, according to its producer, although it is thought to have greater local anesthetic effects, similar to amitriptyline or quinadine.

As the abusive intake of both substances appears to be increasing, it is clear that additional behavioral and experimental studies of them need to be undertaken.

MEPROBAMATE

Meprobamate is another antianxiety drug investigated in a number of studies. On the market for many years, it has been seriously abused.

Table 4 presents the results of eight studies of this drug. Six used single-dose administration of 400, 800, 1,200, and 1,600 mg. Normal volunteers, mostly students, were the subjects in all studies reviewed.

Two studies used chronic administration. Figarola and Billings (1966) found that 400 mg, when provided three times daily, resulted in impairment of tracking but did not yield differences in a vigilance test or problem solving except under the influence of hypoxia at 8,000 feet. Similarly, after 4 days of administration of a combination of meprobamate and Listica, Lawton and Cahn (1962) found no effect on cancellations, digit symbol substitution test, dotting test, pegboard, and steadiness. The Porteus Maze, however, required more time to complete under the Listica-meprobamate regimen.

Other studies relied on single-dose administration. Few significant results appear at 400-mg or 800-mg dose levels (Costello, 1961; Jansson, et al., 1966; Kornetsky, 1958; Townsend & Mirsky, 1960). However, Kornetsky found that both serial reaction time and choice reaction time were impaired at 1,600-mg levels while a learning task using the same stimuli was affected by 800-mg and 1,600-mg doses. Jansson et al. (1966) also found that a 1,200-mg dose resulted in a decrease in critical flicker frequency threshold. Townsend and Mirsky (1960) reported that 1,600-mg doses disrupted performance on the DSST and yielded no results on the vigilance test, the continuance performance test.

In contrast to these results, Margolis (1966) found that 400 mg decreased interference by an earlier list in learning a new list, suggesting proactive interference. This is a stressful situation, and the substance was able to alleviate some of the incumbent stress.

In summary, the types of performance that appear to be most affected are cognitive activity (such as coding) and learning tasks, both occurring at the rather high dosage levels of 1,200 and 1,600 mg.

GENERAL SUMMARY

BARBITURATES

Barbiturates have their most profound effects on intellectual functioning. These effects are dose dependent and consistent (Bixler et al., 1973; Evans & Davis, 1969; Hart et al., 1976; Idestrom & Schalling, 1970; Kornetsky & Orzack, 1964). Also consistently affected are tasks requiring one or more mental or coordinated processes. These include hand-eye coordination, adaptive tracking tasks, visual or auditory tracking tasks, and all driving simulation tests (Belleville & Fraser, 1957; Borland & Nicholson, 1974; Dalton et al., 1975; McKenzie & Elliott, 1965; Saario & Linnoila, 1976). Less predictably affected are attention and vigilance tests (Belleville & Fraser, 1957; Hart et al., 1976; Kornetsky & Orzack, 1964; Mirsky et al., 1959; Saario & Linnoila, 1976). Performance on tests of motor behavior such as tapping and symbol copying are dose related but not consistently impaired (Kornetsky & Orzack, 1964; Legg & Steinberg, 1962; Potvin et al., 1975). Athletic performance, such as running and swimming, was generally depressed by 300 mg of amylobarbital and 100 mg of secobarbital. In contrast, physiological and neurological measures such as pulse rate can be either increased or decreased depending on the type of barbiturate ingested (Dalton et al., 1975; Frankenhaeuser & Post, 1966; Legg & Steinberg, 1962). Memory was measured specifically by Evans and Davis (1969), who found that the greatest effect of secobarbital was dose related and that the simplest tasks were the ones most affected. Memory for rote learning was impaired to a greater extent than was memory for tasks requiring more involvement and effort.

DIAZEPAM

The bulk of diazepam studies were designed to measure driving skills and physiological variables. In the latter category, critical flicker fusion was the most consistently affected by doses of either 10 or 20 mg (Haffner et al., 1973; Masuda & Bakker, 1966; Saario et al., 1976). Pupil dilation (Kotzan, 1978) and auditory flutter fusion (Besser & Duncan, 1967) decreased when subjects were given 10 mg of diazepam. Galvanic skill response decreased under stress conditions after 10 mg of diazepam (Masuda & Bakker, 1966). Attention as measured by a pencil-and-paper test was impaired by chronic administration of 15 mg a day (Lawton & Cahn, 1963); acute administration of 10 mg (Linnoila & Matilla, 1973; Marjerrison et al., 1973). Impairment of reaction time was demonstrated in a number of studies after single-dose administration of diazepam (Borland & Nicholson, 1974; Kortilla & Linnoila, 1975; Liljequist et al., 1978; Linnoila, 1973; Linnoila & Matilla, 1973; Seppala et al., 1977). Kortilla (1976), using both IV and IM injections, demonstrated impairment of reaction time. Performance on

intelligence and achievement tests was impaired significantly after both acute and chronic administrations of diazepam (Jaattela et al., 1970; Lawton & Cahn, 1963; Liljequist et al., 1978; Masuda & Baker, 1966). Memory and learning, as demonstrated by digit span, visual scanning, and wordlists, suffered impairment after as little as 5 mg (Jones et al., 1978) and 10 mg, each level by oral administration (Jaattela et al., 1970; Liljequist et al., 1978). Finally, motor tasks such as tapping, dot tracing, sorting, and peg boards were not affected consistently. Chronic administration of 5 mg three times a day caused some impairment on the peg board test, but the effect of acute administration of 20 mg on sorting performance was not significant (Haffner et al., 1973). Ten mg of diazepam had no effect on tapping (Milner & Landauer, 1971). Finally, the driver simulation tasks which combined various skills proved to be very sensitive to the effects of 5 and 10 mg diazepam (Linnoila & Matilla, 1973; Seppala et al., 1976). Dureman and Norrman (1975) found that chronic administration of increasing doses from 5 mg to 20 mg had no effect on simulated driving or steering precision but did significantly increase brake reaction time. This was similar to Milner and Landauer (1971), who found no effect of 10 mg on performance in a driving simulator.

BENZODIAZEPINE AND MISCELLANEOUS AGENTS

The effects of the other benzodiazepines, including nitrazepam, nordiazepam, chlordiazepoxide, flurazepam, exazepam, and clobazam, are very similar to those of diazepam except for one important point. These are derivatives of diazepam and in some cases have longer half-lives than does the original agent. For instance, Clarke and Nicholson (1977) showed that the effects of nordiazepam persisted far longer than the original substance, diazepam. The subsequent hangover effect was significant. One study, Hindmarch (1977), demonstrated that the morning-after effect was evident even with subclinical doses of flurazepam (15 mg), flunitrazepam (1 mg), and nitrazepam (5 mg) when alcohol was given the next day. The response to performance on the Serial F test was significantly decreased.

Nonnarcotic hypnotics were also examined. These included glutethamide, ethchlovynol, and flurazepam. In one study, the first two substances were compared with barbiturates; glutethamide was found to have the greatest effect on pursuit metering of the three drugs tested (Kaplan et al., 1968).

Some of these medications are used for reasons other than the tranquilizing aspect of hypnotics. This is illustrated by a comparison of anesthetics done by Gale (1976). The subjects in this study were patients undergoing either dental or minor general surgery. Nitrous oxide combined with halothane and methohexitone was compared with diazepam. The greatest effect on attention, as measured by an arithmetic test, was from diazepam as long as 3 hours after administration was stopped.

PROPOXYPHENE AND METHAQUALONE

Both of these drugs are highly abused. Methaqualone is considered one of the most abused drugs, yet there seems to be only one behavioral study on it in the literature. This study by Saario et al. (1976) showed no decrement of performance in a driving simulator test, but the subjects became sleepier than when they were exposed to flurazepam, amylobarbitone, and diphenhydramine, all hypnotics.

MEPROBAMATE

Generally this drug, which has been studied extensively, shows effects similar to the barbiturates. Intellectual tasks such as the DSST are impaired, but no effects are shown on the vigilance tasks such as the CPT (Townsend & Mirsky, 1960). However, a dose of at least 800 mg is necessary for an effect (Costello, 1961; Jansson et al., 1967; Kornetsky, 1958; Townsend & Mirsky, 1960). The responses were dose related, and 800 and 1,600 mg produced the most significant effects (Jansson et al., 1967; Townsend & Mirsky, 1960). One author, Margolis (1966) found that 400 mg interfered with list learning.

CONCLUSION

Differences in each of three vital circumstances exist. These are (1) populations, (2) dosages, and (3) modes of administration.

Populations

Most studies cited in the report were carried out on normal young male adults. Age by itself may in fact be the discrepancy of smallest magnitude. The age of abusers generally corresponds closely to that of the subjects participating in the studies. However, laboratory subjects are specifically selected for normality. They may be screened not only for physical normality and for "good" health but frequently have to undergo some form of psychological screening. Some hint of the problems which may occur with nonpsychiatrically screened subjects is shown in those studies in which neurotic subjects are employed instead of normals. For instance, the effects of secobarbital on individuals vary in relation to the degree of psychasthenia (Idestrom & Schalling, 1970).

Many abusers experience anxiety and stress, deriving from a variety of life situations. Such persons characteristically use antianxiety drugs to relieve anxiety or to obtain "highs" that free them from manifestations of their problems. Frequently, drugs such as diazepam are used by reformed alcoholics as substitutes for alcohol. Habitual patterns may emerge

and this can account for the current concern with the excessive prescription use and abuse of such a drug.

The physical health of abusers is typically uncontrolled, and impairments can obviously be related to the effects of abused substances.

Dosages

Dosage is clearly measured and administered in the behavioral studies found in the scientific literature. The subjects are commonly furnished with fixed amounts pursuant to experimental protocols. A further control is that the substances furnished are secured by the investigators from established sources with the consequence that expiration dates are respected and the amounts and quality of the substances employed are assured.

These conditions can never be assumed when drugs are used recreationally and in an abusive fashion. Sources are governed by cost and idiosyncratic convenience, and no assurances exist concerning expiration, amounts, or quality of the materials ingested.

Dose levels of abused substances can never be assumed to be under control.

Drugs and alcohol are often consumed concurrently by abusers, with the distinct consequence of potentiation.

The relations between the doses in scientific studies and their effects can never be readily treated as homologous to street doses and their consequences.

Modes of Administration

Modes of administration vary widely from experimental subjects to abusers. The timing of administration by abusers may be casually planned and therefore irregular. Wide variations in eating and sleeping regimens in relation to the time of the abusive ingestion of drugs confound any simple inferences about such uses.

Abused drugs are often ingested in concert, with nonrational mixtures of various substances in uncertain amounts occurring very commonly. The personal and social circumstances under which drugs are ingested for abusive purposes are highly varied. Stress, excitement, the alteration of norms, the change or elimination of inhibitory expectations--all contribute to impacts of the abused substances, which in turn induce alterations in such environmental patterns.

Guidelines for further studies of substances remain to be formulated. A good deal of further research is clearly needed and should include the following:

1. Careful manipulation of stress situations to determine the conditions under which various levels and kinds of stress contribute to the impact of substances on behavior.

2. Systematic studies of physical, personality, and environmental variables to determine how such factors affect the taking of substances and their impact.

3. Further studies of drug-drug interactions, including combinations of abused substances, to determine interaction effects.

4. Studies designed to replicate as nearly as possible the characteristics of the naturalistic circumstances under which drugs are abused to determine their contribution to effects.

5. Studies of variations in sleeping and eating patterns to determine their relation to drug effects.

Table 1. Effects of Barbiturates on Performance

Authors	Number and Population	Drug	Dose	Type of Administration	Test	Effects	Conclusions
Belleville & Fraser, 1957	18 postaddicts	secobarbital pentobarbital	0.4 g/day for 90 days qid	C p.o.	Temperature Blood pressure Respiratory Calorie intake Body weight Hours of sleep Vertical tracing path Pursuit rotor Visuomotor reaction time	No effect. No effect. No effect. No effect. No effect. Steady decrease throughout study. Significant impairment. Significant impairment. Significant slowing.	Tolerance reached by 86-90 days. During initial days of intoxication considerable impairment occurred.
Mirsky et al., 1959	12 normals	secobarbital chlorpromazine	100, 200 mg 100, 200 mg	A p.o.	CPT-X tasks: absolute relative AX tasks: absolute relative	 No effect. No effect. No effect. No effect.	Even at peak effect, the effect of secobarbital on an attention test is much less than the effect of chlorpromazine.
Smith & Beecher, 1960a	57 normal athletes	amphetamine secobarbital	14 mg 50, 100 mg	A p.o.	Athletic performance Subjective evaluation	Significantly impaired by 100 mg secobarbital Secobarbital produced intoxication, elation "deactivation," and distortion in judgment.	Secobarbital affected mood and impaired performance with 100 mg, but affected only mood with 50 mg.
Smith & Beecher, 1960b	15 athletes	amphetamine secobarbital	14 mg 100 mg	A p.o.	Swimming Evaluation of performance	Significantly impaired performance. Significant distortion in judgment.	Impairment of judgment and performance.

Table 1. Effects of Barbiturates on Performance (Continued)

Authors	Number and Population	Drug	Dose	Type of Administration	Test	Effects	Conclusions
Legge & Steinberg, 1962	4 groups of normals	cyclobarbitone amphetamine	300 mg 15 mg	Alone and combination	Arithmetic Tapping Dotting Pulse Subjective feelings	No significant change v. control. Impaired by cyclobarbitone. Impaired by cyclobarbitone. Amphetamine increased significantly. Results were not significant.	Mixtures gave intermediate results demonstrating compensation by amphetamine for impairment by cyclobarbitone.
Kornetsky & Orzack, 1963	7 normals	secobarbital chlorpromazine	100, 200 mg 100, 200 mg	A p.o.	DSST CPT Symbol copying test Subject paced test	200 mg secobarbital significantly impaired. No effect. Significantly impaired.	Secobarbital impaired self-paced and timed cognitive tasks but had no effect when cognitive aspect removed.
Starkweather & Hargraves, 1964	12 normals	pentabarbital	75, 150 mg	A p.o.	Reading Free speech Differential visual reaction time Clyde Mood Scale Scale Reading-speech rate	No consistent effect. No consistent effect. Significant slowing effect. Significant effect. Significant lengthening.	Changes in mood show subjects less energetic and clear-thinking. Reading rate may be a simple measure of effect.
McKenzie & Elliott, 1965	48 normals	secobarbital amphetamine	200 mg h.s. 5 mg	A p.o.	Multidimensional pursuit test (simulated air mission)	Significant degradation of performance. Combination increased latency and lowered peak performance.	Secobarbital still impairs behavior 12-24 hr after ingestion.

Table 1. Effects of Barbiturates on Performance (Continued)

Authors	Number and Population	Drug	Dose	Type of Administration	Test	Effects	Conclusions
Talland & Quarton, 1965	36 normals	methamphetamine pentobarbital	15 mg/150 lb 100 mg/150 lb	A i.v.	Manual complex reaction time Counterpressing Cancellation Manual dexterity	Significantly slowed. Significantly slowed. Significantly retarded. Significantly impaired.	Effect of pentobarbital shown most on simple tasks.
Frankenhaeuser & Post, 1966	30 normals	d-amphetamine pentobarbitone	15 mg 200 mg	A p.o.	Pulse rate Reaction time: Simple visual Complex auditory Mirror-drawing task Tapping Spokes test A Stroop test	Decrease. Significant impairment. Significant impairment. Effect overcome by practice effect. Significant impairment. Significant impairment. Significant impairment.	Overestimation of performance speed with pentobarbitone.
Evans & Davis, 1969	6 normals	secobarbital	100, 200, and 250 mg for males 100, 150, and 200 mg for females	A p.o.	Proactive inhibition on retention Memory span-serial recall 1/sec Rote memory-no activity Memory span: 1/4 sec, total correct Longest list DSST Rote memory: Arithmetic activity Arithmetic errors Rote memory-serial recall Running span-1/4 sec Serial learning trials Memory span-1/sec: Total correct Longest list Rote memory-nonsense activity Running span-1/sec Rote memory-meaningful words CPT errors	Significant effect. No effect. Significant effect. Significant effect. Significant effect. Significant effect. No effect. No effect. No effect. Significant effect. Significant effect. No effect. No effect. No effect. Significant effect. Significant effect. Significant effect.	Drug had the greatest effect when the task difficulty "effort stress" was the least. Effects on attention, practice and rehearsal, distractibility, and the formation of higher order memorizing strategies, not memory input, immediate storage, or retrieval.

Table 1. Effects of Barbiturates on Performance (Continued)

Authors	Number and Population	Drug	Dose	Type of Administration	Test	Effects	Conclusions
Bustamante et al., 1970	70 normals	amphetamine amnbarbital	20 mg 20 mg	C (6 days) p.o.	Memory-drawing	With both drugs, retrieval impaired on 2d, 4th, 6th days and improved on 3d, 5th days.	Effects of drugs are actually affected by conditions of the experimentors, therefore state-dependent.
Idestrom & Schalling, 1970	22 normals, high and low psychasthenia	d-amphetamine amobarbital	5, 15 mg/70 kg 150, 300 mg	A p.o.	Choice reaction time Tapping Hand steadiness Standing steadiness Mirror tracing CFF DSST Color naming (Stroop test)	300 mg had significant effect (high P). Effect at 300 mg (high P). Significant effect (high P). Significant effect (high P). Significant effect (high P). Significant effect at 150, 300 mg (high P). No effect.	Secobarbital produced much more impairment on psychological test in high psychasthenia groups. Amphetamine had significant cardiovascular effects for high-P, low-P.
Potvin et al., 1975	6 normals	secobarbital	100 mg	A p.o. h.s. tested in first stage 4 of sleep and a.m.	Tapping Hand coordination Critical tracking Visual-auditory tracking Auditory tracking Step reaction time Addition Steadiness (hand): Static hold Dynamic hold EEG	Speed: slight effect, 5%-10% impairment. No effect. Slight effect. Moderate (20%-40%) impairment. Moderate effect. Slight effect. Slight effect. Improvement. No effect. Significantly reduced stage 1 and 4 time; increased stage 2 sleep.	Impairment of unpredictable tasks with fast reactions and increased complications, but impairments evident during sleep interruption gone by morning.

Table 1. Effects of Barbiturates on Performance (Continued)

Authors	Number and Population	Drug	Dose	Type of Administration	Test	Effects	Conclusions
Saario & Linnoila, 1975	20 normals	amylobarbital fluazepam methaqualone glutethimide diphenhydramine	100 mg 30 mg 250 mg 250 mg 25 mg	A p.o.	Driving test Choice reaction time Attention Coordination: I. Fixed speed II. Free speed Serum levels	Amylobarbitone: No effect. No effect. Increased mistakes (numbers and percentages). No effect.	Impairment of hand-eye coordination.
Hart, et al., 1976	12 normals	diazepam amylobarbitone	2.5, 5 mg 50, 100 mg	A p.o.	Auditory vigilence (Wilkinson) Digit recall Reaction time (auditory, white noise) Visual search time Tapping DSST Subjective ratings Blood level	Significant impairment, 50 mg at 45 min. Significant impairment, dose-related. Significant impairment, 100 mg up to 5 hr. No effect. No effect. Significant impairment, 50, 100 mg. No significant differences.	Impairment is drug-related on long or monotonous tests with low motivation or short term memory.
Betts et al., 1972	113 normals	chlordiazepoxide amobarbital trifluoperazine haloperidol interaction with alcohol	5 (10 mg) 5 (30 mg) 5 (2 mg) 5 (0.3 mg)	A p.o. alone and combination	Vehicle handling test: Weaving Parking Gap estimation Subjective assessment	No effect. No effect. No consistent effect. No significant changes.	

Table 1. Effects of Barbiturates on Performance (Continued)

Authors	Number and Population	Drug	Dose	Type of Administration	Test	Effects	Conclusions
Borg, et al., 1972	34 normals	amobarbital not combined amphetamine	0.3 g 10 mg	A p.o.	Cycling strength and endurance	Significant change in endurance with amphetamine; strength decreased by amobarbital.	Amobarbital causes a general decrease in performance level and relates to work motivation.
Bixler, et al., 1973	4, 3, 2 normals	glutethimide chlordiaze-poxide chloral hydrate secobarbital flurazepam	500 mg 50 mg 1,000 mg 100 mg 30 mg	A p.o. 4 hr sleep	Wilkinson Continuous Addition DSST Pursuit rotor Flow maze (eye-hand coordination) Moskowitz Vigilence and Divided Attention	Not significant; increased time and errors. Decrement not significant. Improvement not significant. Improvement not significant.	Peak action was decrement on cognitive association. Tests and motor coordination are still evident up to 8 hr.
Borland & Nicholson, 1974	7 normals	heptabarbitone	200, 300, 400 mg	A p.o. h.s.	Adaptive tracking task Subjective estimate Blood level	Significant decrement for all doses. Inconsistent effects. Concentrations dose-related.	Significance is dose-related and time-related with maximum effect at 400 mg and still effective at 18 hr.

Table 1. Effects of Barbiturates on Performance (Continued)

Authors	Number and Population	Drug	Dose	Type of Administration	Test	Effects	Conclusions
Dalton, et al., 1975	12 normals	secobarbital marihuana (THC)	150 mg/70 kg 25 mg/kg		Pulse Stability of stance. Pursuit meter Delayed auditory feedback (5 tests) Manual coordination ("suitcase" test) Modified Cornell Medical Index Tapping	Combination effect elevated pulse. Combination additive; decreased stability. Combination increased scores. Combination additive; produced significant impairment. Secobarbital. Combination increased subjective effect. Secobarbital decreased number.	Effects caused by marihuana not changed by presence of secobarbital but the combination is additive.

Table 2. Effects of Diazepam on Performance

Authors	Number and Population	Dose	Type of Administration	Test	Effects	Comparative Drugs
Lawton & Cahn, 1963	20 normals	5 mg tid for 3 days; 1 dose 4th day	C p.c.	Cancellation of e's speed Pegboard test DSST Addition	No significant effect. Some impairment. No significant effect. No effect.	ethanol
Masuda & Bakker, 1966	30 high anxiety, 30 low anxiety normals	10 mg 20 mg	A p.o.	Galvanic skin response Written math test A with shock and with white noise	Significant effect. Impairment.	none
Besser & Duncan, 1967	10 normals	10 mg	A p.o.	Auditory flutter fusion Decrease of CFF	Decreased threshold. Decreased threshold at 30 minutes, at 8 hours	chlorpromazine amylobarbitone quinalbarbitone
Jaattela et al., 1970	270 normals	10 mg	A p.o.	Reflex counter DSST Digit span Physical activity	No effect. No effect. Significant decrease. Significant decrease.	diphenhydramine
Brunia, 1972	24 normals	10 mg	A i.v.	Hoffman reflex Achilles tendon reflex	Nonsignificant decrease in amplitude during a mental task.	none

Table 2. Effects of Diazepam on Performance (Continued)

Authors	Number and Population	Dose	Type of Administration	Test	Effects	Comparative Drugs
Linnoila & Mattila, 1972, reconfirmed Linnoila, 1973	400 normals 360 normals	5 mg 10 mg	A p.o.	Driver simulator: Reaction time Coordination Attention	Impaired. Increased latency. Increased mistakes. No effect.	chlordiazepoxide thioridazine haloperidol flupenthixole alcohol
Haffner et al., 1973	normals	10 mg 20 mg	A p.o.	Letter cancellation Sorting CFF Coordination Mirror-tracing Clinical signs	Decrease at 10 mg and 20 mg. Decrease 20 mg. *Decrease in threshold.* Decrease in performance. Increased time needed. Memory impaired.	ethanol
Marjerrison et al., 1973	26 normals	10 mg	A p.o.	Attention Mood	Significant impairment. Significant decrease.	clorazepate
Milner & Landauer, 1973	12 normals	10 mg	A p.o.	Dot tracing Pursuit rotor Tapping Driving simulator	No effect. No effect. No effect. No effect.	none
Borland & Nicholson, 1974	5 normals	10 mg	A p.o.	Adaptive tracking Reaction time	Impaired latency. Increased initially. Decreased at 9.5 hr.	chlordiazepoxide clobazam

Table 2. Effects of Diazepam on Performance (Continued)

Authors	Number and Population	Dose	Type of Administration	Test	Effects	Comparative Drugs
Linnoila & Hakkinen, 1974	70 normals	5 mg 10 mg	A p.o.	Driving simulator Pulse rate Subjective ratings	Drove too fast. Increased. Impaired.	 codeine alone w/alcohol
Dureman & Norrman, 1975	24 normals	15 mg 5, 10, or 20 mg	C p.o.	Simulated driving: Steering precision Brake reaction time Saccadic eye movement	No effect. No effect. Increase in duration. Decrease in velocity.	none
Ghoneim et al., 1975	10 normals	10 20 mg	A i.v.	Tapping Reaction time, simple and choice Short term memory Delayed recall Benton visual retention test Digit span Serial learning	Significant impairment. No effect. No effect. Significant impairment. Significant impairment. Significant impairment.	none
Kortilla & Linnoila, 1975	11 normals	10 mg	A IM	CFF Choice reaction time Tracking tests	No effect. Decrease in cumulative time at 5 hours. Increased mistakes up to 5 hours.	meperidine

Table 2. Effects of Diazepam on Performance (Continued)

Authors	Number and Population	Dose	Type of Administration	Test	Effects	Comparative Drugs
Kortilla, 1976	12 normals	0.15 mg till 5 mg at 1 min	A i.v.	Choice reaction time	Increase in latency.	none
				Coordination:		
				Walking straight line	No effect.	
				Picking up matches	No effect.	
				Countdown test	No effect.	
				Rotary nystagmus	No effect.	
				Bender Gestalt test	Decrease, not significant.	
				Speech	Slurred.	
Molander et al., 1976	6 normals	5, 10, 20, 40 mg	A p.o.	CFF	Decrease threshold at 20, 40 mg.	methylperone
				Coordination	Decrease at 20, 40 mg.	oxazepam
				Mood-alertness	Increase at 5 g.	
				Concentration	Decrease.	
Saario et al., 1976	75 outpatients	5-10 mg for 14 days tid	C p.o.	Choice reaction time (driving)	Increased mistakes initially; at 14 days less evident.	lorazepam medazepam
				Proprioception	Increased response on day 14.	
				Coordinated skills	Impairment.	
				CFF	Threshold decreased.	
Seppala et al., 1976	10 normals	10 mg	A p.o.	Reaction time (driving)	Increased latency.	medazepam lorazepam
				Coordination	Increased mistakes.	
				CFF	Decreased threshold.	
				Perceptual speed	Decreased # lines.	

Table 2. Effects of Diazepam on Performance (Continued)

Authors	Number and Population	Dose	Type of Administration	Test	Effects	Comparative Drugs
Jones et al., 1978	78 normals	5 mg	A p.o.	Short term memory Visual search	Significant impairment. Significantly fewer letters.	none
Kortzan, 1978	20 normals	10 mg	A p.o.	Choice reaction time Random digit (memory) Pupil dilation	Significant increase. Significant impairment. Less than placebo.	chlorpromazine
Liljequist et al., 1978	20 normals	10 mg	C p.o.	Learning tasks Association pairs Acquisition test Tracking Choice reaction time CFF	Significantly impaired. Recall impaired. Not significant. Mistakes increased. Decrease in time. Decrease in threshold.	chlorpromazine

Table 3. *Effects of Benzodiazepines and Miscellaneous Agents on Performance*

Authors	Number and Population	Drug	Dose	Type of Administration	Test	Effects	Conclusions
Kaplan, et al., 1968		ethchlorvynol glutethimide secobarbital	500 mg 500 mg 500 mg	A p.o., h.s. aroused from sleep and a.m.	Pursuit meter, 4 patterns Verbal output Reverse reading Reverse counting Progressive counting Addition Subtraction Addition of 7 Subtraction of 7 Color discrimination	Glutethimide worst; secobarbital best. Glutethimide worse than ethchlorvynol. Glutethimide worse than ethchlorvynol. Slight effect. No effect. No effect. Glutethimide, significant effect. No effect. No effect. Ethchlorvynol, significant effect.	The levels are glutethimide, secobarbital, and ethchlorvynol, with significant effects at 4 hr and lessening of those effects at 8 hrs. Mental tests were not consistently impaired but motor tests were. Subjective evaluation results were inconsistent.
Holgate, 1973	4 normals	diazepam sodium amobarbital methylphenidate	5 mg 25 mg 10 mg	i.v.	Human operant performance	Most errors with sodium amobarbital and methylphenidate. Diazepam produced significantly more errors than saline but less than other two. Sodium amobarbital has hangover effect.	Drug effects and individual variability prevent any conclusions.
Strasser, 1973	10 normals	oxazepam	20 mg	A p.o.	80 dB noise, difficult working conditions Pursuit rotor Heart rate	Noise had no effect. Deterioration significant. Depression of rate but not significant.	Tranquilizer effect. Oxazepam facilitated performance under severe stress but without stress it diminished mental capacity.

Table 7. Effects of Benzodiazepines and Miscellaneous Agents on Performance (Continued)

Authors	Number and Population	Drug	Dose	Type of Administration	Test	Effects	Conclusions
Ashton, et al., 1974	35 students	nitrazepam caffeine cigarette smoking	25 mg 300 mg	A p.o.	CNV VEP Heart rate Blood pressure	Decrease in amplitude. Decrease in amplitude of N_1P_2 at maximum drug effect. No effect. No effect.	Less than with caffeine and nicotine.
Gale, 1976	16 normals 7 8 8	methohexitone halothane and N.O. short N.O. long diazepam and local analgesia	1.51 mg/kg 0.31 mg/kg	i.v. inhaled inhaled	Reaction time: Auditory Visual Static ataxia Tracking Arithmetic Stroop test	Impaired by methohexitone and diazepam. Results inconsistent. Impaired by all but short term halothane. Accuracy impaired but speed only in diazepam. Impaired by diazepam in incongruous word test.	There is evidence that recovery time is related to doses in diazepam and was prolonged and still incomplete at 3 hr.
Hindmarch, 1977	30 normals	nitrazepam flunitrazepam flurazepam	5 mg 1 mg 15 mg	C, h.s. p.o.	Choice reaction time CFF Serial subtraction by 7's Subjective quality of sleep	No effect. No effect rebound (after withdrawal flunitrazepam and flurazepam). Significant effect on number of correct responses. Perceived to improve with flunitrazepam.	Subclinical doses can produce a hangover effect the next morning.
Saario, 1976	20 volunteers (19 male, 1 female)	bromazepam	6 mg	C p.o.	Coordination 1 test Choice reaction time CFF Proprioceptive test Divided attention test	 Increase at 30 min. Decrease at 30 min. No significant effect. Decrease in correct responses.	Effect of these subacute drugs with minimal effect showed considerable deterioration with ethanol.

Table 3. Effects of Benzodiazepines and Miscellaneous Agents on Performance (Continued)

Authors	Number and Population	Drug	Dose	Type of Administration	Test	Effects	Conclusions
Hindmarch et al., 1977	10 volunteers	clobazam	20 mg	C p.o.	Choice reaction time DSST Car driving: Estimation of width Reverse parking Garaging a car Maneuvering ability	No effect. No effect. No effect. Worse than placebo. No effect. No effect.	True driving test. Quality of sleep does not affect early morning behavior.
Clarke A Nicholson, 1977	6 normals	nordiazepam diazepam	5 mg 10 mg	A p.o.	Visuomotor coordination	Nordiazepam caused impairment at 6.5 hr. 10 mg impaired at 0.5 hr; 2.5 hr.	Brief, unclear paper.
Peck et al., 1977	10 light and 10 sound sleepers as measured by latency	nitrazepam	2.5 mg 5 mg 10 mg	A p.o.	Auditory reaction time Auditory vigilance Tapping Short term memory DSST	Light sleepers improved; sound sleepers no effect. Light sleepers improved; sound sleepers improved. Light sleepers improved; sound sleepers no effect. Light sleepers decreased; sound sleepers no effect. Light sleepers improved.	Improvements in dull, monotonous tasks.
Lahtinen et al., 1979	34 normals	clobazam	10 mg 5 mg at 5 hr	A p.o.	Manual skills Reaction time Grip strength Subjective ratings	Exact skills impaired by 10 mg. No effect. No effect.	Residual effects overnight.

Table 3. Effects of Benzodiazepines and Miscellaneous Agents on Performance (Continued)

Authors	Number and Population	Drug	Dose	Type of Administration	Test	Effects	Conclusions
Parrott & Hindmarch, 1978	8 normals	clobazam	10 mg 20 mg	A p.o.	OFF Complex reaction time with low reinforcement High reinforcement Personality tests	No effect. 10 mg significant effect early, none late. Speed change early with 10 mg. Differential effects.	Subjects with high anxiety perform better with high-reinforcement performance.
Church & Johnson, 1979	12 poor sleepers 12 good sleepers	flurazepam	30 mg	C (10 days) p.o., h.s.	POMS Mood scale (neuro-psychiatric) Digit span DSST Choice reaction time (Wilkinson) Sleep	No effect. No effect. No significant difference. Significant decrease, then improvement-drug tolerance effect. Significant increase.	Cognitive tests and subjective states were affected, but no significant differences occurred in any of the mood scales.

Table 4. Effects of Meprobamate on Performance

Authors	Number and Population	Dose	Type of Administration	Test	Effects	Comparative Drugs
Kornetsky, 1958	8 normals	800 mg 1,600 mg	A p.o.	Serial reaction time Choice reaction time Simple learning	Impaired at 1,600 mg. Impaired at 1,600 mg. Impairment at both doses.	phenobarbital d-amphetamine
Townsend & Mirsky, 1960	8, 10 normals	800 mg 1,600 mg	A	CPI DSST	Not impaired. Impaired-similar to phenobarbital.	phenobarbital d-amphetamine
Costello, 1962	20 normals	800 mg	A p.o.	Time estimation with feedback	No effect.	none
Lawton & Cahn, 1961	48 normals	not given	C (4 days) p.o.	Cancellations DSST Dotting test Pegboard Steadiness Portrus Maze	No effect. No effect. No effect. No effect. No effect. Time increased in Listica-meprobamate group.	hydroxephenamate (Listica)
Margolis, 1966	21 normals	400 mg	A p.o.	Paired associates (two lists learned)	Interference from earlier list decreased.	none

Table 4. Effects of Meprobamate on Performance (Continued)

Authors	Number and Population	Dose	Type of Administration	Test	Effects	Comparative Drugs
Misiak et al., 1965	5 normals	400 mg 800 mg	A. p.o.	CFF	Equivocal effects.	none
Figarola & Billings, 1966	6 normals	400 mg	C p.o., tid	Tracking test Vigilance test Problem solving Combination of 3 tests	Increased mistakes. No effect. No effect. Effect at 8,000 ft.	
Jansson et al., 1966	12 normals	1,200 mg	A. p.o.	Pupil size CFF Apparent motion test Heart rate Blood pressure Choice reaction	No effect. Decreased threshold. Decrease. No effect. No effect. No effect.	trioxazine

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6. EFFECTS OF HALLUCINOGENS ON HUMAN PERFORMANCE

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HALLUCINOGENS

DEFINITIONS

Strictly and etymologically speaking, a hallucinogen is a drug that produces a hallucination. The word hallucination, in turn, comes from the Latin hallucinari, meaning to dream or to wander in mind. To the extent that drugs produce a wandering in mind or attention, most if not all psychoactive drugs can become hallucinogens at suitable dosages. Even if the definition is restricted by current psychiatric opinion to the production of false sensory impressions in the absence of external stimuli (this can occur in any of the senses), the term hallucinogen is not completely satisfactory since it overemphasizes the perceptual elements of the response to these drugs. Other unsatisfactory terms applied to these drugs include psychotomimetic (psychosis mimickers), psychotaraxics (mind disturbers), psychedelics (mind expanders), and delirients (delirium producers). However, in both pharmacological and psychological tradition, hallucinogens have come to refer to those drugs that in nontoxic doses produce changes in perception, mood, and thinking.

CAVEAT

There is a traditional belief among many people that hallucinogens are magical elixirs that magically transform people's behavior. On one extreme, some people believe that minutes or hours after taking a particular hallucinogen, LSD for example, users become wild and confused psychotics who are no longer in control of their behavior. On the other extreme, some people believe that after taking the same drug, the user becomes a fully self-actualized, creative artistic genious capable of wondrous feats and thoughts. Hallucinogens do not work in such magical ways despite the continuing presence of these two belief systems. Rather, they work as a resultant combination of both pharmacological and psychological variables. Psychological variables include the personality of the user, set (expectation and attitude), setting (environmental variables), and previous drug experiences. Pharmacological variables include preparation, purity, dosage form, route of administration, time course of action, absorption and distribution in the body, rate of metabolism, rate of inactivation, and rate of elimination, among other factors. The resultant myriad of drug-induced changes in behavior cannot be understood fully unless all of these underlying variables are specified. Furthermore, recent advances in neurochemical research suggest that many hallucinogenic effects on behavior are mediated by neurochemical events and that these relationships are reciprocal in the sense that changes in one may affect the state of the other. If all of these possible combinations and permutations appear hopelessly confounded, it

should simply caution us against making any premature generalizations about hallucinogenic effects, especially on performance. The presence of all these drug and user variables should temper our initial desire to simplify the psychopharmacology of hallucinogens and encapsulate it in misleading cliches (e.g., "LSD helps you solve problems more creatively," "Mescaline gives you more energy," or "Psychedelics improve communication"). Such attempts in the past have probably contributed to the belief in hallucinogens as magic and, indirectly, to the need for this review.

THE HALLUCINOGENS

Many plants and some fungi produce hallucinogenic alkaloids as defensive mechanisms to deter herbivores from eating them. The hallucinogenic chemicals give the plants a bitter taste and, when ingested, produce a wide range of physiological and psychological aversive effects including dizziness, nausea, and even convulsions. Accordingly, in an evolutionary sense, plants have survived by producing these compounds and animals have survived by learning to avoid these compounds, by eating them sparingly, or by developing effective livers with which to detoxify the drugs and eliminate them rapidly from the body. Nonetheless, contemporary humans continue to use hallucinogens, primarily in plant forms.

The major plant hallucinogens (Schultes, 1976) used recreationally (to varying degrees) today are:

1. Hallucinogenic mushrooms
    a. Amanita muscaria (fly agaric) containing ibotenic acid, muscimole, and muscazone.
    b. Conocybe spp., Paneolus spp., Psilocybe spp., and Strophana spp. (magic or sacred mushrooms) containing psilocybin and psilocin.
2. Hallucinogenic cacti
    a. Trichocereus pachonoi (San Pedro) containing mescaline.
    b. Lophophora williamsii (peyote) containing mescaline.
3. Cannabis (marihuana and hashish) containing tetrahydrocannabinols and related active constituents.
4. Solanaceae or nightshade family of plants
    a. Atropa belladonna (belladonna) containing hyoscyamine, scopolamine, and atropine.

b. Hyoscyamus niger (henbane) containing hyoscyamine and scopolamine.

c. Mandragora officinarum (mandrake) containing hyoscyamine and scopolamine.

d. Datura spp. (angel's trumpet or devil's trumpet or jimson weed or thorn apple) containing atropine and scopolamine.

5. Banisteriopsis caapi and Banisteriopsis inebrians (ayahuasca or caapi or yage) containing harmine, harmaline, and tetrahydroharmine.

6. Morning glory seeds

a. Rivea corymbosa (ololiuqui, flying saucers, summer skies, blue star) containing alkaloids similar to LSD including ergine and isoergine.

b. Ipomoea violacea (tlitliltzin, heavenly blue, pearly gates, or wedding bells) containing ergine and isoergine.

7. Miscellaneous

Numerous other plant hallucinogens are used recreationally including catnip (nepetalactone oils), nutmeg (myristicin and elemecin oils), ginger, and cinnamon. In addition, obscure hallucinogenic plants from both South America and Africa are gradually being introduced to experimental recreational users elsewhere in the world.

A number of hallucinogenic chemicals have been synthetically prepared and are employed in recreational settings. The major ones include:

1. LSD (lysergic acid diethylamide)
2. Mescaline
3. DMT (dimethyltryptamine)
4. DET (diethyltryptamine)
5. STP or DOM (2,5-dimethoxy-4-methyl-methylphenethylamine)
6. MDA (3,4-methylenedioxyamphetamine)
7. Substituted hallucinogenic amphetamines (MMDA, MDM, PMA, TMA, DOEM, DOB)
8. PCP (phencyclidine)

HUMAN STUDIES

SENSORIMOTOR FUNCTIONS

General Activity

There are many studies of hallucinogenic effects on general activity in animals. The findings are supported by a smaller number of careful investigations using a small number of human subjects taking fixed dosages. Nonetheless, these human studies have been replicated by several laboratories (Hoffer & Osmond, 1967; Hollister, 1968; Sandoz Pharmaceuticals, 1968; Sankar, 1975). More human research is still necessary to confirm the effects of small doses of hallucinogens as well as the ever-increasing variety of the drugs themselves.

Most hallucinogens, with the exception of the rarely abused scopolamine and atropine, have a number of physiological effects in common. These effects include: mydriasis, elevated heart rate and blood pressure, hyper-reflexia, tachypnea, increased muscle tension, occasional ataxia, nausea and vomiting, salivation, lacrimation, leukocytosis, and increased sensitivity to internal and external stimuli. Most of these effects are concomitants of physiological arousal. Stimulation of the autonomic nervous system and central nervous system is noted for mescaline, LSD, and structurally related compounds such as the substituted amphetamines.

Following moderate doses of LSD, mescaline, or similar compounds, human EEG's are altered, albeit not dramatically, typically showing low amplitude, high frequency. This indicates general neurophysiological arousal (Goldstein, 1963). At low doses, LSD lowers the threshold for cortical arousal produced by noises or brain stimulation. With higher doses high voltage slow rhythms often result, and the arousal threshold may be raised. Thus, low doses of LSD result in hyper-reactivity whereby responses to stimuli can be exaggerated. Higher doses are more associated with lowered activity levels (lethargy, drowsiness) whereby responses to stimuli are greatly diminished, if not eliminated completely, and activity is greatly reduced. Nonetheless, even at high doses, the brain itself is in a state of hyperarousal and much cognitive activity continues to occur within the subjective experience of the subject. Objectively, little activity appears to occur.

Wake-Rest Cycles

Relatively few systematic studies have been done on hallucinogenic effects on sleep, dreams, and other wake-rest cycles. The primary reason is that the hallucinogens exert strong stimulant

effects and it is difficult to obtain experimentally reliable sleep or rest states following their administration. Most of the research has been done with LSD, and the other hallucinogens, although probably similar to LSD in these effects, remain to be investigated.

Sleep. In one early study (Green, 1965), LSD was shown to increase dream time even though the dream periods on the LSD night were different from other nondrug nights. LSD caused a marked delay in the onset of dreaming after sleep and an increased gross body reading on galvanic skin resistance (GSR). After the onset of sleep, a repetitive cyclic pattern in the GSR occurred during the sleep-dream cycles. These early findings have generally been confirmed by later well-controlled studies (Sankar, 1975). In a study (Sankar, 1975) with normal subjects, LSD, in a wide range of doses, increased the duration of dream sleep (REM periods) from 24 percent to 245 percent compared with placebos. There were also increases in body movements during sleep and frequent arousals which were related to the REM periods.

Another well-controlled study investigated the effects of LSD taken after one or two nights' loss of sleep (Safer, 1970). Here it was observed that the onset of characteristic LSD behavior and attentional impairments was more rapid in those men who received LSD after loss of sleep than those given LSD after normal sleep. The sleep-loss subjects showed inaccuracies in problemsolving and vigilance tests not shown by control subjects. Thus, sleep deprivation appeared to increase dramatically the effects of LSD on performance.

Rhythms. Animal studies provide considerable evidence that administration of LSD leads to regular cyclic fluctuations of several psychobiological activities, including walking by goats, rope climbing by rats, aggressive displays by mice, limb flicking and jerking by cats, and fear and aggression in monkeys. The cyclic nature seems to be dependent on the species while the amplitude is dose dependent, but not dependent on blood levels of LSD.

In human studies (Hoffer & Osmond, 1967; Sankar, 1975), administration of LSD leads to cyclic fluctuations in rectal temperature, pupillary size, attentional disturbances, hallucinations, and urinary excretion of several metabolites. These effects also appear to depend on dose and time course of action. The fluctuations in imagery and other hallucinatory phenomena appear the same for all hallucinogens.

Work Capacity and Endurance

No studies are available on the effects of hallucinogens on work capacity or endurance in humans. However, a number of physiological studies on humans and behavioral studies on animals are relevant to understanding these performance variables.

Despite the often dramatic psychological effects of hallucinogens in humans, studies (Hollister, 1968) with LSD have found no concomitant changes in cerebral blood flow, vascular resistance oxygen or glucose utilization, or respiratory quotient. There was, however, a small increase in mean arterial blood pressure and a moderate increase in arterial hemoglobin in concentrations (Sankar, 1975). Thus, oxygen consumption and endurance could be (theoretically) increased under LSD. Animal studies have indicated that these effects would be intricately and unpredictably involved with endocrine functioning.

In studies of wheel running with rats, small doses of LSD did not affect the mean running time. However, with the introduction of novel stimuli, the running time of treated rats was significantly longer. This result does not appear to be related to effects on muscular activity but on the animal's ability to work around a new hurdle or to become distracted. High doses of LSD, however, significantly reduce activity in rats as measured by wheel running, rope climbing, and other tasks. Other animal behaviors that require high capacity for work as well as endurance, such as nest building in mice, are also impaired by LSD. In general, hallucinogens appear to impair sustained goal-directed work in animals and to increase the time necessary to run mazes. Even under survival motivation, as when rats are tested in water mazes requiring them to swim underwater in order to escape and thereby survive, goal-directed behavior is substantially slowed down with high doses (Uyeno & Benson, 1965). Low doses may facilitate work performance on simple tasks.

Sensorimotor Coordination

Simple reaction time is significantly prolonged by low doses of LSD (Orsini & Benda, 1959). Conversely, other psychomotor functions may be enhanced, for example, an improvement in skill on the rotary pursuit test with low doses of LSD (Rosenbaum, Cohen, Luby, Gottlieb & Yelen, 1959). A dual pursuit task, in which two pointers, one horizontal and one vertical, must be kept fixed on a moving object, revealed significant impairment under LSD which cleared after 5 hours (Silverstein & Klee, 1960). This latter effect occurred at a time when all mental effects of the drug might be waning, and the results can be interpreted as due mainly to difficulty in concentration during the early learning period. Low doses of LSD also cause a moderate deterioration both in the time required and in the accuracy of a test of mirror-image drawing (Orsini & Benda, 1960). In more complicated sensorimotor tasks, LSD slowed down the pace of handwriting, addition, and dealing of playing cards, but the drug did not affect the pace of tapping or of drawing lines.

In a series of studies with several hallucinogens (Fischer, Kappeler, & Wisecup, 1970; Fischer, Thatcher, & Kappeler, 1969), it has been determined that these drugs increase the area used

in handwriting while they concomitantly decrease the motor force necessary for handwriting. This has been interpreted as an increased sensory-to-motor ratio whereby there is a predominance of sensory-mental experiences (increase in handwriting area) at the expense of voluntary motor performance (decrease in handwriting force). In other words, subjects gradually shift their attention from outward tasks and stimuli to inner sensory experiences. As the dose of the hallucinogen is increased, the shift increases, thereby impairing performance on normal sensorimotor tasks but increasing subjective cognitive experiences. There appears to be some electrophysiological evidence for changes in brain electrical activity that may account for this phenomenon (Siegel & West, 1975).

Summary

A paucity of information exists concerning the effects of hallucinogens on human sensorimotor function. There is abundant evidence from several clinical studies indicating that hallucinogens induce states of general neurophysiological arousal (e.g., Gastaut, Ferrer, Castelis, Lesevre, & Lushnat, 1953; Goldstein, 1963; Hidalgo, 1960; Sankar, 1975), but how such effects translate into effects on general activity or wake-rest cycles is basically unknown at this time. There appears to be good evidence that LSD increases dream time, but the clinical significance of this finding is vague. No information is available on the effects of either LSD or other hallucinogens on work capacity and endurance, and speculations stemming from the animal literature, which suggests varying effects depending on the type of task, deserve to be more fully investigated in controlled human studies.

The studies on sensorimotor coordination are poor and lack testing of high doses of LSD as well as other hallucinogens. There is evidence that LSD impairs simple reaction time (Orsini & Benda, 1959) and other tests of sensorimotor coordination (Orsini & Benda, 1960; Rosenbaum et al., 1959; Silverstein & Klee, 1958). However, most of these studies did not control for time or dosage variables, and the use of basic simple psychomotor tasks is of dubious significance to clinical situations. The findings that several hallucinogens change sensorimotor variables used in a handwriting task are more certain (Fischer, Kappeler, Wisecup, 1970; Fischer, Thatcher, & Kappeler, 1969) but, again, they are of questionable significance to understanding effects on performance.

COGNITIVE FUNCTIONS

Perception, learning, and thinking have traditionally been referred to as the cognitive processes since they all deal, to some extent, with the problem of knowledge. Perception can

generally be defined as the process by which an organism receives or extracts certain information about the environment. Learning is defined as the process by which this information is acquired through experience and becomes part of the organism's storage of facts. Thus, the results of learning facilitate the further extraction of information because the stored facts become models against which cues are judged. The most complex of these cognitive processes, namely, thinking, is an activity that is inferred to be going on when an organism is engaged in solving problems, which also involves the use of models.

The solution of complex problems requires the use of mediating symbols like language, mathematics, or some other powerful tool. The difficulty of the problem can be determined by the relative ease with which the information required for its solution can be extracted. An individual who can extract the information almost immediately has no problem. The problem becomes more difficult as the potential information is less available or more abstract. We extract abstract or more hidden information by using concepts. The greater our conceptual abilities, the better are our general problem-solving abilities.

In general, moderate doses of hallucinogens impair complex discrimination tasks, but simple tasks are more resistant. Immediate memory is impaired, whether measured by ability to draw geometric figures from memory, remembrance of digits or paired words, or many other tests. A low dose of LSD markedly impairs the ability of subjects to repeat a numerical series backwards and forwards (Orsini & Benda, 1959). Simple problem solving, such as simple additions or serial subtraction, tests of spatial relation abilities, attention and concentration, recognition and recall, and color naming and color reading are also impaired (Weintraub, Silverstein, & Klee, 1959). LSD produced more errors and slower reactions in a word association test than control drugs; it also abolished the differential response to emotionally traumatic and nontraumatic stimuli (Weintraub et al., 1959). In other words, LSD appeared to bland affect to external stimuli this test. Using three tests of part-whole relationships (Heiss-Sandler figure, Muller-Lyer illusion, and circle illusion), researchers found that a small dose of LSD caused subjects to operate at a less mature level (Krus & Wapner, 1959). The Porteus maze test, construed as a test of ability to inhibit impulsive solutions and to execute critical planning, revealed that subjects using the drug lacked the ability to carry out well-planned and adaptive behavior (Aronson & Klee, 1960). Abstract thinking, as measured by the Gorham Proverbs Test, was significantly impaired by small doses of LSD. Incorrect abstractions were more common than concrete responses (Silverstein & Klee, 1958). Close analysis, in which typescripts of speed with every fifth word deleted were completed by subjects in one experiment to test the effects of LSD on understandability of speech. LSD impaired understandability in this test (Honigfeld, 1965). Also, much clinical evidence suggests that critical judgment is markedly impaired in

subjects using LSD; however, actual testing of this observation has rarely been done. For example, despite a demonstrable decrement in intellectual function, most subjects given hallucinogens think their abilities are enhanced.

Thus, the evidence is overwhelming that any dose of hallucinogens with appreciable clinical effects is quite likely to impair most or all intellectual functions as assessed by standard psychometric instruments and tests. These effects do not represent a primary effect on brain mechanisms for intelligence. Rather, they simply represent the secondary result of a diminished ability to attend, to concentrate, and to maintain motivation. Subjects are more preoccupied with subjective than with objective experiences.

Attention

Although the objective studies, primarily conducted with LSD and summarized above, indicate that hallucinogens impair attention to objective stimuli, ample clinical evidence demonstrates that a subject's attention is shifted to internal stimuli thereby enhancing awareness of bodily sensations and processes (Siegel & West, 1975). Performance on standard cognitive tasks can be impaired, but concomitantly the subject experiences a rapid flow of ideas and images. These sensations may alert subjects to notice things that they would not otherwise notice and to see old and familiar stimuli in a new (novel) light. Thus, although subjects may experience negative hallucinations (not see things that are in fact present), they may also notice details of stimuli that normal observers may overlook or gloss over. Thus, subjects may report that visual, auditory, and other sensory modalities are enhanced and that these new perceptions so distract them that their cognitive performance on standard tests is impaired.

Problem Solving

Objectively, problem-solving ability is impaired by clinically effective doses of hallucinogens. However, the phenomenology of the subjective experience indicates that many users report new insights into problems, creative thoughts, novel associations, and new solutions to longstanding personal and intellectual problems. Most objective tests of this creative problem-solving ability fail to prove that artists, for example, are more creative under LSD or mescaline. However, verbal creativity does appear to be improved. To the extent that problem solving is based on new associations between thoughts and images, hallucinogens do provide a rich data base of such experiences with which individuals may subsequently solve problems. This approach has been utilized in psychotherapy with hallucinogens and appears to have some therapeutic benefit.

Information Processing

Objectively, information processing appears to be impaired by hallucinogens. Subjectively, relatively impaired information processing can isolate images and thoughts and evoke an alien quality that contributes to the prototypic hallucinatory experience. Impairment of information processing probably accounts for the experiencing or labeling of some quite dim and fleeting images as hallucinations. States of general cognitive impairment, high conflict, stress, or great need for fantasy gratifications will increase the likelihood of such episodes. Hallucinogen-induced disruption in short term memory can lead to a retrospective hallucination--that is, a misjudgment about a remembered image. Such dim images and retrospective errors are frequent during hallucinogenic intoxication because the more dramatic sensory effects occupy the subject's attention.

Decisionmaking

No direct tests have been made of the effects of hallucinogens on decisionmaking in either animals or humans. However, the clinical descriptions of hallucinogenic intoxication indicate that many subjects feel that decisions are difficult to make during acute intoxication. Decisions considered during hallucinogenic episodes can often be carried out with stronger emotional conviction after the acute symptoms have worn off.

Communication Skills

In a number of clinical studies (Sankar, 1975), both LSD and psilocybin have been shown to significantly slow and reduce verbal responses (Honigfeld, 1965). For example, speech under LSD is marked by pauses, shortened phrases, and incomplete phrases. In addition, LSD and psilocybin appear to decrease volubility and communicability of speech that is not suppressed. LSD also causes an impairment in the ability to learn and to retain connected verbal material. LSD impairs the ability to understand verbal communication and spontaneous speech; the effects of other hallucinogens on this behavior have not been assessed.

In group studies, changes in formal characteristics of interaction and communication were studied in normal subjects under LSD (Slater, Morimoto, & Hyde, 1963). The quantitative aspects of verbal output and interaction rate were measured (distribution of verbal activity, frequency and tempo of participation, duration of verbal utterance, and direction of communication). After administration of LSD, the average duration of verbal statements decreased and the number of nonverbal behaviors increased. These effects altered social relationships in unpredictable ways.

Complex Simulation Environments

No animal or human studies in this area are available.

Summary

A number of well-done studies (e.g., Hollister, 1968; Honigfeld, 1965; Orsini & Benda, 1959; Weintraub et al., 1959) indicate that hallucinogens, when administered in dosages with appreciable clinical effects, will impair cognitive functions. However, the tests used in these studies have since been replaced by more sensitive and informative psychometric instruments designed to measure drug-induced changes in cognitive tasks that are more reflective of human intellectual functioning. Thus, renewed studies are indicated. In addition, previous research has strongly indicated that the major effect of hallucinogens is on attentional processes. Furthermore, these attentional changes appear to underlie subsequent changes in problem-solving, information-processing, decisionmaking, and communication skills. The nature of these changes needs to be precisely determined in controlled studies with various hallucinogens and varying dosages, instead of the fixed doses of LSD that have generally been administered. In addition, the apparent shift in attention from external to internal events needs more precise description in terms of both verbal and nonverbal behavioral assessments. No studies exist on complex simulation environments; these kinds of studies also need to be done with low dosages that accurately reflect human recreational patterns of use.

DRUG STATES

PREFACE

No animal or human studies have been done on performance as a function of hallucinogenic drug state in terms of the variables of acute drug effects, chronic drug effects, time-course effects, withdrawal/termination effects, interactions with stressors, or drug-drug interactions. Nonetheless, an understanding of the clinical symptoms associated with hallucinogenic drug states may help to explain and clarify those performance effects discussed above. Controlled human studies are quite necessary here in order to assess precisely performance as a function of drug state. As it stands now, the data discussed above have been generated from single-dose studies in which subjects are tested during acute intoxication, usually at a fixed interval following drug administration. No other acute drug variables, time variables, or chronic use variables have been studied systematically. Such research is needed for a full understanding of these effects.

OVERVIEW

Although may variables external to the drugs themselves influence the clinical reactions to hallucinogens, three of the more commonly studied agents (LSD, mescaline, and psilocybin) produce similar drug states when given in equivalent doses. The chief somatic symptoms include dizziness, weakness, tremors, nausea, drowsiness, paresthesia, and blurred vision. The perceptual symptoms of most dramatic effect include altered shapes and colors, difficulty in focusing vision, sharpened sense of hearing, and synesthesia. The psychological symptoms commonly observed include alterations in mood, tension, distorted time sense, difficulty in expression, dreamlike feelings, dissociation, depersonalization, and visual hallucinations. Common physical symptoms include dilated pupils, hyper-reflexia, increased muscle tension, and ataxia. Repeated doses of these drugs produce tolerance to the effects. Cross-tolerance between LSD, mescaline, and psilocybin has been demonstrated.

ACUTE DRUG EFFECTS

The acute physiological effects of LSD intoxication are relatively few. The most common signs are dilated pupils, hyper-reflexia, increased muscle tension, incoordination, and ataxia. Effects on pulse rate, respiration, and blood pressure are variable and relate to the subject's level of anxiety. Changes in appetite and salivation are inconstant, increasing in some users and decreasing in others. Psychological effects are largely a function of subject personality as well as set and setting. However, commonly reported effects during acute hallucinogenic intoxication include altered mood (acting silly), distorted and slowed subjective time, difficulty expressing thoughts, depersonalization and feeling detached from self and others, dreamlike state, loss of control over thoughts and feelings, difficulty concentrating, poor memory and retention, impaired judgment, rapid or recurrent thoughts, and visual hallucinations. The most commonly reported somatic feelings include dizziness, weakness and difficulty in moving, hot or cold feelings, nausea, numbness and paresthesia, body feeling lighter or heavier than normal, shaking and trembling of the body, drowsiness, decreased appetite, feeling ill, and dry mouth often with a metallic taste. The most commonly reported perceptual effects are altered shapes and colors, blurred vision, clearer visual contrasts, more acute hearing, and changes in body imagery.

The acute drug effects following mescaline intoxication are similar to those reported above for LSD. Nausea and vomiting with mescaline are more common than with other hallucinogens. Psilocybin effects are generally milder than those of other hallucinogens.

The subjective psychological effects resulting from acute hallucinogenic intoxication are often very dramatic. Subjects

frequently experience a feeling of loss of control in a number of areas with resultant fright or anger or panic because of this loss. Loss of control generally involves intellect, emotions, and body functions in equal ways. Various individual reactions to these acute effects are largely dependent on the personality of the user. One type of reaction is characterized by apathy, psychomotor retardation, and "ego constriction." Other users show euphoria, increased psychomotor activity, intensified self-awareness, and "ego expansion." Still other users may show primarily perceptual changes with no concomitant ego change. All subjects may experience psychological feelings reflecting a mixture of these reactions.

A number of adverse reactions to acute intoxication with hallucinogens have been well documented. The primary adverse reactions are anxiety and a state of fear or panic. Other less common reactions include slurred speech, depression, amotivational syndromes, paranoia, psychosis. Conversely, strong positive reactions may include religious and mystical experiences, transcendental experiences, contemplative feelings, sexual excitement and arousal, euphoria, ecstasy, and loss of aggressive motivations and behavior.

CHRONIC USE

Chronic use of hallucinogens generally leads to psychological and physiological tolerance. Tolerance can be overcome and drug effects of full intensity obtained by simply increasing dosage or waiting 4-7 days between drug administrations. Furthermore, when hallucinogens are used chronically, but intermittently, many subjects report a reverse tolerance or increased sensitivity to the drug. Consequently, these users need less dosage to achieve desired effects.

Physical dependence does not develop to the hallucinogens even after extended chronic use. Psychological dependence has been reported to occur in certain individuals who become preoccupied with the drug experience and feel emotionally depressed and unsatisfied without it. Normally, however, hallucinogen use is intermittent and periods of weeks or months may separate experiences even in confirmed chronic users.

Recurrence of certain aspects of hallucinogenic experiences (flashbacks) of varying duration and intensity has been reported over periods ranging from a few months to several years after last drug use. The quality of these experiences, which usually last only a few minutes or less, is triggered by stimuli associated with the original intoxication and is generally regarded as involuntary reminiscences, similar to strong emotional memories. Stress or other drug intoxications may trigger these flashbacks.

There are no confirmed longlasting effects of hallucinogens on normal people, although many users claim to be changed by the experiences of chronic use. For example, even though subjective reports of an increase in esthetic appreciation were supported by behavioral activities, subjects with histories of chronic LSD use showed no enhanced performance on art tests or on creativity measures.

TIME-COURSE EFFECTS

The clinical syndrome following hallucinogenic intoxication tends to follow a sequential pattern with somatic symptoms first, perceptual and mood changes next, and psychic changes last, although these phases overlap considerably. With LSD, the peak symptoms occur between 2 and 5 hours after oral administration, and the entire experience may last for only a total of 8 hours. With mescaline, the peak effects occur between 2 and 5 hours after oral administration and the entire experience lasts for approximatley 12 hours. With psilocybin, peak effects are experienced approximately 1-1.5 hours after oral use and persist for only a total of 4 hours. Depending on rates of absorption from the stomach, initial effects for all three drugs may begin within 10 minutes of ingestion and lingering effects have been reported for several days following high dosages.

WITHDRAWAL/TERMINATION

No withdrawal syndromes are associated with hallucinogens, although subjects frequently report drowsiness and lethargy following the acute effects. Paradoxically, subjects also report mental stimulation and excitement from the experience. Headaches, depression, and other mood changes are also commonly observed upon termination of the intoxication.

INTERACTIONS WITH STRESSORS

Hallucinogens interact with personality trends, unsteady reality testing, and related factors in a complex way that makes accurate predictions of a response to stressors virtually impossible. Because of drug-induced hypersensitivity to stimuli, users may have exaggerated responses to stress. It is equally possible that users may totally ignore stressful stimuli due to a preoccupation with subjective and cognitive states. Thus, in either case, reactions to stress are often inappropriate, but the direction of that reaction is unpredictable.

DRUG-DRUG INTERACTIONS

Because hallucinogens are generally stimulants, the intensity and duration of the drug states they induce can be enhanced by the additional use of other stimulants such as amphetamines, cocaine, marihuana, Ritalin (methylphenidate), caffeine, and nicotine. Conversely, sedative-hypnotic drugs and narcotics will generally suppress the intensity of the drug state and shorten its duration. Clinically, antipsychotics such as Thorazine (chlorpromazine) are used to terminate the hallucinogenic reaction, although high doses of Valium (diazepam) are also effective. Once the acute effects have disappeared, there are no significant drug interactions. However, subsequent use of stimulants or marihuana, especially during the first week following hallucinogen use, may precipitate flashbacks. Users sometimes interpret this effect in terms of becoming more sensitive to other drugs and their effects.

GENERAL SUMMARY[1]

ESTABLISHED FINDINGS

As with the other classes of psychoactive drugs, the effects of the hallucinogens vary with the user's personality, past experience and set; the setting within which the drug is administered; and a variety of physiological and drug characteristics, including dosage, purity, route of administration, and time course. Recent findings indicating that hallucinogenic effects are mediated by complex neurochemical events make attempts to specify the impact of these drugs even more difficult.

Most of the studies on hallucinogens to date have employed LSD, under limited conditions. These have generally been single-dose studies in which subjects were tested under acute intoxication, usually at a fixed-time interval following administration. Most of what is known about LSD--and the other hallucinogens as well--comes from attempts to understand clinical symptomatology, rather than from well-controlled human or animal studies.

Hallucinogens typically produce neurophysiological arousal, with a strong stimulant effect. The chief clinical symptoms seem to be a strong internal focusing of attention and a reduction of attention toward external stimuli. Evidence indicates that any dose of a hallucinogen that has an appreciable clinical effect diminishes the user's ability to attend, concentrate, and maintain motivation. These diminished abilities seem to produce pronounced defects on a wide range of cognitive and performance functions. These attentional changes seem to underlie subsequent changes in problem solving, information processing, decisionmaking, communication skills, discrimination tasks, and the like. Simpler skills in these areas seem to be less impaired by the hallucinogens than are more complex skills and behaviors. There is some evidence from animal studies that performance effects may be dose dependent, though these studies have not been replicated in humans. Low doses may result in a sort of hyperactivity where responses are exaggerated, while higher doses are associated with lowered external activity levels. It has been suggested that higher dosages produce the internal focusing of attention noted above, which may mediate these seemingly paradoxical effects.

NEEDED RESEARCH

Very little well-controlled human research has been conducted in any of the areas under consideration in this review. There is, then, a need for a variety of well-controlled studies that impose controls, especially for time-course and dosage variables, and that utilize a variety of relatively complex cognitive and performance tasks.

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[1]Prepared by a member of the Staff of Associate Consultants, Inc.

Studies are needed on the precise nature of the attentional changes caused by hallucinogens. These studies should employ a variety of hallucinogens at a number of dosages. There is a need for studies on the effects of low (clinically relevant) dosages of hallucinogens on complex stimulation environments and on tasks that are militarily pertinent.

Studies are also needed on the acute and chronic effects of hallucinogens on a variety of performance measures, as well as studies of time-course effects, withdrawal/termination effects, interaction with stressors, and drug-drug interactions.

In short, a program of controlled studies is needed that attempts to answer virtually every one of the questions concerning hallucinogens posed in these reviews.

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7. A CRITICAL REVIEW OF THE DRUG/PERFORMANCE LITERATURE ON PHENCYCLIDINE

by

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INTRODUCTION

Phencyclidine--1-(1-phenylcyclohexyl) piperidine or PCP)--has emerged as a major recreational drug in recent years. It is representative of a group of compounds that is chemically, pharmacologically, and behaviorally distinct from other classes of psychoactive compounds. PCP was originally developed in the late 1950's for medical use as a "dissociative anesthetic." It produces a characteristic anesthesia with little effect on respiratory or cardiovascular function.

During clinical trials it became apparent that emergence from PCP anesthesia was frequently complicated by unusual effects. Patients sometimes became delirious, excited, or fearful, reported hallucinatory experiences, and exhibited motor disturbances that occasionally were quite prolonged. As a consequence of these behavioral disturbances, clinical trials were discontinued and no further attempt has been made to find a medical use for this drug. However, attention was directed toward a chemically and pharmacologically similar compund, ketamine, which subsequently was approved for humans and is still in use.

Although not approved for medical use in humans, PCP was developed as a veterinary product for use in the immobilization of nonhuman primates. Concurrently with these clinical investigations of PCP as a potential anesthetic, other investigators became interested in PCP as a psychotomimetic. A number of studies examined the psychological effects of PCP (usually identified by the trade name of Sernyl) in normals and various clinical populations. In general, these studies led the authors to conclude that PCP produces a reversible schizophreniform intoxication.

In the 1960's PCP resurfaced as a recreational drug. This use of PCP has had three phases in the United States. Initially the drug emerged as a new "hallucinogen." Generally used orally, it often produced unwanted effects and quickly fell into disrepute in the drug-using subculture. During the late sixties and early seventies street samples containing PCP were generally misrepresented as other more desirable drugs, most typically tetrahydrocannabinol, mescaline, or LSD. In the mid-seventies PCP reestablished itself as a recreational drug in its own right, attracting groups of users who sought its effects. This last phase began on the west coast, and in the intervening years it has spread throughout the United States. Typically PCP is now smoked in "crystal joints" under such street names as angel dust, crystal, or commonly just PCP. It is also used by insufflation, [illegible], and (rarely) intravenously.

[illegible] is one of a series of compounds which can be termed [illegible]hexylamines. Many analogues have been synthesized (Kalir [illegible]; Maayani et al., 1974; Maddox et al., 1965; Shulgin [illegible]; Weinstein et al., 1973). Biological data exist [illegible] these, however, and only ketamine has been

demonstrated unequivocally to have a pharmacological spectrum of activity similar to that of PCP. The importance of this lack of data in the present context is that many of these analogues have found their way into street usage. Since one purpose of this review is to identify areas of needed research, it should be pointed out that although I have confined this report to the effects of PCP, the problem extends to PCP analogues as well. About these we know practically nothing. It is necessary to move forward quickly to ascertain the pharmacological, behavioral, and toxicological effects of these compounds, for they may dominate the abuse scene in a few years if efforts to control the illicit availability of PCP are successful.

Preliminary tests of behavioral activity for some of the analogues that appear in the synthesis papers (Kalir et al., 1969; Maayani et al., 1974) indicate many of them to be as active as or more active than PCP. Whether the activity is qualitatively similar to that of PCP is unknown. The possibility remains that some of the more dramatic instances of PCP toxicity seen in the clinics may have been due to one or another of these analogues. Another possibility is that products of missynthesis or precursors to PCP or its analogues may possess greater toxicity than PCP. Baily et al. (1976) have suggested just such a possibility. 1-Piperidinocyclohexane carbonitrile (PCC) is one of the intermediates in illicit PCP synthesis that can be difficult to remove completely (Shulgin & MacLean, 1976) and has been found in police seizures (Baily et al., 1976; Helinsten & Shulgin, 1976). It is apparently more toxic than PCP (Baily et al., 1976), and unpublished data by MacLean (cited by Shulgin & MacLean, 1976) suggest that chronic exposure to PCC can result in an "aggravated psychotic" condition.

ANIMAL STUDIES

We have written two reviews of this area within the last three years (Balster & Chait, 1976, 1978a). This section will be based largely on the latest of these; however, additional details can be obtained from these publications.

SPECIES DIFFERENCES IN THE BEHAVIORAL EFFECTS OF PCP

One of the most interesting aspects of the behavioral pharmacology of PCP is the obvious species differences in its gross behavioral effects. These differences were noted in the early preclinical studies of PCP by Chen and coworkers (1959). In rats and mice, PCP produces behavioral effects qualitatively similar to those of psychomotor stimulants such as the amphetamines. In rats, for example, intraperitoneal doses above 3 mg/kg produce increased motor activity, while doses between 5 and 10 mg/kg result in repetitive movements (including cage circling, side-to-

side head movements, and repetitive sniffing) not unlike the stereotyped behaviors seen with stimulant administration in this species. These behaviors differ from the effects of stimulants, however, in that the animals also are markedly ataxic. A similar constellation of behavioral effects occurs in mice, although mice are, if anything, more stimulated. At intraperitoneal doses above 3 mg/kg they race around the cage, and in the range of 10 mg/kg they run off the edge of any flat surface on which they are placed. Convulsions are not uncommon at doses above 20 mg/kg.

The amphetaminelike properties of PCP in mice have also been seen in schedule-controlled behaviors. Wenger and Dews (1976) compared the effects of PCP with the effects of d-amphetamine, pentobarbital, and ketamine, using a multiple fixed-interval fixed-ratio (mult RI FR) schedule of food reinforcements. The effects of PCP were qualitatively more similar to those of d-amphetamine than to those of pentobarbital in that at some doses both PCP and d-amphetamine increased FI response rate and decreased FR response rate. Interestingly, the effects of ketamine were also much like those of PCP and d-amphetamine. A very similar effect of PCP and ketamine on mult FI FR performance has also been reported in the pigeon (Wenger, 1976).

PCP shares other pharmacological properties with psychomotor stimulants in rodents. Like methamphetamine and cocaine, PCP increases blood pressure, promotes urination, and decreases electrically induced tonic extensor seizures (Chen et al., 1965). In short, PCP looks a great deal like a sympathomimetic that produces ataxia when studied in rodent species. This similarity of PCP to stimulants leads to the suspicion that PCP may enhance the behavioral effects of amphetamine in rats.

The gross behavioral effects of PCP in subhuman primates are substantially different from those we described for rodents. In the rhesus monkey, for example, intramuscular doses of between 0.2 and 0.4 mg/kg produce mild ataxia and a calming effect. Normally aggressive monkeys become easier to handle, and no signs of repetitive or stereotyped behaviors are seen. At doses above 0.8 mg/kg the animals are cataleptic. Nystagmus is frequent, and occasionally marked salivation occurs. Although the monkeys are immobile, they may show exaggerated limb and mouth movements; their eyes remain open and most reflexes remain intact. The animals, however, are unresponsive to environmental events. The sequence of unresponsiveness, gross ataxia, motor restlessness, and nystagmus is very similar to that produced by large doses in humans.

In spite of the differences between the effects of PCP on gross behavior in rodents and in monkeys, its effects on schedule-controlled behavior appear qualitatively similar. There has been no systematic research comparing the effects of PCP on operant behavior in various species, but some generalizations can be

made on the basis of studies using similar schedules in different laboratories. The most consistent finding so far is that PCP produces a rate-dependent effect on fixed-interval performance in mice pigeons, and squirrel monkeys (Chait & Balster, 1978a; Wenger, 1976; Wenger & Dews, 1976). Low rates of responding during the early portions of each interval tend to be increased by PCP, whereas higher rates during the later portions of each interval tend to be decreased. During the fixed-interval component of complex schedules in mice, pigeons, and squirrel monkeys, overall response rate increases can be seen at low doses, although these increases are considerably more dramatic in the mouse than in the pigeon or squirrel monkey, even though average baseline rates in all three species were comparable (0.56 to 0.74 responses per sec). PCP produces only dose-related decreases in fixed-ratio response rates in all three species.

PCP INTERACTIONS WITH OTHER DRUGS OF ABUSE

It is important to study the effects of PCP in combination with other drugs of abuse since multiple drug use is widespread, and street samples of PCP are often mixed with other drugs. Undoubtedly PCP is often used concurrently with nicotine, alcohol, and marihuana, particularly nicotine and marihuana, since PCP is often administered by adulteration of smoking materials. PCP combinations with other drugs of abuse are also likely, and the possibility of increased toxicity associated with these combinations should be thoroughly investigated.

There have been no behavioral studies of the interaction between PCP and nicotine or alcohol. Such studies are clearly indicated. Pryor et al. (1977) have completed an extensive series of experiments on the interaction between PCP and Δ9-tetrahydrocannabinol (THC) in rats. In general, PCP enhanced the depressant properties of THC. For example, acute doses of PCP, which had little or no effect when given alone, enhanced the effects of THC (1.25 to 2.5 mg/kg intraperitoneally) on conditioned avoidance responding, photocell activity, heart rate, and body temperature. On the other hand, THC antagonized the motor activity increases produced by a high dose of PCP (5 mg/kg).

PCP Interactions with Pentobarbital (PB)

We have used a PCP-PB combination for anesthesia with rhesus monkeys for years. The advantage of this combination for short surgical procedures is that the dose of PB necessary to reach a surgical plane of anesthesia is reduced twofold to threefold. As a consequence, the animals recover consciousness in substantially less time than when PB is given alone at higher doses, reducing the risk of postsurgical complications. This use of PCP-PB combinations obviously suggests that PCP enhances the depressant effects of PB; therefore, we have sought to examine this interaction in a number of species using a variety of measures. In

a recent study (Chait & Balster, 1978b) PCP was found to enhance PB lethality in mice and its behavioral effects in rhesus monkeys.

PCP Interactions with Amphetamine

As mentioned earlier, PCP shares many behavioral effects in common with psychomotor stimulants in rodents. As might be expected, therefore, we recently showed that PCP enhances the stereotyped behavior produced by d-amphetamine in rats (Balster & Chait, 1978b).

Conclusions

Since human data are lacking on drug interactions with PCP, we have to rely on animal data to estimate the problems likely to be encountered in multiple abuse situations. It appears from this animal research that PCP enhances the behavioral effects of THC, pentobarbital, and amphetamine. Although data are presently lacking, the presence of an important interaction between PCP and pentobarbital suggests that PCP may also enhance the effects of other CNS depressants such as alcohol and benzodiazepines. More research on this possibility is needed.

TOLERANCE TO THE BEHAVIORAL EFFECTS OF PCP

There also are no data on tolerance development to the behavioral effects of PCP in humans. The animal literature presents conflicting evidence on the degree of tolerance development associated with chronic PCP administration. Some evidence from the veterinary use of PCP indicates that the duration of anesthesia decreased with repeated use (Martin et al., 1972). We reported a preliminary study of tolerance development in rhesus monkeys (Balster & Chait, 1976). PCP was given daily, 7 days a week, over a period of 4 months at doses beginning at 0.2 mg/kg/day increasing to 1 mg/kg/day. Dose-response curves for PCP effects on food-reinforced operant behavior were obtained before and after this chronic regimen. In two of the three monkeys a greater than fourfold shift in the dose-response curve was obtained; however, the third monkey showed less evidence of tolerance development. In addition, the duration of observable motor disruption in these three animals after chronic PCP administration was shorter than in three untreated monkeys.

Chait and Balster (1978a) recently completed a more systematic study of the behavioral effects of chronic PCP administration in squirrel monkeys. Five squirrel monkeys were given chronic PCP at doses beginning at 0.2 mg/kg once a day increasing to 0.6 mg/kg four times a day (2.4 mg/kg/day) over a period lasting from 82 to 126 days. Prechronic and postchronic dose-response curves for the effects of PCP on operant behavior revealed approximately

a twofold tolerance development. The most dramatic indication of tolerance was in the duration of PCP-suppressed responding by a dose of 0.6 mg/kg given before and after chronic dosing. At this dose, operant behavior was suppressed for an average of 125 minutes before chronic PCP and only 35 minutes after chronic PCP.

Two more recent studies in rats confirm that tolerance to the behavioral effects can develop after repeated PCP administration (Murray, 1978; Woolverton & Balster, 1979). Both found evidence that tolerance development to PCP is due predominantly to pharmacological rather than behavioral factors.

HUMAN STUDIES

Relatively few researchers have studied the effects of PCP on human subjects, and all the experiments were completed in the late 1950's and the early 1960's. At that time, PCP abuse was unknown; consequently, no study was carried out expressly to determine the effects of PCP under conditions of abuse. None of these studies used the smoking route of administration common among abusers of PCP today. Since PCP was withdrawn from clinical trials, only one study has involved PCP administration to human subjects (Meltzer et al., 1972), and that study was designed to examine the effects of PCP on serum crestine phosphokinase and aldolase activities.

Undoubtedly a major factor limiting the experimental investigation of PCP effects in humans is that PCP is not used therapeutically; therefore, prospective researchers must obtain an investigational new drug (IND) permit from the FDA. It is unclear at this time what documentation would be necessary to obtain an IND to study PCP in behaviorally active doses. I am aware of no studies in progress of PCP in humans, and I assume that considerations relating to experimentation on human subjects are a factor in limiting this important research direction. Until these problems are solved, we will have to rely on animal research to answer the important questions that have been raised by the current epidemic of PCP abuse.

As I indicated, very few studies of the effects of PCP in humans have been conducted. These studies were carried out within the context of three research questions that prompted PCP research:

1. Clinical trials of PCP as an anesthetic or preanesthetic
2. PCP intoxication as a model of psychosis
3. The use of PCP as an abreactive agent to facilitate psychotherapy

The major portion of these studies used either simple narrative descriptions of behavior (focusing mainly on physiological

measures relevant to anesthesia) or verbal reports of the subjects. These studies are not of much relevance to the present project, but due to the paucity of other data I will review them briefly later under "Acute Drug Effects." The few experimental studies using psychological tests or behavioral assessment techniques will be reviewed in some detail in this section. A final source of information on the effects of PCP in humans is clinical studies of PCP abusers seen during or after a period of acute intoxication. Information on acute effects, chronic use, time course, withdrawal, interactions between PCP and various stressors, as well as drug-drug interactions will be discussed under "Drug States."

The remainder of this section on human studies will focus on the seven experimental studies that measured behavioral and/or psychological variables quantitatively. I will attempt to discuss these studies using the categories of human performance supplied to us. Most of these studies were multivariate, however, and therefore are included under more than one performance category. The details of the methodology will be presented only the first time the study is described. The seven studies to be reviewed in depth in this section are Bakker and Amini (1961), Beech et al. (1961), Cohen et al. (1962), Davis and Beech (1960), Morgenstern et al. (1962), Pollard et al. (1965), and Rosenbaum et al. (1959). It can be seen that they were all completed within the span of a few years about 15 to 20 years ago.

SENSORIMOTOR FUNCTION

General Activity

Under this section I will review one study of the general effects of PCP on normal human subject volunteers and three studies on the effects of PCP on sensory phenomena.

The first study to be discussed was conducted by John C. Pollard and his associates at the University of Michigan Medical School (Pollard et al., 1965). Although published as part of a book called Drugs and Phantasy in 1965, there is reason to believe that this study was actually conducted prior to 1960, since a preliminary report was published in that year (Pollard et al., 1960). This study did not use a sophisticated research design and studied only the transcribed verbal reports of subjects under the influence of PCP. What is remarkable about it, however, is the insight it provides into the subjective experience of PCP intoxication. The verbal reports of these subjects 10 years before PCP was a drug of abuse correspond very well with the types of experiences subsequently described by illicit users of PCP.

Normal college student volunteers were recruited for this study (eight were apparently given PCP, but the data from only two are presented). The subjects were placed in a "sensory attenuation situation." They were loosely strapped to a foam rubbur pad with hands placed in mitts and "white noise" broadcast through earphones. A homogeneous white field of plastic 36 inches in diameter was placed above the subjects' heads. PCP in a dose of 10 mg was administered orally. Tape recordings were made of the subjects' responses to some standard questions and their spontaneous vocalizations. The publication consists almost entirely of these transcribed recordings. The subjective experience proceeded in three stages: (1) changes in body image, sometimes accompanied by feelings of depersonalization, (2) perceptual distortions, rarely evidenced as visual or auditory hallucinations, and (3) feelings of apathy or estrangement. Also reported are feelings of drowsiness, inability to verbalize, feelings of "nothingness" or "emptiness," difficulty in thinking, poor concentration, and preoccupation with death. The changes in body image are characteristic of PCP intoxication. These stages of intoxication are very similar to those reported in human smokers of PCP (Siegel, 1978).

A research group at Bethlem Royal and Mandsley Hospitals in Great Britain has conducted two studies assessing the effects of PCP on sensory function (Beech et al., 1961; Morgenstern et al., 1962). Both these studies were conducted in normal human subject volunteers. In both studies 7.5 mg PCP was given orally. This dose is in the range of doses abused by humans, perhaps slightly in the high range, although it is hard to compare oral doses with smoking doses. In the first study (Beech et al., 1961) PCP was compared with sodium amobarbital (200 mg). It was done double-blind, 11 subjects given PCP and 10 given amobarbital. Two dependent variables were measured--a test of thought disorder to be discussed later and an auditory threshold measure. These tests were apparently administered about 45 minutes after dosing. The auditory threshold was obtained using a standard Peter's audiometer. It was obtained for only one frequency, 1,000 Hz, in 10 ascending and 10 descending trials. The effect of PCP and amobarbital was compared with predrug thresholds. Although PCP lowered the threshold and amobarbital raised it, neither effect achieved statistical significance. It appears safe to conclude that this rather high dose of PCP does not raise auditory thresholds at the frequency of 1,000 Hz.

The same research group also conducted a more extensive study of the effects of PCP on sensory ability (Morgenstern et al., 1962). Twelve experimental subjects given 7.5 mg PCP orally were compared with six controls. The paper does not state whether the study was conducted single- or double-blind, or even whether a placebo tablet was used. A battery of seven sensory performance tests was conducted every 15 minutes after drug administration. The seven tests were of perimetry, audiometry, visual acuity, taste thresholds, touch sensitivity, two-

point tactile discrimination, and position sense. Fairly standard procedures were used for each of these. Control subjects tested for 2 hours showed either no change or gradually lowered thresholds for each of these measures due to practice effects. On the other hand, the subjects given PCP showed a raised threshold for all seven measures comparing the immediate postdrug scores to scores over the next 2 hours. Comparison of the PCP and control groups by analysis of variance showed that all but the changes in peripheral vision and taste were significant. It is clear from the data that the two somatosensory measures (two-point tactile discrimination and touch) were the most affected by PCP. The rather pronounced effects of PCP on somesthesis in this study are consistent with reports by human subjects intoxicated on PCP. These individuals report numbness and somesthetic perceptual distortions. Increased somatosensory thresholds are also consistent with the clinical use of PCP as a surgical anesthetic and the clinical observation that PCP users are less sensitive to pinprick (Burns et al., 1975). The effects on the other sensory systems were less dramatic, and in the case of the auditory threshold findings were contradictory to those from these investigators' previous study (Beech et al., 1961). It is also unclear whether these effects on sensory ability reflect the effects of PCP on the willingness of the subjects to cooperate with the test procedure (i.e., a response bias) or whether they reflect a direct effect on sensory threshold (i.e., changes in sensitivity). Clarification will require studies using designs that attempt to assess sensory and response components of these tasks independently--by use of signal detection theory, for example.

In conclusion, there is some evidence that PCP can raise sensory thresholds. The evidence is strongest for somesthesis. A thorough psychophysical examination of the effects of PCP in humans as well as in animal models is needed.

Work Capacity and Endurance

There are no experimental data on the effects of PCP on work capacity or endurance. In the study by Pollard et al. (1965), noted earlier, verbal reports of normal subjects under the influence of PCP describe feelings of apathy and estrangement as well as drawsiness. It is unlikely that these subjective experiences are consistent with the performance of work, especially work requiring endurance. On the other hand, numbness and possible raising of somesthetic thresholds may facilitate the ability to tolerate pain or discomfort, particularly when the source is cutaneous.

Sensorimotor Coordination

Two studies used measures of sensorimotor coordination to study the effects of PCP. The first, Rosenbaum et al. (1959),

was designed to compare the effects of PCP with those of LSD and amobarbital. It was conducted to explore the use of PCP intoxication as a model of schizophrenia; consequently, the performance of normal subjects given these three drugs was compared with the performance of schizophrenics on the same tests. The details of the experimental methodology are sketchy. Apparently 10 normal subjects were given 0.1 mg/kg PCP i.v. over a period of 12 minutes. Ten other subjects received 1 mg/kg LSD i.v. and five subjects received 500 mg of amobarbital combined with 15 mg of amphetamine sulfate i.v. The doses of both LSD and amobarbital are quite high, and the inclusion of 15 mg of amphetamine (a very high i.v. dose) makes the interpretation of the results with amobarbital impossible to interpret. The report does not indicate whether either the subjects or the experimenters were blind as to the dosing conditions. Nor does it describe the test situation or any characteristics of the subjects. In my judgment, little confidence can be placed in these results because of the limited information we are given on the experimental methodology.

This study employed two standard measures of sensorimotor coordination: the simple reaction time to an auditory stimulus and a rotary pursuit task. The reaction time test was performed about 60 minutes after the injection of PCP or amobarbital-amphetamine and apparently about 4 hours after the injection of LSD. Reaction time was recorded as the time to release a telegraph key following the sound of a buzzer. Twenty trials were separated by 10 seconds. For the first 10 trials an unusual procedure of shocking the finger concurrently with the buzzer presentation was used. With shock, no differences in median reaction time appeared between subjects given any of the drugs and schizophrenic subjects. Nor were there differences between predrug and postdrug reaction time with the buzzer-shock stimulus. In my judgment the addition of shock probably makes the test a simple spinal reflex; therefore, it is not surprising that there were no differences. In the last 10 trials, without shock, schizophrenics performed substantially more poorly than any of the drug groups did predrug. There was no difference between predrug latencies in the three drug groups, and no difference between LSD and amobarbital subjects predrug and postdrug. When subjects were given PCP, however, they showed a significant increase in latency to release the key, though they were not as slow as schizophrenics. One might be tempted to conclude that this rather high i.v. dose of PCP slows reaction time. However, since this high dose of amobarbital, a drug known to affect reaction time seriously, did not do so under these conditions, this conclusion is hard to accept.

The other measure in this study, a rotary pursuit task, was given 75 minutes after PCP and amobarbital and more than 4 hours after LSD. A standard apparatus was used, revolving at 60 rpm (a quite high speed). Fourteen trials in all were given, the

first 2 and last 2 with the nonpreferred hand and the middle 10 with the preferred hand. Only the data from the preferred hand are presented. On a predrug test the three groups of normals performed better than the schizophrenics. Unfortunately for purposes of comparison, the PCP group performed much better than the other two drug groups predrug. In spite of this superior performance predrug, the group given PCP performed most poorly postdrug, nearly as badly as the schizophrenics; that is, there was a substantial decrease in time on target in the PCP group, which also showed little improvement with practice. LSD subjects continued to improve their pre-drug performance, whereas the amobarbital-amphetamine group showed a moderate disruption of performance and rapid improvement with practice. The conclusion is that this high dose of i.v. PCP disrupts rotary pursuit performance.

A second study that included tests of sensorimotor coordination was carried out by Davies and Beech (1960). They used three tests of perception, two of motor effects, and a test of paired-associates learning. I will describe the results of the motor tests in this section. The study was carried out in 12 allegedly normal volunteers-- 8 psychiatrist trainees and 4 psychologists. Although familiar with the testing situation, the subjects did not know they were to be given PCP. The dose for 2 subjects was 0.1 mg/kg i.v., but for the next 10 subjects it was lowered to 0.075 mg/kg i.v. due to emesis in the first 2 subjects. These are high i.v. doses. One of the subjects became catatonic and unresponsive, but most were able to speak, though with some difficulty. The test battery was administered according to a very flexible protocol. Some subjects were tested predrug, others apparently on another occasion; some were tested 15 minutes after the injection and occasionally thereafter up to 90 minutes. No subjects were given the entire test battery, and there is no evidence that the experimenters were blind as to the dosing conditions. This lack of an explicit protocol, the lack of a placebo control, and the potential bias of the experimenters make it difficult to place much confidence in the results of this study. The rather selective nature of the subject sample also makes it difficult to generalize to a normal population.

The two tests of motor function used in this study were handwriting and tapping speed. Handwriting (the subject's name and "United States of America") was examined in four subjects, and three of the four increased the area of writing. No data are given and no statistical tests were performed. The tapping test was two 10-second trials. Subjects were asked to tap a stylus on a metal plate as rapidly as possible. The sums of the numbers of taps between drug and nondrug conditions in the seven subjects were compared. Tapping was significantly slower under drug conditions, though the difference was small and only barely significant.

Neither of these studies of sensorimotor coordination is of much help in assessing the effects of PCP on this performance

battery. The experimental methodology was very weak in both. Perhaps more important, the doses were very high, higher than would normally be encountered in a human abuse situation. The effect of these doses (0.075-0.1 mg/kg i.v.) would be so obvious to an observer that a question of fine sensorimotor coordination would be moot. These studies provide some evidence that PCP can disrupt these standard psychomotor tasks (reaction time, rotary pursuit, and tapping), but the dose threshold for these effects is unknown. Clearly, more research is needed on the effects of PCP on sensorimotor coordination under dosing conditions likely to be encountered in a user.

Perception

Two of the studies already described included tests of perception. The study by Rosenbaum et al. (1959) comparing the performance of subjects given PCP, LSD, and amobarbital-amphetamine with the performance of schizophrenics (methodology presented and critiqued in the foregoing section) used a weight discrimination procedure as a measure of proprioception. The test was a modification of the method of constant stimuli in which upper difference thresholds were obtained by asking subjects to designate which of two weights held simultaneously, one in each hand, was heavier. The constant weight was 44 g, and the comparison weights were 46, 48, 50, and 52 g. Eight trials were administered for each comparison. Schizophrenics were poorly able to judge correctly which was the heavier weight, and even when the weight difference was 8 g they never achieved the 75 percent correct criterion. All three drug groups showed a linear relationship between weight difference and correct judgments when tested predrug. Amobarbital-amphetamine had no effect and LSD had little. PCP, on the other hand, substantially affected this weight discrimination task such that the subjects did not achieve criterion even at 8 g difference. In this respect, their performance was as poor as that of the schizophrenics.

The study by Davies and Beech (1960), also described previously, used four tests of perception to assess the effects of high i.v. dose (0.075-0.1 mg/kg) of PCP in mental health professionals. The four tests were size estimation, spiral aftereffect, critical flicker fusion, and time estimation. It should be recalled that a very flexible protocol with no placebo control and nonblind experimenters were used in this study. The tests were apparently conducted anywhere from 15 to 90 minutes after injection.

Facility of size estimation was assessed in two ways. The first used seven index cards each containing a single circle, one the size of a penny, three larger (2, 4, and 6 mm larger), and three smaller (2, 4, and 6 mm smaller). The subject was asked to identify which was the size of a penny. Subjects performed a similar task using a 1-inch line. Performance of six

subjects before and 20 minutes after PCP showed no significant effect, although subjects tended to overestimate after PCP.

The duration of aftereffect of looking at an "Archimedes spiral" was compared in three subjects before and after PCP. The aftereffect was shorter in all subjects after, but no test of statistical significance was performed.

Flicker fusion thresholds were obtained in seven subjects before and about 30 minutes after PCP. Both up and down trials were used. After PCP all subjects had a lowered threshold; that is, they perceived a lower rate of flicker as a constant light. This effect was statistically significant.

Eleven subjects were asked to estimate the passage of 10, 15, and 20 seconds under drug and nondrug conditions. Three trials were given for each time interval under each condition. Under nondrug conditions subjects tended to overestimate time intervals, whereas after PCP the tendency was to underestimate. The difference was significant.

In conclusion, PCP at high i.v. doses probably has some effects on perception, although the relevant studies were replete with methodological problems. This conclusion is strengthened, however, by the common report of perceptual distortions experienced by PCP users. Effects on perceptual processes may be an important component of the effects of PCP on human behavior and needs to be examined more closely.

COGNITIVE FUNCTIONS

Attention

There have been no studies on the effects of PCP on attention. Reaction time, a test requiring attention, has shown to be disrupted by PCP (Rosenbaum et al., 1959).

Problem Solving, Information Processing, and Decisionmaking

Bakker and Amini (1961) studied the effects of PCP on a number of "paper-and-pencil" standard psychological tests. The tests used were digit span, letter association test, word digit memory test, digit comparison test, the Stroop test, digit symbol substitution, work association, and Raven's progressive matrices. The procedures for each of these tests will be described when I summarize the results.

The subjects in this study were 25 Federal prisoners who were selected to be free of major psychiatric disorder. They were blacks and whites between 20 and 45 years of age and apparently all male. The subjects were given capsules after fasting. The capsules contained either placebo, 5 mg PCP (a normal oral

recreational dose), or 10 mg PCP (a high normal oral recreational dose). Eighteen of the 25 subjects received all three treatments. The order of these treatments as well as the different test sequences and use of different forms of the same tests were counterbalanced. We are not told how many days intervened between treatments, nor whether the data from only the 18 subjects completing the series are presented. Although it is not stated explicitly, we can assume that the subjects were blind as to the dosing conditions. It is not stated whether the experimenters were blind when they administered the tests. We have to assume they were not. Even though lacking double-blind conditions, this is an important study, since it used a placebo control, a fairly representative subject population, a larger number of subjects, and dosing conditons comparable with those encountered in the abuse situation. The lack of a double-blind design is the only major fault, and this is not too serious, since most of the dependent variables were fairly objective.

I will discuss the results test by test. The digit span test was conducted as recommended by the WAIS. Results showed a dose-dependent decrease in the number of correct answers, the difference between placebo and the high dose being statistically significant.

The letter association test asked subjects to write as many words as they could think of beginning with a specified letter of the alphabet. No statistically significant effects of PCP were observed, although there was a trend toward dose-dependent decreases in the number of associations and increases in the number of repetitions and meaningless words.

For the word digit memory test, the subject was presented with a list of 15 pairs of nouns and two-digit numbers. After 2 minutes for study the subject was presented again with the list of nouns in a scrambled order and asked to provide the corresponding numbers. Subjects showed a dose-dependent decrease in the number of correct answers, with both doses significantly different from placebo.

The digit comparison test simply asked subjects to compare two rows of digits to determine whether the numbers were the same. PCP produced a dose-dependent decrease in the number of correct answers, with both doses significantly different from placebo.

The Stroop test could possibly be considered a measure of short term attention. Subjects were asked to name as fast as possible the colors of a series of dots (designated without conflicting data) or to name the colors of a series of words (with conflicting data). There was a dose-dependent increase in the time to complete this test for both conflicting and nonconflicting series. Both doses were significantly different from placebo. Interestingly, at the 5-mg dose, the slower speed was accompanied by a significant decrease in the number of errors.

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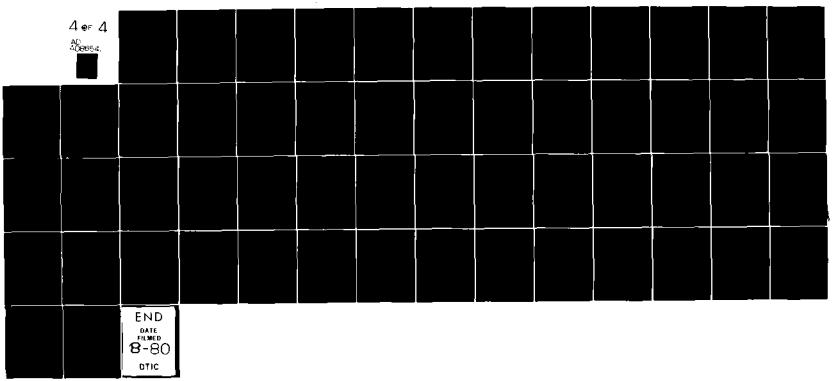

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The digit symbol substitution test was taken from the WAIS. PCP produced a dose-dependent decrease in the number of correct answers, with both doses significantly different from placebo.

For the word association test the latency to respond with an association to a spoken trigger word was recorded for 30 words. This test proved relatively insensitive to the effects of PCP, with an increase in mean response time of 20 percent after the high dose. No statistical comparisons were made.

The last test, which used Raven's progressive matrices, requires logical deductions and can be considered a test of decisionmaking. The subjects were presented with an incomplete pattern, which they had to complete by choosing from six possibilities. The time required to complete the test was increased in a dose-dependent fashion. The number of correct answers was decreased by PCP, particularly at the high dose. The increase in number of errors was greatest in the series of greatest complexity.

It is clear from this well-done study that 5 and 10 mg of oral PCP produce a dramatic effect on these simple paper-and-pencil tests of cognitive function. Generally the effects were dose-dependent, and for most tests even the low dose was significantly different from placebo. The emerging pattern of effects is that subjects slow down in their responses, perhaps in a sometimes successful attempt to reduce errors. At the high dose, both speed and accuracy were always compromised. The doses in this study are within the ranges used recreationally. Intoxication to this degree could be expected to occur in situations demanding cognitive functioning, and on the basis of these data even simple tasks are readily disrupted.

Communication Skills

No direct studies have been done on the effects of PCP on communication skills.

DRUG STATES

ACUTE DRUG EFFECTS

Studies of the acute effects of PCP on humans studied under laboratory conditions were described in detail under "Human Studies." The other sources of information on the acute effects of PCP come from clinical trials in which it was used as a surgical anesthetic and clinical studies in which it was used as an abreactive agent for psychotherapy. The former are not of much value in this context because of the high doses used, and the latter contain very limited descriptions of the effects.

Clincial studies of PCP as a general anesthetic have been carried out by Camilleri (1962), Catenacci et al. (1959), Collins et al. (1960), Greifenstein et al. (1958), and Johnstone et al. (1959). These studies agree substantially on the effects of anesthetic doses of PCP. Initially they produce an alcohollike intoxication, with generalized numbness. With increasing doses, mild agitation, gross ataxia, and catatonic rigidity may occur. Common side effects include nystagmus, sweating, salivation, diplopia, and vertigo. With still higher doses, analgesia and then anesthesia result. A dose of 0.25 mg/kg PCP given intravenously produces unresponsiveness with complete anesthesia. However, unlike anesthesia with other CNS depressants, the eyes remain open and the patient appears to be awake. This type of anesthesia has been termed "dissociative" because the patient appears to become dissociated from the environment without actually losing consciousness. Also, unlike other general anesthetics, PCP does not produce respiratory or cardiovascular depression at anesthetic doses. Typically a moderate hypertensive response associated with tachycardia is observed. Muscle relaxation is poor. Higher doses (0.5-1.0 mg/kg i.v.) cause progressive development of severe agitation, muscle rigidity, and generalized seizure activity.

Five papers have described the potential use of PCP in psychiatry (Davies, 1960, 1961, 1963; Lambert, 1963, 1964). Davies suggests the use of 3 to 5 mg of PCP i.v. or orally to help facilitate psychotherapy. His papers contain general descriptions of the verbal reports of patients given these doses; they are consistent with those I have already described. Lambert also used PCP i.v. in psychotherapy sessions. Again, the descriptions of these cases differ little from what has been described earlier.

CHRONIC USE

There are no experimental studies of the effects of chronic PCP administration in human subjects, but some evidence form the animal literature reviewed previously suggests that tolerance can develop to the behavioral effects of PCP. The magnitude of tolerance development (twofold to fourfold), however, is not large relative to that produced by such drugs as opioids and psychomotor stimulants.

Research on the effects of chronic PCP administration in humans is particularly important in light of recent reports of chronic PCP abuse (Burns & Lerner, 1976; Fauman & Fauman, 1978; Lerner & Burns, 1978). These chronic abusers of PCP primarily use it by smoking. The pattern of use varies widely from individual to individual, but generally these chronic users smoke one to two street joints two or three times a day, every day. Lerner and Burns (1978) report that these chronic users can increase their dosage to quite high levels, which indicates tolerance development.

The most important aspect of this chronic abuse pattern is its association with the production of severe psychopathology in users. Although these behavioral pathologies have been reported to occur after acute PCP administration (Allen & Young, 1978; Luisada & Brown, 1976; Rainey & Crowder, 1975), they appear to be most common in chronic heavy users (Fauman & Fauman, 1978; Lerner & Burns, 1978). The symptoms bear a marked similarity to schizophrenia and, as noted earlier, there is considerable interest in PCP intoxication as a model of schizophrenia. In any case, the "PCP psychoses" are quite distinct from the acute intoxication phase itself, since they can last days and months after the last dose. So far most attempts at treatment have used hospitalization and neuroleptic medications.

At this point it is completely unclear whether these occasional PCP psychoses are the direct result of PCP use itself, the use of PCP combined with other drugs, or the precipitation by PCP of an already existing psychopathology. The relevant dosage conditions, frequency of use, subject characteristics, and the like that are prone to produce PCP psychosis are simply not known.

TIME-COURSE EFFECTS

We have a good idea of the time course for the effects of PCP from the human research literature for the intravenous route of administration. The time course for the effects of the oral route and smoking have not been documented and can only be estimated based on reports of experienced users.

An excellent description of the time course of PCP effects after intravenous administration in humans is reported in the study by Davies and Beech (1960). The effects of 6.4 mg PCP begin almost immediately after an intravenous injection. They remain strong for 30 to 60 minutes with rapid recovery thereafter. By 75 minutes the subjects feel nearly normal, and by 100 minutes only very slight effects were seen with essentially complete recovery in 2 hours. The subjects report feeling tired for an additional 2 to 3 hours. Clearly at lower doses the intensity of effects would be expected to be lower with an even more rapid recovery.

In one study of oral PCP administration (Beech et al., 1961) we are given a general estimate of the time of onset and peak effects of PCP. The researchers report that subjects given 7.5 mg of PCP show an onset of activity of about 45 minutes with peak effects 90 minutes after administration. The published literature does not provide a good estimate of the duration of PCP effects after oral administration.

The only information we have on the time course of PCP effects after smoking is from reports of experienced users (e.g., Lerner & Burns, 1978). After smoking, the effects begin within

1 to 5 minutes, peak between 5 and 30 minutes, and last 4 to 6 hours. Again, users report a "hangover" effect of feeling somewhat tired for up to 24 hours.

An important recent series of findings also provides information about the time course of PCP effects (Aronow et al., 1978; Domino & Wilson, 1977; Done et al., 1977). It appears that the rate of elimination of PCP in the urine depends on urinary pH. It has emerged that the time course of PCP effects (particularly in overdose situations) may be considerably shortened by acidification of the urine.

WITHDRAWAL FROM PCP

Withdrawal symptoms due to the discontinuation of chronic PCP usage in humans have not been reported (Lerner & Burns, 1978).

INTERACTION WITH PHYSIOLOGICAL AND PSYCHOLOGICAL STRESSORS

There have been no direct studies of the interaction between PCP administration and physiological or psychological stressors. There is reason to believe, however, that the effects of PCP in schizophrenics or in individuals with latent schizophrenic tendencies may be more severe than in normals. I have already referred to the recent evidence that PCP can produce a schizophreniform psychosis in some (particularly chronic) users. I indicated that a number of investigators suggested that PCP may precipitate a psychotic episode in individuals with a premorbid history of schizophrenic tendencies. Some more direct data support this clinical impression. Itil et al. (1967) gave PCP to 29 schizophrenic patients who had been free of psychiatric medication for at least 8 weeks. The effect of PCP in general was to increase existing symptoms and to result in the occurrence of new symptoms. In short, there is some reason to believe that the existence of psychopathology may increase the likelihood that PCP use will result in long term behavioral changes.

DRUG-DRUG INTERACTIONS

There are no studies in humans on the possibility of interactions between PCP and other drugs of abuse. Since PCP is commonly used by the adulteration of smoking materials and in a multiple-drug-abuse context, these studies are clearly needed. Animal studies suggest a potentially important interaction between PCP and marihuana, amphetamine, and barbiturates.

GENERAL SUMMARY

ESTABLISHED FINDINGS

PCP (phencyclidine piperidine) is a representative of a group of drugs chemically, pharmacologically and behaviorally distinct from the other classes of drugs used recreationally. PCP produces anesthesia with little respiratory or cardiovascular effect. Complications frequently result upon emergence from anesthesia; with frequent emotional, motor and perceptual disturbances. Early research, in fact, indicated that PCP produces a reversible intoxication resembling schizophrenia.

PCP was developed in the 1950's for use in immobilizing non-human primates. Recreational use began in the 1960's, and has grown in popularity in recent years. It is most often used in combination with other drugs. A number of PCP analogues have been synthesized, and some have also found their way into recreational usage. About these we know practically nothing. However, there are indications that some of these analogues are extremely toxic and may themselves produce psychotic behavior.

There are very few experimental studies as yet of the effects of PCP on human subjects. Most of the existing work was done in the late 50's-early '60's. Subsequent work has largely focused on animals. Research on humans would require investigators to obtain special permit from the FDA. Apparently no such research is in progress.

The very limited research to date indicates that:

1. PCP enhances the effects of cas depressants.

2. There is a potentially important interaction--as shown in animal studies between PCP, marijuana, amphetamines, and barbiturates.

3. PCP can raise sensory thresholds, especially for somasthesis.

4. PCP can disrupt standard psychomotor tasks (simple reaction time, pursuit motor tasks, tapping, etc.).

5. PCP produces a dramatic effect on cognitive functioning--readily disrupting even simple behaviors. Behavior is slowed down, and accuracy is impaired.

6. PCP produces dramatic perceptual changes--hallucinations, distortions, and the like.

Almost none of the research conducted to date has focused on dosages or administration routes that are similar to those employed in recreational usage, however.

NEEDED RESEARCH

Little is known concerning the variety of PCP analogues, many of which are likely to be more dangerous than PCP. Studies are needed of the effects of PCP in combination with other recreational drugs, since PCP is typically mixed with other substances. There need to be studies of interactions in particular, between PCP and a variety of CNS depressants.

A systematic program of PCP research is needed that employs administration routes and dosage ranges that are similar to those employed recreationally. This research program should cover virtually every area of interest in this review. For instance, a thorough psychophysical examination of PCP is needed, in both humans and in animal models. There have been no studies of the effects of PCP on work endurance and capacity; attention; communications skills; interaction between PCP and either physiological or psychological stressors; or drug-drug interactions. And there has been very little work in the other areas of interest.

There need to be experimental studies of the effects of chronic PCP administration in humans especially in light of recent reports of chronic abuse (by smoking). There is limited time-course data for intravenous use, but only clinical reports for oral ingestion and smoking. There is no data on development of behavioral tolerance in humans. Studies are also needed in these areas.

(This summary was prepared by the staff of Associate Consultants, Inc. based on Dr. Balster's paper.)

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8. VISUAL PERFORMANCE ACROSS SEVERAL DRUG CLASSES

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INTRODUCTION

It is virtually impossible to investigate drug effects in real world performance situations such as driving or flying; many factors remain uncontrolled, the risk to subjects (and experimenter) is unacceptable, and subjects' knowledge that they are under investigation is likely to produce compensatory behaviors that may mask the drug effect. Investigators of road "accidents" find that drugs are often present in drivers, passengers, and involved pedestrians; however, these incidents are so complex that the exact relation between drug use and a specific "accident" is obscured. Statistically one may point to drug use as a major factor in accident causation; in an individual case the causal relations are often impossible to determine.

However, the investigation of visual performance in the laboratory is still a valuable part of efforts to reduce accident rates, because most information relating to complex tasks is gathered through the visual system. Controls and information displays (inside and outside the vehicle) should be designed to present and allow assimilation of the appropriate information, even to the intoxicated driver. Caution should be exercised in extrapolating from laboratory studies to the real world, because the laboratory environment is so much more simplified.

For this review visual performance includes any aspect of vision and visual function that has an effect on the performance of complex tasks or subtasks that are generally considered to be components of complex performance. Thus this review includes (a) studies of driving and flying, where the primary sensory input is visual; (b) studies of drug effects on tracking tasks and reaction time; and (c) studies of more elementary visual functions such as visual acuity and color vision. Studies of the effects of drugs on memory, motivation, and emotion are excluded. Studies of cognitive functions in general are excluded, except in cases where there is a large visual component to the performance task.

ALCOHOL

A number of excellent reviews of the effects of alcohol on general functioning in humans and animals are available. Wallgren and Barry (1970) is a comprehensive source for all aspects of alcohol effects. Visual performance studies, especially in relation to driving, have been reviewed by Carpenter (1962), Perrine (1973), and Moskowitz (1973); these reviews are recommended to the reader.

No animal studies are included in this review; as noted above, emphasis will be placed on sensorimotor function and on complex and simulation environments.

SENSORIMOTOR FUNCTIONS

Sensorimotor Coordination

Alcohol degrades sensorimotor coordination. In complex tasks, the effects are measurable at blood alcohol levels (BAL's) of about 0.03 gram percent and are significant in most people at levels above 0.08 gram percent. Less complex tasks show a greater apparent resistance to alcohol effects, but it is clearly established that maximum information transmission rates are reduced by alcohol. There is less "spare capacity" available during apparently adequate performance of simple tasks to meet suddenly increased performance demand.

Tracking performance. It is clearly established that alcohol degrades performance on compensatory tracking tasks, especially in the presence of other attention-demanding tasks. For example, Hughes and Forney (1964) showed significantly reduced pursuit tracking performance at alcohol levels of approximately 0.05 gram percent. Klein and Jex (1975), using a "critical tracking task," which becomes more difficult as time progresses, showed that 11 of their 20 subjects had significantly decreased performance at a BAL of 0.05 gram percent.

Hamilton and Copeman (1970) investigated relations between pursuit tracking performance, detection of peripheral signals, and auditory noise level. The noise was employed to increase arousal level and thus improve performance; tracking performance was increased at higher noise levels, but peripheral detection was decreased. Alcohol depressed both tracking performance and peripheral signal detection. The results were interpreted as demonstrating that alcohol produced a reduction in the information-processing rate and an attentional bias to high-priority tasks, resulting in the decreased detection performance in the peripheral field.

Blood alcohol levels of 0.1 gram percent significantly depress compensatory tracking performance in the presence of otner monitoring and reaction tasks. Chiles and Jennings (1970) showed that two-dimensional compensatory tracking, choice reaction times, and meter-monitoring performance were degraded at 0.1 gram percent BAL. Earlier experiments (e.g., Pearson, 1968) had shown no compensatory tracking deficit at BAL's up to 0.08 gram percent. Moskowitz (1973) provides an extensive discussion of these and other tasks as they relate to driving and traffic safety.

At what alcohol level will a significant proportion of subjects have their tracking performance depressed? Evans, Martz, Rodda, Kiplinger, and Forney (1974) examined 14 subjects in pursuit tracking performance at target BAL's of 0, 0.025, 0.05, 0.075, and 0.1 gram percent. At 0.077 gram percent, 11 of the 14 subjects showed statistically significant impairment on some tests, while at 0.089 gram percent all subjects showed significant impairment.

More precise descriptions of tracking tasks and performance have been used by a number of investigators, who view the human subject as a component of a total control system. Linear mathematical models have been proposed to describe tracking performance both before and after alcohol ingestion, and it is proposed that the increased error in steering responses occurring after alcohol ingestion is caused by intermittent lapses of attention (see, e.g., Allen, Jex, & McRues, 1975; Reid & Ibraham, 1975).

Reaction time. Reaction time (RT) is a component of skilled performance that has been widely studied in alcohol-intoxicated subjects. The effects of alcohol on RT have been relatively small (about 10 percent increase in RT at BAL of 0.1 gram percent in simple reaction time tasks). Tasks that require decisionmaking before reaction are more susceptible to the effects of alcohol. Carpenter (1962) and Wallgren and Barry (1970) should be consulted for reviews of this extensive literature. Huntley (1973) studied the effects of alcohol and task difficulty on choice reaction time with increased BAL, with increased foveal task difficulty, and with target eccentricity. Foveal task performance was not influenced by increased BAL; the subjects appeared to concentrate on the foveal task to the detriment of the peripheral task performance.

Increases in choice reaction time in alcohol-intoxicated subjects have also been reported by Chiles and Jennings (1970) and Le Dain (1972).

Vision and visual system effects. The visual performance measures discussed above are dependent on intact sensory functioning. In attempting to understand how performance is degraded by alcohol, many investigators have examined more elementary aspects of visual functioning: acuity, visual fields, glare resistance and recovery, dark adaptation, visual-temporal discrimination, and color vision. Early studies (e.g., Colson, 1940; Newman & Fletcher,

1942) showed few effects, but they used relatively crude measures and suffered methodological problems.

Visual acuity has been most recently and most satisfactorily investigated by Adams et al. (1975); these investigators, using two doses of alcohol and placebo in a double-blind procedure, found no decrement of static acuity at BAL's up to 0.08 gram percent. They used the psychophysical method of limits for measuring threshold and were unable to show significant changes in acuity levels.

Although alcohol has little or no effect on static acuity for high-contrast targets, it has large and significant effects on acuity for moving targets (dynamic visual acuity--DVA). Brown et al. (1975) showed that DVA for targets moved with constant angular velocity in the horizontal plane was degraded 40 minutes after alcohol administration; the DVA returned to predrug levels 4-5 hours after drug ingestion. This experiment was conducted double-blind, using a placebo and two doses of alcohol. Two doses of marihuana were also included in the study; marihuana produced smaller changes in dynamic acuity.

Brown et al. (1975) speculated that the effect of alcohol on DVA was mediated through effects on the voluntary oculomotor system. These effects have been studied by Drischel (1968), Wilkinson, Kime, and Purnell (1974), Flom, Brown, and Adams (1976), and Levett and Karras (1977), among others. The general findings were that alcohol increases saccadic eye movement latency, decreases saccadic velocity, and decreases smooth eye movement velocity; the activities would all act to reduce DVA performance. The effects of alcohol on reflex oculomotor performance have been examined by Schroeder, Gilson, and Guedry (1973), who noted an inability to inhibit the vestibular-ocular reflex in alcohol-intoxicated subjects.

Depth perception is important in many visual performance tasks; the binocular sense of depth (stereopsis) is dependent on accurate alinement of the two eyes. While it is known that binocular vision can be disrupted after alcohol ingestion, producing double vision in extreme cases (Brecher, Hartman, & Leonard, 1955), there have been few reports of the effects of alcohol on stereoacuity. It is likely that stereoscopic vision would be disrupted by alcohol-induced degradation of oculomotor control.

In driving and flying, the person's ability to change the eye's focus from far to near and back is an essential component of performance. Levett and Karras (1977) found that the time taken to change the state of focus of the eye was prolonged at BAL's between 0.05 and 0.1 gram percent.

Moskowitz, Sharma, and Shapers (1972) reviewed their work on the effects of alcohol and marihuana on vision functions (visual field, dark adaptation, acuity, heterophoria range of fusion eye vergence) and reported results in accordance with those discussed above.

The ability to adapt to changing light levels is an important aspect of real world military and civilian performance. Alcohol has significant effects on adaptation phenomena, which may be mediated at the retinal level. Early attempts to show alcohol effects on dark adaptation were unsuccessful (Blomberg & Wassen, 1959); however, it is known that alcohol affects the electroretinogram in dark-adapted subjects (Ikeda, 1963). Alcohol effects have recently been shown on retinal readaptation after glare. Adams and Brown (1975) and Adams, Brown, and Flom (1976) demonstrated significant alcohol-dose-related increments in time needed to recover visual sensitivity after glare. This result was confirmed by Sekuler and MacArthur (1977) and by Adams et al. (1978), although the mechanism of the effect is in dispute. Nevertheless, alcohol prolongs the period of relative "blindness" after exposure to glare by up to 50 percent; the sky may act as an extended glare source just after sunrise and before sunset; and in military environments, especially during the night and during continuous operations, many glare sources exist. An additional 30-50 percent delay in seeing critical detail may have severe consequences.

There has been dispute over the long term effects of alcohol on color vision. Cruz-Coke (1972) hypothesized a sex-linked genetic association between alcoholism and color vision defects. However, Swinson (1972) and Smith (1971a, 1971b, 1972) produced evidence that the color vision defects in disease are secondary to the nutritional deficits that often accompany alcoholism. Acute color vision changes after alcohol and marihuana ingestion have been reported by Adams et al. (1976) in double-blind, multiple-dose experiments, using a sensitive color vision test (the Farnsworth Munsell 100 Hue test). These investigations showed dose-related decrease in color discrimination, especially in the blue region of the color circle. Although the changes were small and temporary, such unstable color vision may cause performance problems in occupations requiring acute color perception.

COGNITIVE FUNCTIONS

Attention

Before objects can be tracked and identified they must be detected, and in tasks such as driving or flying, detection of relevant objects most often occurs in the peripheral visual field. Alcohol has been shown to produce "tunnel vision" or reduced ability to perceive objects on the peripheral visual field when a second task must be attended to in the primary position. In an experiment conducted by Moskowitz and Sharma (1974), alcohol reduced the field limit by about 12^{o} for an alcohol dose of 0.828 gram/kilogram and by $3\text{-}6^{o}$ for an alcohol dose of 0.414 gram/kilogram. These changes were noted only when a central detection task was concurrently required of the subjects. Von Wright and Mikkonen (1970) were able to show reduced perception in the retinal

periphery for experienced subjects only; they concluded that their inexperienced subjects overcame any alcohol-induced disability because of increased motivation level. Zunder (1977) measured reaction time for peripherally presented targets in intoxicated subjects and found an alcohol-induced deficit only when an unexpected response was necessary. This result indicates that alcohol interferes with response selection rather than with stimulus processing and categorization.

Information Processing

In a broad sense, information processing involves detection of targets or events of relevant sensory information. The many studies discussed under tracking, driving, and flying involve information processing. In a more specific sense, Moskowitz and Murray (1976) used a backward visual masking paradigm in alcohol-intoxicated subjects to demonstrate that alcohol acts to increase the time taken to transfer information from initial sensory storage into short term memory. Alcohol does not appear to act on transmission of information through the visual system to the "iconic" image.

COMPLEX SIMULATION ENVIRONMENTS

Driving

Alcohol use is a significant factor in nighttime accident rates. Carlson (1972) compared BAL's in the general nighttime driving population with BAL's in drivers involved in single vehicle accidents. Both groups had significant numbers of persons with alcohol levels greater than 0.05 g percent, at a level which some performance decrement would be expected in most drivers. More

high BAL's were noted between 1 a.m. and 3 a.m.; this corresponds with the peak time for occurrence of single vehicle accidents.

Simulations of driving and flying in the laboratory provide approximations to the real world that have been used to demonstrate the effects of drugs on performance. Moskowitz (1973) reviewed a large number of these studies and concluded that alcohol-intoxicated subjects have their information-processing capacity reduced and thus fail to process some information inputs that might normally be processed concurrently. Linnoila (1974), in a review of drug effects on driving, reached a similar conclusion regarding alcohol effects.

Early studies of alcohol and driving tried to determine the BAL's at which driving should be legally permissible. Newman, Fletcher, and Abramson (1942) gave eight of their subjects (tested at BAL's up to 0.1 g percent) a driving test on a closed course and found only moderate diminution of performance. In their simulation test (a simple pursuit tracking task with no extra perceptual load), only at BAL's of 0.15 g percent were all of the 150 subjects affected.

Hansteen, Miller, Lonero, Reid, and Jones (1976), in a detailed report of studies conducted for the Le Dain Commission (1972), found that the performance of subjects on a closed course driving task was poorer when they were intoxicated. The course was marked with traffic cones, and significantly more cones were hit by the drivers when intoxicated. Alcohol also produced greater use of controls (steering wheel, brakes, accelerator) by drivers who drove a closed course (Huntley & Centybear, 1974). Sleep deprivation combined with alcohol diminished the use of controls. These authors also noted that personality variables (introversion/extroversion) influenced control use; they cautioned against using control measures in driving studies without accounting for such factors.

The problems associated with experimental determinations of alcohol effects on driving in real traffic situations are almost insuperable. Many investigators have retreated to the laboratory in the hope that simulations of driving performance will provide valid and reliable findings which can be extrapolated to the real world. In the simplest simulations, subjects are shown films of traffic situations and must detect or react to specific potentially hazardous incidents (e.g., Buikhuisen & Jongman, 1972). In sucn situations, alcohol (at levels of 0.08 - 0.10 g percent and above) causes a reduction in visual search behavior and reduced ability to perceive events, even though eye movement records may indicate that ocular fixation takes place. Events at the edges of the screen are especially likely to be missed. This alcohol-induced "tunnel vision" has been fairly extensively investigated and has been discussed above.

There are hazards in the simulation approach, however; Moskowitz, Ziedman, and Sharma (1976) showed a film of traffic

situations to both sober and intoxicated subjects and required the subjects to react to a subsidiary task (the direction of arrows projected onto the film). They found that "the spatial distribution of dwells (eye fixations) is highly dependent upon the immediate stimulus presentation, such as the distribution of the arrows in the subsidiary task." Thus, providing an information-processing load led to a contaminating change in behavior, unrelated to the driving task. Nevertheless, Moskowitz et al. did show that alcohol leads to greater dwell length, decreased dwell frequency, and increased pursuit duration and frequency, thus confirming and extending the results of Buikhuisen and Jongman (1972).

More elaborate simulations have subjects watch a film presentation while operating a steering wheel, a brake, and an accelerator to control "speed"; Crancer, Dille, Wallace, and Haykin (1969) used 36 subjects in an experimental comparison of alcohol (at about 0.1 g percent) and marihuana (22 mg THC) and found that alcohol increased the number of response "errors" scored during a 23-minute film presentation, but marihuana did not. Crancer et al. accepted the positive finding--that alcohol is likely to impair driving performance--but were unwilling to conclude that marihuana did not do so. (This result is discussed in greater detail in the review of the marihuana literature.)

Nighttime driving implies a reduced sensory input and also includes the possibility of glare from approaching headlights. Mortimer (1963) demonstrated that glare can have deleterious effects on simulated driving at low and moderate BAL's (0.018 and 0.068 g percent); performance under simulated day and simulated night conditions without glare was affected only at a BAL of 0.068 g percent.

Alcohol effects on vision per se are relatively small, especially at low and moderate BAL's. However, alcohol reduces information transmission rates, and in complex task situations (such as driving), alcohol causes concentration on the primary tracking task with concurrent neglect of subsidiary monitoring and detection functions. Thus the alcohol-intoxicated driver is at great risk when unexpected events occur. If these events demand rapid, efficient, evasive action, the alcohol-intoxicated driver is not equipped to decide and react; disaster may result.

Other Performance Areas

Alcohol was found to be the most prominent drug associated with aircraft accidents and incidents reviewed by Zeller (1975). He found that, of 89 U.S. Air Force incidents occurring between 1962 and 1973, 31 percent had some association with alcohol use. He is careful to point out that the relation noted is associative and not necessarily causative, but it is known that alcohol diminishes flying performance. Underwood Ground (1975) reported a 40 percent alcohol association with light aircraft crashes in the

United Kingdom and concluded that alcohol was a contributory factor in 11.6 percent of them.

There appears little doubt that alcohol can and does contribute to aircraft-to-aircraft incidents and accidents. Billings, Gerke, and Wick (1975) studied alcohol effects on flight performance and found that BAL's of 0.04 g percent are associated with substantial and significant increased in the number and seriousness of procedural errors in both experienced and inexperienced pilots. At BAL's of 0.12 g percent the pilots "flew in a grossly unsafe manner on 16 occasions during 30 flights." Billings et al. believed that the BAL at which flight performance is not affected is extremely low. This belief is reinforced by the findings of Henry et al. (1974), who were able to observe small decrements in simulated flight performance (in a Link GAT-1 trainer) at BAL's as low as 0.01 g percent. However, Billings et al. (1975) advised caution in extrapolation of simulation data to the flight environment.

Klein (1972) used the data of Billings et al. (1975) and his own psychomotor performance data to derive an "alcohol calibrated test method," which allows prediction of flight performance decrements for other drugs. Using this method researchers can extrapolate from performance/dose curves and derive the maximum dose of a particular drug at which performance will be affected.

In flying, especially at high speeds or in turbulent conditions, vestibular stimulation may have significant effects on visual performance. Collins, Gilson, Schroeder, and Guedry (1971) examined the effects of alcohol on eye-hand tracking. They found that, while alcohol (at levels of 0.07 g percent) may have little effect on eye-hand tracking under static conditions, it significantly degrades tracking performance during motion. The degradation is greater at low levels of illumination. Eye movement recordings indicated that intoxicated subjects were unable to inhibit vestibular-induced reflex eye movements, and this was hypothesized to be the cause of the performance decrement.

From the above studies and the previously presented data, it may be concluded that even low BAL's have detrimental effects on flight performance. These performance decrements may be mediated by influences as diverse as reduced information processing, increased reaction time, and reduced ability to override reflex eye movements induced by vestibular stimulation.

DRUG STATES

Acute Drug Effects

For practical purposes, the acute effects of alcohol intoxication parallel the blood alcohol curve, although there is some evidence for different effects in rising and falling phases.

This may be due to the development of a short term tolerance effect, but the cause is not clear. Alcohol is metabolized and "cleared" from the body at approximately 0.015 g percent per hour, and thus the length of the acute phase depends on the peak BAL reached. Visual performance decrements will probably become apparent at BAL's of about 0.03 g percent and significant at levels above 0.05 g percent.

Chronic Use

There are no known effects of chronic moderate use of alcohol and visual performance. Chronic alcohol abuse may lead to an acquired color vision deficit, but whether this is due to the effects of alcohol, is in part genetically determined, or is secondary to malnutrition and avitaminosis, is still in dispute.

Withdrawal/Termination

Although there is extensive literature on withdrawal from alcohol intoxication by alcoholics, visual performance is largely unstudied in these subjects. The visual effects of the hangover phase of acute intoxication deserve further study. Hogman (1977) reported prolonged glare recovery after alcohol ingestion; the recovery followed the blood alcohol time course and then became prolonged once more during the period from 400 to 600 minutes postingestion, when BAL is zero. This provocative result should be confirmed and extended.

Interaction With Physiological and Psychological Stressors

There is some evidence that, under stressful conditions, alcohol-intoxicated subjects can perform at levels that would not be expected from their BAL's. Wallgren and Barry (1970, p. 354 ff.) reviewed the early experiments in this area; pain, exertion, fatigue, and cold may have such effects. Recently, Frankenhaeuser, Dunne, Bjurstrom, and Lundberg (1974) showed diminished alcohol impairment in a choice reaction time paradigm when mild shock was intermittently delivered to one hand during the task.

Sleep deprivation has similar effects; Huntley and Centybear (1974) examined the driving performance of sleep-deprived subjects after the subjects ingested alcohol. Sleep deprivation plus alcohol improved driving performance (diminished control use) when compared with the same subjects' performance under alcohol but without sleep deprivation. Similar results were found by Wilkinson and Colquhoun (1968) in a choice serial reaction time task.

It appears that a wide range of stressors can improve the performance of alcohol-intoxicated subjects on fairly complex tasks. The theoretical implications of these results are unclear (see Hamilton & Copeman, 1970, for a discussion of the Wilkinson & Colquhoun result), but the practical implications of the results must be welcomed if they can be confirmed for real world performance.

Drug-Drug Interaction

The combined effects of alcohol and other drugs were reviewed by Forney and Hughes (1968). Ashford and Cobby (1975) provided an elaborate model for studying the interactions of alcohol and meprobamate and discussed the extensive problems associated with providing a full description of drug-drug interactions.

In general, the pervasive adverse effects of alcohol are not readily reversible by stimulant drugs, although nicotine may counteract alcohol effects to some extent (Tong, Knott, & McGraw, 1974). Additive effects of alcohol and other depressant drugs taken for medical or recreational reasons are fairly commonplace. For example, alcohol and marihuana effects are "additive" in tracking tasks (Manno, Kiplinger, Scholz, & Forney, 1971); Linnoila and Hakkinen (1974) showed that diazepam produced greater performance decrement in a simulated driving task when it was taken with alcohol. In their experiment, codeine produced the greatest performance decrement (number of "collisions"), but this number was reduced when codeine and alcohol were combined.

Some hypnotics may produce interactions with alcohol after use of the drug has been discontinued. Roden, Harvey, and Mitchard (1977) showed that residual concentrations of methaqualone (Mandrax) apparently enhanced the depressant action of alcohol 3 days after ingestion of a single dose of Mandrax. Significantly, the performance measure chosen was kinetic visual acuity, which is a task similar to the dynamic acuity discussed above; dynamic acuity performance is the vision measure that correlates best with driving performance (Burg, 1967).

Other drugs that might frequently be consumed with alcohol are antimotion sickness medications such as Dramamine. Tang and Rosenstein (1967) measured subjects' performance on a complex coordination task after placebo, alcohol (BAL's 0.04-0.05 g percent), Dramamine (100 mg), and alcohol plus Dramamine. Alcohol produced a 12 percent decrement in performance, Dramamine produced a 6 percent decrement, and the combined dose produced a 25 percent decrement. The time course of the effects was about 3-4 hours. Thus it seems inadvisable to combine Dramamine (and drugs with similar mechanisms of action) with alcohol if one must perform complex tasks.

The industrial work environment is often contaminated with low levels of chemical agents used in manufacturing; alcohol use and abuse are significant industrial problems. Interactions of alcohol and agents such as trichlorethylene may lead to hazardous conditions. Ferguson and Vernon (1970) demonstrated markedly decreased performance on depth perception and hand steadiness tasks after alcohol was taken (BAL's 0.02 to 0.03 g percent) in the presence of trichlorethylene. The effects of these performance changes on workers engaged in hazardous tasks are obvious.

MARIHUANA

It is a long-established fact that the major active constituent of marihuana is 9-tetrahydrocannabinol (THC), although many other cannabinols, present in smaller amounts, also have central actions. Marihuana has been less extensively studied than alcohol, although in visual performance tests, especially when "divided attention" is necessary, it can have very debilitating effects. In many ways marihuana is more of a problem than alcohol: there are fewer outward signs of intoxication, and in simple tasks the marihuana user can perform adequately. More complex behaviors may break down, with severe consequences.

Marihuana use (or abuse) became a major issue in the United States and Canada in the mid- to late-1960's, and many of the references reviewed here date from that period. The Le Dain Report of the Royal Commission of Enquiry into the Non-Medical Use of Drugs (1972) is a valuable source of information regarding the acute effect of marihuana on physiological, psychological, and performance variables. The report contains accounts of many controlled experiments on alcohol and marihuana effects on performance, memory, and visual function and has pointed the way for future experiments of marihuana effects in these areas. Waller, Johnson, Buelke, and Turner (1976) provided an excellent reference source in their book, Marijuana: An Annotated Bibliography. Dawson (1976), reviewing the specifically ocular effects of short and long term cannabis use, stated that cannabis produces some transient anterior segment irritation but has no cumulative effects of long term clinical significance.

SENSORIMOTOR FUNCTIONS

Sensorimotor Coordination

Individual sensory and motor functions when tested in isolation are remarkably unaffected by marihuana. Marihuana does not affect visual thresholds (Caldwell, Myers, Domino, & Merriam, 1969), static visual acuity (Adams et al., 1975), or eye tracking movements (Flom, Brown, & Adams, 1976). Moskowitz et al. (1972) showed small marihuana effects on ocular parameters such as heterophonia and ductions.

When more complex information processing is required, however, marihuana does produce performance decrements. Moskowitz (1972) showed that marihuana produced decrements in performance in a continuous central detection task. When a simultaneous peripheral detection task was added, performance on both the central and the peripheral tasks was degraded by the drug. Casswell and Marks (1973) confirmed that marihuana produced performance decrements in a divided-attention task in marihuana-intoxicated subjects; both experienced and naive subjects showed the decrement.

Dynamic visual acuity (DVA) or acuity for moving targets is a task that is dependent on intact sensory, motor, and cognitive functioning. DVA is reduced in marihuana-intoxicated subjects for about 2-3 hours after smoking (Brown et al., 1975).

Marihuana reduces the ability to recover from the effects of glaring light sources; Adams et al. (1978) reported prolonged glare recovery after marihuana (and after alcohol). They felt that the effect is at the retinal level, a speculation which is supported to some degree by the acute marihuana-induced decrements of color vision which they have reported (Adams et al., 1976).

Reaction time is clearly dependent on sensory and motor integrity; it is slightly affected by marihuana intoxication in a simple stimulus-response paradigm and more severely degraded in complex situations where decisionmaking is part of the response process. Clark and Nakashima (1968) showed simple reaction time increasing from 330 to 405 ms after an oral dose which "produced a mild 'high' in all subjects." At the same time the subject's complex reaction time increased from 440 to 650 ms. Hollister and Gillespie (1970) showed increased simple auditory reaction time 1.5 and 3.5 hours after oral ingestion of 32 mg of THC. The Le Dain Commission Report (1972) confirms these effects in subjects who have smoked marihuana. Complex reaction time was increased after smoking 6.8 mg of marihuana. There has been some confusion in the literature as to whether reaction time is increased by marihuana, but in the performance context, it is probably best to

assume that marihuana does produce small increases in reaction time, especially on multiple-choice tasks.

Tracking performance demands continuous monitoring of a display and response to any accumulated error. Marihuana effects on such tasks are relatively small when the tasks are conducted in isolation, without other concurrent performance tasks. Kiplinger, Manno, Rodda, and Forney (1971) showed a significant dose-related decrease in pursuit tracking for marihuana doses from 0 to 50 µg/kg. Manno et al. (1971), using the same equipment, confirmed this result and demonstrated that alcohol combined with either 2.5 or 5.0 mg of THC further degrades performance. Reid and Ibraham (1975) also noted degraded compensatory tracking performance. Twenty-two subjects and six drug conditions were used; at each session subjects smoked a marihuana cigarette and drank a beverage containing alcohol mixed with fruit juice. The six experimental conditions were (1) placebo (no alcohol, no THC); (2) no alcohol, 21 µg/kg THC; (3) no alcohol, 88 µg/THC; (4) alcohol to reach 0.03 g percent BAL, no THC; (5) alcohol to reach 0.07 g percent BAL, no THC; (6) alcohol to reach 0.03 g percent BAL, 21 µg/kg THC. Tracking performance was measured 70, 110, and 310 minutes following the beginning of drug ingestion. Human operator describing functions were derived assuming a linear control systems model. Gain, phase, and error of the subjects' responses were among the parameters estimated from the model. Significant degradation of performance (compared with placebo) was noted for conditions 3, 4, 5, and 6. Significant effects were present at 70 and 110 minutes after drug ingestion; they dissipated by 310 minutes. The describing function technique appears to be a sensitive indicator of drug effects; marihuana appears to increase the "noise" in subjects' response, reduce gain, and slightly reduce effective time delay. Alcohol appears to increase "noise," in subjects' response, decrease gain, and increase effective time delay. Roth, Tinklenberg, Whitaker, and Darley (1973) were also able to show performance decrements in a paced tracking task after oral administration of 20 mg of THC.

Stoller, Belleville, and Belleville (1976) used 22.5 mg THC administered orally and examined "critical tracking performance." In this task the subject uses a joy stick to track a line shown on an oscilloscope; the task becomes more and more difficult as errors are accumulated, until at last the operator is unable to maintain control. Performance degraded steadily over 3 hours after the THC was ingested, while under placebo conditions performance improved. This experiment emphasizes an important difference between orally ingested and smoked THC: higher doses must be taken orally to achieve a given level of intoxication and the effect is considerably prolonged.

In degraded sensory environments, skilled performance demands stable and accurate input information. Sharma and Moskowitz (1972) found that the autokinetic effect is enhanced by marihuana administration (at doses up to approximately 14 mg). They noted that

marihuana-induced instability of perception of reference points (beacons, signal lights, etc.) may be important factors in nighttime driving and flying accidents.

COGNITIVE FUNCTIONS

Most studies of cognitive function under marihuana involve nonvisual tasks such as digit span tests, digit symbol substitution tests, subtraction tasks, time estimation and mood scales. (See, e.g., Miller, 1974; Weil, 1978.)

COMPLEX SIMULATION ENVIRONMENTS

Driving

The incidence of traffic accidents directly related to marihuana use is not known. There have been some attempts to determine the magnitude of the problem, but satisfactory statistics are unavailable. Klein, Davis, and Blackbourne (1971) surveyed a junior college, a university, a medical school, and a law school; 571 of the 2,000 questionnaires they distributed were returned. Although the number of users who had driven under the influence of marihuana was not given, 18 percent of infrequent users and 53 percent of chronic users had been stopped by police while under the influence of marihuana. Klonoff (1974) noted that 64 percent of his 64 subjects had driven while under the combined influence of marihuana and alcohol, but his sample is probably not representative of the general driving population.

It is likely that many people drive while intoxicated with marihuana and that marihuana intoxication does contribute to traffic accidents. In driving situations marihuana has been shown to produce degraded performance; Klonoff (1974) reported experiments in which 38 marihuana-intoxicated subjects were rated for performance by driving instructors as the subjects drove a fixed course in city traffic. Some of these subjects showed slight performance increments, but most showed a decrement or little effect after 4.9 or 8.4 mg THC. At the higher dose, 63 percent of the subjects showed a performance decrement. These subjects appeared to show transient episodes of preoccupation or confusion. Sixty-four subjects participated in a further experiment on a closed driving course; the experiment involved turns, backing, and precise maneuvering of the vehicle. Marihuana (placebo, 4.9 mg, 8.4 mg THC) reduced performance significantly from the expected values; however, once more there was considerable individual variability. Klonoff advised against driving under the influence of alcohol or marihuana. Hansteen et al. (1976) also reported degraded performance on a closed course driving task after subjects smoked 5.9 mg of THC.

Simulations of driving offer an opportunity to examine performance in a more controlled situation and in greater detail. In a very elaborate simulator, which included steering, braking, and speed control, Crancer et al. (1969) were unable to show increased error rates (compared with placebo) in subjects who had smoked 22 g of THC. The reasons for this are unclear, although Kalant (1969) advanced the possibility that subjects biased their performance against alcohol (which did show a significant effect) and toward marihuana. Manno et al. (1971) questioned the potency of the marihuana preparation used by Crancer et al.

In another driving simulation study, Rafaelsen and colleagues found that 1-4 hours after oral THC (8, 12, or 16 mg), brake time and start time (after "change to green") were significantly increased. One of the subjects "drove through" 8 of 10 red lights presented in the 10-minute simulation (Rafaelsen, Bech, Christiansen, Christup, Nyobe, & Rafaelsen, 1973). Other simulation studies using oral THC have shown performance decrements up to 24 hours postdrug (Kielholz, Goldberg, Hobi, Ladewig, Reggiani, & Richter, 1973; Kielholz, Hobi, Ladewig, Miest, & Richter, 1973).

Other Complex Environments

Getting "high" before and during flying is apparently not uncommon (Janowsky, Meacham, Blaine, Schorr, Bozzetti, 1976). These authors (and Meacham, Janowsky, Blaine, Bozzetti, & Schorr, 1974) reported aircraft simulation experiments in which pilots flew relatively simple flight patterns after placebo or 90 µg/kg of THC. There was a statistically greater occurrence of "major" errors, "minor" errors, and altitude and heading deviations after marihuana ingestion. These effects peaked about a half hour after smoking and persisted for at least 2 hours; there were no measured effects 4-6 hours after smoking. The authors concluded that "marihuana affects a number of cognitive functions which are required in the process of flying and, in this way, greatly diminishes the ability of pilots to operate an aircraft simulator."

DRUG STATES

Acute Drug Effects

The literature on this topic has been reviewed above. The major point of interest with respect to marihuana effects is the difference in time course between smoked and orally ingested marihuana.

Chronic Use

While most marihuana research has been carried out in acute experiments, Dawson, Jimenez-Antillon, and Perez (1977) reported an extensive set of vision measures on 39 matched pairs of chronic marihuana users and nonusers in Costa Rica. The subjects were matched for age, marital status, education, occupation, and alcohol and tobacco use. The users had 10 or more years' experience with marihuana, while the nonusers had never had a verified experience with the drug. Visual functions tested were visual acuity, dark adaptation, color vision, pupil size, intraocular pressure, and lacrimal gland function.

There were only small differences in visual function between the groups, with users showing lower acuity through a large luminance range and less-adequate dark adaptation. However, the users had more acute color vision (smaller matching range) when tested on a Hecht-Schlaer anomaloscope. The user group showed greater lacrimal secretion, slightly elevated intraocular pressure, and smaller mean pupil diameter during illumination of the eye. The authors' findings are discussed in terms of THC-induced imbalance between sympathetic and parasympathetic nervous systems and possible anterior eye irritation.

The differences between user and nonuser groups are slight; in most cases the user values fall within the accepted normal range, and thus the consequences of long term use for visual performance appear slight. However, in the acute intoxication state, there are visual and central effects which are of great import, as detailed above.

Interaction With Physiological and Psychological Stressors

There do not appear to have been any studies of visual performance in this area. A number of studies in the alcohol literature indicate that alcohol effects can be reversed (at least temporarily) by stress such as pain, cold, or fatigue. In view of the anecdotal reports of subjects that they can "come down" under stress (as in driving or in confrontations with law enforcement officers) this area deserves further study.

Drug-Drug Interactions

Alcohol and marihuana are frequently ingested together, and the effects of their combined use have been studied in a number of visual tasks such as manual tracking (Manno et al., 1971) and glare recovery (Adams et al., 1978). In view of the performance decrements by these two drugs in what appear to be different areas of information processing and cognitive and motor functioning, and in view of their frequent use together, this appears to be a high-priority area for future study.

OPIATES

The effects of opiates on visual performance have not been well studied. Since the advent of methadone maintenance programs for heroin addicts, there is recognition that the performance levels which can be expected of maintained addicts should be studied. Should such people drive or operate complex machinery? Not enough research has been done to give definitive answers to such questions.

SENSORIMOTOR FUNCTIONS

Sensorimotor Coordination

Rothenberg (1977) addressed a number of questions relating to performance by methadone-maintained addicts; he measured reaction times (with and without incentives) and continuous letter-sequence recognition performance. While there were no differences between the groups on this latter task, the methadone addicts were superior to the controls on both reaction time tasks; 5 and 10 mg methadone (amounts which are above their maintenance dose) had no effect on their performance. Control subjects showed significantly slowed reaction times after both 5 and 10 mg of methadone. This result confirms the earlier result of Gordon (1970); and the experimental design, by including two incentive conditions, ruled out possible contamination by motivation effects, which may have operated in Gordon's experiment.

Eye movement patterns in visual search and recognition appear to be altered in heroin addicts. Monty, Hall, and Rosenberger (1975) showed that their sample of 23 addicts, all of whom had used heroin in the previous 12 hours, made fewer eye fixations of longer duration than control subjects in the word- and object-scanning tasks. The significance of this finding is not clear, but Monty et al. hypothesized a basic alteration in information processing in addicts.

Monty et al. (1975) noted that many of the addict subjects complained of poor vision, even though they all had 20/20 acuity. This is surprising because, with constricted pupils produced by opiates, depth of field will improve, and hence slight or even moderate refractive errors should have little depressing effect on acuity. One would expect, on optical grounds, that this group of subjects would have good acuity. Their visual complaints then may be of neural origin; investigations of this phenomenon are indicated.

In nondependent subjects, methadone produces altered function in saccadic and smooth pursuit eye movements. Saccades have greater latency and their accuracy is reduced; significantly greater undershoot is observed with doses of 5 mg of methadone. Rothenberg and colleagues implicated sensory rather than motor aspects of the oculomotor system, since latency of the secondary corrective saccade (which is thought to be "preprogramed") is unaffected by methadone. Smooth pursuit eye movements in response to sinusoidal target motion were of lower gain in methadone-intoxicated subjects (Rothenberg, Peck, Schottenfeld, Betley, & Altman, 1979; Rothenberg, Schottenfeld, Gross, & Selkoe, 1979; Rothenberg, Schottenfeld, Selkoe, & Gross, 1979).

Rothenberg, Peck, Schottenfeld, Betley, and Altman (1979) demonstrated that methadone depresses signal detection performance in nonaddicts; the authors used a signal detection paradigm which excludes changes in response criteria as a possible cause of the results. They again concluded that sensory aspects of the visual system were affected by the drug, since concurrent measures of the visual evoked response also showed a drug effect.

Complex Environments

No studies of the effects of opiates on performance in complex simulation or real-world environments were found. This area needs close attention and further work if the problems produced by acute and chronic use of opiates are to be evaluated and rationally dealt with. The type of performance changes to be expected, their time course, and any after-effects should be investigated. Whether there are effects produced by chronic use of opiates is not known. If methadone maintenance produces effects on performance tasks such as driving, vigilance or other sensory-motor skills which create hazards, we should be aware of those problems. Combined use of opiates and other drugs is another neglected area, which calls for further study, both in acute and chronic studies.

DEPRESSANTS

Central nervous system depressants include agents which range from general anesthetics to marihuana. In the current review the term will be restricted to sedative and hypnotic drugs which are commonly used in general medical and psychiatric practice. Of course many of these drugs are abused substances, and are obtained for such purposes from legitimate and illegitimate sources.

SENSORIMOTOR FUNCTIONS

Sensorimotor Coordination

Depressant drugs in general reduce sensorimotor performance. This is true for the most commonly used drugs in this classification, barbiturates and benzodiazepines, as well as for less widely prescribed medications.

Pentobarbital depresses tracking performance at doses of 75 or 150 mg for 4 to 8 hours after administration (Stoller, Belleville, & Belleville, 1976; Stoller et al., 1976). Diazepam, oxazepam, temazepam, nordiazepam, and lorazepam depress performance in tracking tasks and in complex reaction time tasks (Clarke & Nicholson, 1978; Stoller, Belleville, & Belleville, 1976) showed that lorazepam depresses tracking performance. Ogle, Turner, and Markomihelikas (1976) also demonstrated increased reaction time and depressed pursuit motor performance after administration of diazepam and lorazepam.

Schroeder, Collins, and Elam (1974), in a continuation of their experiments in vestibular stimulation and drug interactions, showed that secobarbital (100 mg) acts to depress tracking during rotation, while having no demonstrable effect without rotational stimulation. This result is in accordance with a similar result reported for alcohol (Collins et al., 1971). The effect is thought to be mediated by oculomotor effects on visual acuity--an assumption supported in part by the widespread effects of the barbiturate drugs on the vestibulo-ocular reflex (Rashbass & Russell, 1961), various forms of nystagmus (Bender & O'Brien, 1946), vergence movements (Westheimer & Rashbass, 1961), and smooth tracking eye movements (Norris, 1968). The benzodiazepines also have effects on oculomotor function: saccadic eye movements are slowed (Aschoff, 1968) and reading eye movements are disrupted to some degree (Stern, Bremer, & McClure, 1974).

Local anesthetic agents may also temporarily disrupt aspects of visual performance. Korttila (1974) showed prolongation of choice reaction time 1 to 1.5 hours after intramuscular injection of 200-500 mg of lidocaine. With the growing popularity of outpatient surgery, the effects of short-acting anesthetic agents on performance are of some concern. Ghoneim, Mewaldt, and Thatcher (1975) demonstrated effects of diazepam and fentanyl on choice reaction time 4 to 6 hours after drug administration. Patients undergoing outpatient surgery should be cautioned against hazardous activity in the immediate postoperative period.

COMPLEX SIMULATION ENVIRONMENTS

Driving

Just as drugs with sedative or depressant actions may impair sensorimotor coordination, they may impair performance on complex tasks such as driving or simulated driving. Betts, Clayton, and MacKay (1972) advised that patients beginning a course of therapy on a number of sedative drugs (haloperidol, amylobarbitone, chlordiazepoxide, and trifluoperazine) should be warned of possible adverse effects on driving behavior. These authors, testing 100 subjects on a closed course driving task, showed altered driving behavior 36 hours after a normal course of therapy had begun. Alcohol (to produce BAL's of 0.05 g percent), taken after the initial driving test, had no apparent interaction with these drugs on driving behavior tests.

On the other hand, Moore (1977) reported that sedative drugs did not produce changes in simulated driving behavior in anxious patients actually being treated with medazepam; Landauer, Pockock, and Prott (1974) were similarly unable to show effects on simulated driving performance after administration of medazepam.

Other sedative drugs and drugs with sedative side effects (such as antihistamines) may not produce performance decrements alone, but when combined with alcohol at low levels (0.02-0.03 g percent), decrements may emerge on such wide-ranging performance measures as hand steadiness and stereopsis tests (Ferguson & Vernon, 1970).

Flying

The potential for disaster in flight is probably greater than on the road, although pilots in general are better screened and probably more responsible as a population than the general driving population. However, drugs are used by pilots and they do degrade performance. In an attempt to validate a simulator technique for assessing drug effects on flight performance, Billings et al. (1975) had five experienced pilots fly a Cessna 172 and GAT-1 trainer under the influence of 0, 100, and 200 mg of secobarbitol.

Tracking performance and airspeed were monitored in both parts of the experiment. Errors were about twice as large in the simulator (compared with actual flight), although greater and more consistent drug effects were shown in the simulator. A higher level of arousal in flight was hypothesized to explain these differences. However, significant drug effects were present both in the simulator and in flight. Performance was degraded on four of six tracking measures in flight and on all of the six measures in the simulator. This study once more should make the reader cautious about extrapolations from simulations to actual performance.

DRUG STATES

Acute Effects

Barbiturates, benzodiazepines, and phenothiozines are drugs with the most potential for creating problems related to visual performance decrements, because they are most often used for control of anxiety states. Deleterious effects of most of these drugs on visual performance (at therapeutic doses) last from 4 to 8 hours after administration. Effects are severe enough to require warning people that they may occur, and with some drugs, especially at higher doses, hazardous occupations should be avoided.

Chronic Use

Subchronic studies have been performed with some of these agents, and effects on performance may be evident, especially when a second drug (e.g., alcohol) is present. For example, Hindmarsh (1976) showed that temazepam increases reaction time and reduces initial fusion frequency when tests are made the morning after it has been used as a sleep-inducing agent.

Withdrawal/Termination

Hindmarsh (1976) addressed the question of quality of sleep following withdrawal of temazepam; no other studies have been found. Hindmarsh (1976) also measured reaction time during the 4-day period of drug administration and for the 7 days after. Thirty milligrams of temazepam significantly elevated choice reaction time on the 4 treatment days, and choice reaction time returned to placebo levels on the first day the drug was withdrawn and replaced with placebo.

Drug-Drug Interactions

The primary interactions of interest here are those of the depressant drugs with alcohol, and with stimulants. The depressant drug-alcohol combination produces an additive or potentiated depressant effect; the depressant-stimulant combination may serve to negate any performance decrements produced by the depressant.

There is an extensive animal literature on depressant-alcohol combinations, which has been reviewed by Forney and Hughes (1968); alcohol may have additive or potentiating effects, depending on species, dose level, and response measures. Some vision performance measures in this general area are reviewed in the section on alcohol. In general, effects are additive or less than additive. No studies indicating a potentiation of effect in vision performance when depressants and alcohol are simultaneously administered have been found.

Westheimer (1966) noted that the effects of amobarbital on ocular coordination could be reversed by amphetamines; note however that the expected antagonism of a depressant-stimulant combination is not apparent on all tasks.

HALLUCINOGENS

Hallucinogenic agents such as LSD and psilocybin are reported to have striking visual effects, such as transformation of space and enhanced and altered color perception. However, the literature on these effects is not extensive, and the literature on the effects of these agents on aspects of practical visual performance is even less understood.

SENSORIMOTOR FUNCTIONS

Sensorimotor Coordination

No studies directly related to tracking or other complex sensorimotor functions were noted. However, the effects of some of these agents on spatial judgments have been studied.

Hill and Fischer and their colleagues have examined the effects of psilocybin on spatial distortion thresholds. Hill, Fischer, and Warshay (1968, 1969) found that 180 mg/kg of psilocybin reduced the threshold for perception of spatial distortion when compared with predrug values. No placebo was used in their experiments, and neither the subjects nor the experimenters were "blind" as to the drug treatment. Fischer, Hill, and Thatcher (1970) measured the "apparent frontoparallel plane" in psilocybin-intoxicated subjects and inferred a drug-induced contraction of near visual space from their results. Hill and Fischer (1973) measured the apparent vertical in subjects before and after psilocybin ingestion and reported that the drug accentuated the misjudgment of the true vertical. When the head was tilted, the drug-induced misperception was accentuated, but the whole effect could be extinguished by sudden removal of the head tilt.

Shaffer and Hill (1973) performed cross-modal magnitude estimation experiments in psilocybin-intoxicated and marihuana-intoxicated subjects. They found no change in the form of the function relating stimulus and response in these judgments; however, small changes in the slope of the function were seen for both drugs. Involuntary eye movements are altered by psilocybin (Hebbard & Fischer, 1966), and this effect may have some influence on visual acuity although these authors did not examine acuity in their subjects.

Although there are anecdotal reports of altered color perception under LSD and other hallucinogens, objective evidence for such changes is hard to come by. Brown (1969) studied visually evoked response studies in LSD intoxication and found changes in evoked response amplitude after drug ingestion in "visualizer" subjects--those who were classified as having vivid visual imagery. In subjects with poor visual imagery the color responses were

poorly differentiated and changes occurring after LSD were primarily in latency of response components.

STIMULANTS

The stimulant drug in most common use in Western society is caffeine, which is found in effective doses in coffee and tea. Amphetamines are widely used for their stimulant and anorectic properties; they have become drugs of abuse and are freely available from illicit sources. In view of their widespread use, the effects of these drugs on visual performance should be more intensively studied. Weiss and Laties (1962) have reviewed the literature in this area.

SENSORIMOTOR FUNCTIONS

Sensorimotor Coordination

When compared with placebo, stimulant drugs (e.g., amphetamines, caffeine) have been shown to improve performance on some sensorimotor coordination tasks. For example, Brown et al. (1974) showed small improvements after d-amphetamine administration in tapping rate, reaction time, rate of crossing out randomly arranged symbols, and card-sorting rate. Other stimulant drugs such as PIO (5-phenyl-2 imino-4-oxo-oxazoladine) also produced small increments in performance on such tasks (Dureman, 1962). Tracking performance was also improved after d-amphetamine. Schroeder et al. (1974) showed significantly improved performance under stationary conditions, but this improvement was not maintained under angular acceleration.

COGNITIVE FUNCTIONS

Attention

These drugs have also been shown to enhance performance in continuous performance tasks. Talland and Quarton (1966) showed that methamphetamine produced improved performance in a continuous task in which the subjects were required to scan a nine-light array for a number which matched a target. In sustained attention tasks, caffeine also improved performance. Sustained attention tasks are vulnerable to "response block"--a state in which subjects take 2 to 3 times the normal time to respond to a stimulus. Baker et al. (1972) noted that caffeine significantly reduced response blocking in a 4-hour visual monitoring task.

Caution should be exercised in applying these results because the after-effects of short and long term amphetamine or caffeine use have not been well studied. "Hangover" or withdrawal may act to reduce performance levels in subsequent testing on these variables.

Drug-Drug Interactions

Brown et al. (1974) attempted to use the apparent sedative effects of fenfluramine to offset the stimulant effects of d-amphetamine, to produce a nonstimulating anorectic. They were unable to distinguish between d-amphetamine and d-amphetamine and fenfluramine in combination. Fenfluramine alone was indistinguishable from placebo on tests of tapping rate, reaction time, digit symbol transcription, card sorting, and a cross-out test. Westheimer (1966) was able to demonstrate interaction between amobarbital and amphetamine in ocular accommodation/convergence ratio. The drugs when taken in isolation had opposite effects; the amphetamine reversed the effects of the barbiturate when taken approximately 1 hour after taking amobarbital.

Taylor et al (1964) and Wilson et al (1966) showed that amphetamines can reduce the depressant effects of alcohol, but the antagonism is selective; mental arithmetic and some learning tasks were improved by amphetamines (from their alcohol-depressed levels), however, motor coordination tasks were not.

In summary, there is evidence that stimulant drugs may enhance performance on a temporary basis and that they may selectively reverse depression of performance brought about by fatigue or other drug use.

GENERAL SUMMARY

ALCOHOL

Alcohol, even at moderate blood levels, diminishes performance on attention-intensive tasks, decisionmaking, and sensorimotor coordination (Moskowitz, 1973; Perrine, 1973). Tracking performance, reaction time, acuity for moving objects, glare recovery, and visual fields have been shown to worsen after alcohol administration (Adams et al., 1975; Brown et al., 1975; Huntley, 1973; Klein & Jex, 1975; Moskowitz & Sharma, 1974). These deficits, which have been shown in isolation, may be cumulative and mutually reinforcing in complex, stressful environments. For example, prolonged glare recovery may add to the problems associated with detecting and identifying peripheral moving targets; decisionmaking capacity, already diminished by alcohol, may thus be further compromised by the delay in acquiring adequate information through sensory systems.

Effects of alcohol on performance in complex simulation environments (especially those with direct military relevance) have not been adequately studied. The closest approach that has been made is in studies of driving under the influence of alcohol. However, such studies are restricted to simulators or artificial driving courses (e.g., Hansteen et al., 1976; Huntley & Centybear, 1974). No adequate cross-validation of the effects of alcohol found in the laboratory has been done with alcohol effects found under real world performance conditions. Two counteracting factors are in operation in the real world, and the level of performance to be expected will depend on the balance between them. On the one hand, psychological stressors (such as dangers to the performer and colleagues) will reduce the effects of alcohol; on the other hand, real world performance tasks are considerably more complex than those studied in the laboratory, and one would expect greater cumulative performance deficits in many situations, as outlined above.

The threshold level for measurable alcohol effects on performance is a blood alcohol level (BAL) of approximately 0.03 gram percent; however, there is considerable individual variation in this threshold level. Thresholds will vary also from task to task; more complex tasks will show effects at lower BAL's. Alcohol is cleared from the blood at a fairly constant 0.015 gram percent per hour; thus the time course of alcohol effects is predictable from a knowledge of current BAL. A subject with a BAL of 0.1 gram percent (the presumptive level for driving while intoxicated in California) will take 6-7 hour to reach a BAL of zero.

Once this zero BAL has been reached there remains the likelihood of diminished visual performance. The anecdotal evidence for "hangover" effects on performance is overwhelming. There has been virtually no research in this area which is of great importance, since every episode of intoxication is followed by hangover. During the hangover phase, the obvious effects of intoxication have

dissipated; we expect that sober personnel will be able to perform at an adequate level even on complex tasks. This assumption may not be justified.

Physical and psychological stressors can apparently improve the performance of alcohol-intoxicated subjects (Frankenhaeuser et al., 1974; Wallgren & Barry, 1970). This is an area of great potential interest in civilian and military environments and should receive urgent attention. Other factors, such as drug treatments that can reduce the effects of alcohol on performance or reduce BAL's, should also have high priority for future investigations.

Since alcohol is the psychoactive drug most commonly used in Western society, interactions of alcohol and other drugs have received attention from researchers. Forney and Hughes (1968) provide an excellent overview of this area. Actions of alcohol and other depressant drugs on performance are additive, with little evidence for potentiation. Barbiturates, benzodiazepines, and commonly used anti-motion-sickness preparations interact with alcohol to reduce performance. Alcohol and marihuana are commonly used together in social settings and have additive effects in reducing performance (Adams et al., 1978; Manno et al., 1971). Amphetamines may counteract the effects of alcohol on some cognitive tasks yet have little or no effect on other sensorimotor skills (Taylor et al., 1964; Wilson et al., 1966).

MARIHUANA

At socially used doses, marihuana reduces complex performance while producing surprisingly little effect on individual components of performance (e.g. Adams et al., 1975; Caldwell et al., 1969; Flom et al., 1976). For example, only small marihuana decrements can be shown on simple tracking performance, but when a concurrent detection task is added, performance on both tasks is degraded (Moskowitz, 1972). Because such visual performance tasks as driving and flying are divided attention tasks, one would predict from such laboratory data that performance on these tasks would be degraded by marihuana. This is indeed the case (Janowsky et al., 1976; Klonoff, 1974), although the effects are probably less than those produced by alcohol at equivalent levels of intoxication. However, the fragmentation of attention produced by marihuana undoubtedly degrades performance and may produce severe consequences for personnel engaged in hazardous tasks.

Smoked marihuana produces its effects in 5-10 minutes, and the effects last from 1 to 2 hours, depending on the dose. Orally ingested marihuana has a delayed onset (40-60 minutes) and a considerably longer time course of the effect. Most marihuana is ingested by smoking and is commonly associated with the use of alcohol. There is anecdotal evidence that marihuana users can voluntarily override the effects of marihuana use under stress. Some studies have been conducted in this area but it remains a target

for future work, especially in view of the widespread use of marihuana in the military and the potential for stress afforded by the military environment.

Marihuana is reported to produce no hangover phase comparable to that produced by alcohol. If hangover effects do exist, they must be relatively mild; however, subtle effects may persist and influence motor and visual-motor performance. The need for further study in this area is suggested also by the commonly reported combined use of alcohol and marihuana.

The frequency of use of marihuana and other drugs in military or civilian populations is unknown. Sociological and epidemiological research is needed to examine the problem; and if the results warrant, further performance-related studies should be conducted.

Chronic heavy use of marihuana appears to produce no significant effects on basic measures of visual function, although signs and symptoms of chronic anterior eye irritation may be produced (Dawson et al., 1977). Complex performance measures have not been examined in heavy chronic users; functions that involve components of prolonged attention, vigilance, and high levels of motivation should be examined in depth. The effects of the withdrawal of marihuana from chronic users on visual performance should also be assessed.

In reviewing the literature on the effects of opiates, depressants, hallucinogens, and stimulants on vision performance two problems arise. First, the literature is sparse; compared with research on alcohol and marihuana, relatively few studies have been conducted. Second, the extent of the problem produced by use and abuse of the drugs is not clear. To establish priorities for future work, epidemiological studies of the extent of the problem should be conducted.

OPIATES

No references that bear directly on complex visual-motor performance studies were noted. The work of Monty et al. (1975) and Rothenberg and his colleagues suggests that visual and oculomotor processes may be influenced in opiate-intoxicated subjects and that these processes clearly may bear on visual performance. Whether compensatory behaviors can overcome any deficits is not known; further study of complex visual-motor behavior is necessary.

DEPRESSANTS

Depressant and sedative drugs, at commonly prescribed dose levels, may produce decrements in manual tracking and oculomotor performance for up to 8 hours after ingestion (see Stoller and colleagues). In general, skills such as driving and flying are impaired (Betts et al., 1972; Billings et al., 1975), although

in anxious patients driving performance may improve (Moore, 1977). When depressant drugs are combined with alcohol, a further reduction in performance is generally produced (see Forney & Hughes, 1968). The effects of depressant drugs may be offset in some measures by stimulants such as amphetamines; however, such interactions are complex and the expected antagonism is not invariably present.

HALLUCINOGENS

There have been anecdotal reports of alterations in spatial perception and color perception in subjects under the influence of hallucinogens; however, little scientific literature exists in this area. Hill, Fischer, and associates have confirmed that spatial distortions may be produced by psilocybin, but the relationship of these effects to complex visual performance is not clear. No studies of driving or complex motor skills in subjects under the influence of these agents have been found in the present review. This is an area that should receive attention.

STIMULANTS

The use of stimulant drugs to improve performance or to counteract the effects of fatigue or other durgs is an area of obvious military concern. Evidence exists that drugs in this classification may improve some aspects of complex visual performance in such situations, but the effects of the drugs are selective. Some aspects of performance may improve while others stay at the previous levels. Whether there are medium to long term effects of these drugs on aspects of visual functioning is not clear; it is clear, however, that the amphetamines, the most widely used stimulants, are addictive.

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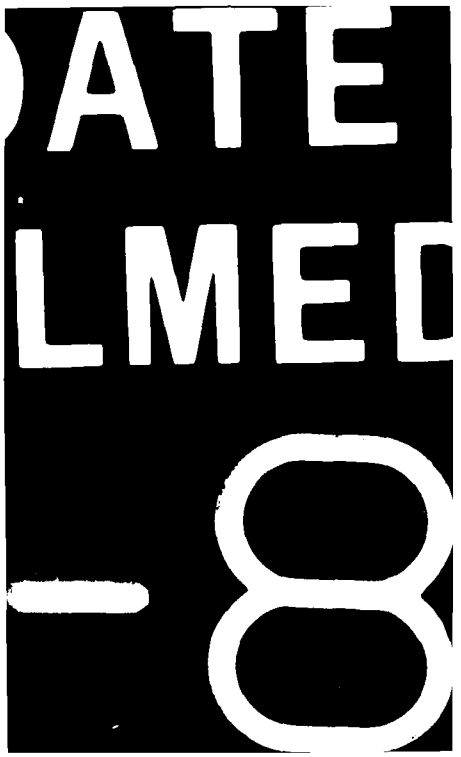
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