National Institute on Drug Abuse

Research 11

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Drugs and Driving

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE • Public Health Service • Alcohol, Drug Abuse, and Mental Health Administration

DRUGS and DRIVING

EDITOR

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ON DRUG ABUSE

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ACKNOWLEDGMENT

A complementary volume to this, entitled *Drugs and Driving: A Research Review* (contract DOT-HS-4-00994) will be available through the National Technical Information Service. In addition, the reader should be aware of an ongoing DOT National Highway Traffic Safety Administration project (*State of Knowledge and Information in Alcohol/Drugs and Highway Safety*; DOT-HS-5-01217) that is critically evaluating existing research pertaining to drug related accident risk, and is preparing a comprehensive outline of the additional research required to assess fully the magnitude and extent of the drug/highway safety problem. The final report will be available towards the end of the year.

NIDA is grateful for the contribution of DOT observers at the conference. The conference summary in this monograph is an initial probe to identify key areas for future research attention where present findings remain uncertain and sometimes controversial. The conference summary should not be taken as representing DOT policy or interpretations.

Thanks are due the people of Research Triangle Institute, who capably organized and coordinated the panel conference, held August 20, 1976 at Rockville, Maryland, under NIDA contract 271-75-1016, from which the papers of this monograph are derived.

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FOREWORD

It is now fashionable to recognize the negative effects of the rapid growth of technology in the 20th century. Nowhere is the negative side of this revolution more striking than in the area of drugs and driving. The world is now on wheels. High-speed vehicles are in the hands of virtually everyone over the age of 16. Impaired driving dramatically raises the risks we each face daily--not only the risks inherent in our own driving performance but those which result from the performance of other drivers.

Not only has technology let us get behind the wheels of cars, it has also opened a treasure chest of old and new mind-altering chemicals. Only in recent years have we begun to grasp the significant role played by alcohol in highway safety. Within the last decade the drug use epidemic has added a complex array of other drugs which influence driving ability. For example, the National Institute on Drug Abuse surveyed the Nation's 1976 high school graduating class finding that just over 8 percent reported daily marihuana use--compared to 5.9 percent who reported daily alcohol use. We know that marihuana intoxication produces severe deterioration in driving performance. We are left to guess at the impact of marihuana use on highway safety--and our best guesses are frightening.

No less of a concern is the problem of prescription drug use and the problem of multiple simultaneous drug use.

This monograph presents a critical review of the available literature relating drug use to driving and other complex human performance. It offers recommendations for the future.

Adequate studies are scarce. Part of the problem is establishing measures of driving skills and relating these skills to the use of different types of drugs, at various dosage levels, at differing periods of time after drug administration, and in a wide variety of settings. The characteristics of the driving drug user--which change with time, often over very short time periods--also vastly complicate the issue. Even determining how many accidents are drug-related is difficult. When the concept of "cause" is introduced, the problem is made even more difficult.

It is now a matter of urgency to know the implications of drug use for traffic safety and accident risk. Once a body of knowledge is assembled, we can begin to consider proposing preventive or legal responses. Towards that end we must isolate a few specific driving components that are acceptable indicators of driving skill and measure the impairment produced by different drugs at various levels.

The first challenge in highway safety is to measure impairment. Then we must get impaired drivers off the highways. One major cause of impairment is drug use--including alcohol use. The drug user--and we now know he is "us"--is responsible for his behavior, including his driving and his drug use. Once having detected impairment of driving, the sanctions imposed could surely be tailored to fit the causes of the impairment. But the critical first question is detecting impairment.

Robert L. DuPont, M.D.
Director
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PREFACE

Research into the relationship between drugs and driving highlights a complex policy question raised by extensive government supported biomedical research efforts. How does one translate incomplete knowledge into appropriate policy decisions, where action or inaction can mean the difference of thousands of lives and hundreds of thousands of serious and maiming accidents? A related question is: How does one avoid an unnecessary tug of war between the need to expand knowledge, on the one hand, and the need for serious inquiry concerning the potential application of available but incomplete data on the other?

Thus, we know that alcohol plays a role in roughly half of all our fatal car crashes - 47,000 deaths in 1976. It plays a role in a fourth to a third of all serious accidents - 1.8 million. Apart from the pain and suffering of the individuals and families involved, the economic costs are astonishing - $25.1 billion.

Though the situation with drugs other than alcohol is not as clearcut, there are disturbing straws in the wind. A recent study of 300 Boston area fatal car accidents indicates that 39% involved driver use of alcohol or a combination of alcohol and other drugs. An additional 9% involved other drugs (marihuana, barbiturates, etc.) without alcohol. Of the total drivers, 16% admitted to being under the influence of marihuana at the time of the crash. In other limited surveys from 60 to 80% of marihuana users indicated they sometimes drive while cannabis intoxicated. To some significant but as yet quantitatively uncertain degree, widely used drugs other than alcohol contribute to the toll levelled by alcohol.

Given these circumstances, some proportion of our current research efforts should be directed towards further elucidation of the mechanism of action of such impairment and its precise degree of impact. And some should be directed to policy research issues which systematically and empirically evaluate alternative options for applying present incomplete knowledge to reduce the unnecessary consequences of driving under the influence of various psychoactive drugs.

We are not aware of any simple formula for determining these proportions. However, it is our strong conviction after reviewing current efforts along both of these dimensions that two conclusions are clear: a) it is essential to maintain a balanced, vigorous program of research along both of these avenues, and b) presently it is the second area, the area of policy research, which is grossly deficient and needs to be substantially strengthened and reinforced.

We need to be more certain, for example, of varying consequences and differential levels of success of different approaches to regulating driving under the influence of drugs. "Hardline" laws in the form of high fines and long prison terms are not necessarily effective, particularly if judges and juries therefore refuse to convict. A more effective approach appears to be engendering two kinds of awareness in the public, of the real danger and cost of intoxicated driving, and of a reasonable certainty that violators will be caught for it. Sustained public education, large numbers of arrests and a justified public fear of arrest appear to reduce crashes.

At the recent Seventh International Conference on Alcohol, Drug and Traffic Safety, in Melbourne, Dr. H. Klette ("Politics and Drunken Driving-The Swedish Experience") reported that Sweden, in an effort growing over a number of years, now has few drivers on the road with BACs (blood alcohol concentrations) from 0 to 0.08 and one tenth as many drivers at high BACs as we do. Sweden's experience suggests that strictly *enforced* laws can greatly decrease the number of social drinkers who drink and drive. Experience from the Netherlands, somewhat like Britain's, suggests two rules that, combined, can effectively reduce the number of crashes and high BACs on the road. Dr. P.C. Noordzij ("The Introduction of a 0.05 Limit in the Netherlands, Effect on Drinking and Driving") reported for the Netherlands a decrease of about 10% in crashes and 25% in high BACs on the road with these two rules in effect. The first rule is that driving at BACs over 0.05 is *itself* illegal, rather than, as with most of our laws, merely presumptive evidence of impairment (at>0.10). The second is that a screening breath test can be *required* of any driver, rather than, as with most of our laws, only if there is "reason to believe" the driver has been drinking. In our own country the "systematic programs" of the Alcohol Safety Action Project suggest that the integration of public education, increased arrests, court capacity and treatment programs may contribute to reducing the number of crashes. Two caveats are relevant. Large scale random testing of drivers on the road is expensive and may be a civil liberties infringement we would be reluctant to accept. Secondly, the measures described do not substantially affect two groups who are overrepresented among drivers in car crashes, the young and the problem drinker. The latter needs much stronger motivations, legal sanctions and treatment to stop drinking and driving.

Policy research, the systematic and intensive effort to study the consequences of regulatory approaches and develop new ones, is an area we hope to strengthen substantially, in conjunction with related agencies such as the National Institute for Alcohol Abuse and Alcoholism and the Department of Transportation. In the meantime, the less dramatic but equally essential efforts to study the other component parts of the jigsaw puzzle continue as a major responsibility.

For drugs other than alcohol, such policy questions are equally relevant, but more basic research questions must still be answered. This volume undertakes to do this. Thus, its emphasis is propaedeutic and prospective. The first two chapters outline recommendations and research directions. But the ultimate objective is the same. Too many people die or are maimed in these avoidable car accidents. This is uncalled for and unacceptable. Drug research needs to determine how many of these are due to which drugs at what dose levels and time elapse from intake. It needs to develop accurate and appropriate quantitative assay techniques, perhaps roadside tests, for these drugs, and justifiable behavioral tests for driving impairment. As this volume indicates, none of these tasks is easy.

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CHAPTER I
INTRODUCTION

Evidence has been accumulating that licit and illicit drug use causes impairment of driving and other complex human performance. This use is believed responsible for accidents and deaths from traffic collisions. Some studies have shown a correlation between drug dose and performance decrements. Assays measuring the presence of drugs in fatally injured drivers have suggested drug use as a significant factor in many of these deaths. Although alcohol alone and combined with other drugs predominates, a high rate of marihuana use among drivers indicates it could be a factor in traffic accident and fatalities.

Primarily for these reasons, the National Institute on Drug Abuse (NIDA) undertook to sponsor a critical review of this research literature, to see how much we know and we still need to know. This was directed specifically to drug effects and is intended to complement earlier surveys and reports published by the U.S. Department of Transportation (DOT).

Illicit, prescription and over-the-counter drugs are included in this review. Some alcohol studies are covered, with strong emphasis on studies of alcohol in combination with other drugs. The critical analysis concentrates on the type of performance functions tested or measured, and methodological approaches used. Detection techniques are also included.

The review was conducted by a panel of nationally recognized experts on the behavioral effects of drug usage. Each expert on the panel prepared an individual summary review and critique of a portion of the literature. The summary reviews are organized by drug clusters, selected according to the World Health Organization's designation and grouping. References for the studies selected by the panelists for review are included at the end of each individual review.

Chapter II is a synopsis of the issues and recommendations developed by participants at the Rockville conference at NIDA. Participants included panel members and staff representatives from NIDA and DOT.

Chapter III consists of a summary of position papers prepared by the panelists to guide discussion of issues identified through the individual reviews. This discussion took place at a conference sponsored by NIDA on August 20, 1976, at Rockville, Maryland. Its purpose was to integrate these many complicated issues into coherent working order.

Chapter IV presents the individual papers of panel members. Since some drug clusters were much larger than others, the panelists divided the larger clusters and some took more than one of the smaller ones. Moreover, there are between-individual reviews variations in approach and degree of detail, variations we elected to preserve on the whole, in deference to the panelists' individual judgment. Nevertheless, the papers read in more or less serial and uniform order.

The task the panelists undertook in writing reviews and critiques is not so very different in kind from journal review articles that are published periodically to keep an audience up to date on what is happening in a given research area. Thus, Dr. Linnoila reviews the literature on anesthetics and impaired performance, and with Drs. Jane Speaker and Morton Mason considers tranquilizer effects on performance. Dr. Mason also covers the opiates. Dr. Sharma considers the sedatives and Dr. Forney the stimulants. Dr. Moskowitz reviews the hallucinogens and with Dr. McBay, marihuana. Other psychotropic drugs, including antianxiety, muscle-relaxant and antihistamine drugs, singly and in combination with ethanol, are reviewed by Drs. McBay, Smart and Stitzer. There is some overlap of the same drug in more than one cluster, but this was preferred to leaving some studies unreviewed simply from incongruence with our drug categories.

But there was a second more unusual and still somewhat novel task asked of the panelists in coming together for the conference. They were asked collectively to do a second-order review of the entire topic of drug-induced driving impairment and on the basis of the individual research reviews they had just completed, pool their judgment in order to focus on what questions now most need answering and what priorities should be adopted for further research. This task calls on research scientists to use their expertise with a broader perspective and more general judgment than is customary, but in a very specific way. It was no easy task, and the documents of chapters II and III are the result.

This is certainly not the last chapter on issues related to assessing the problem of drug effects on driving. It represents an attempt to provide a continuing review and evaluation of our growing knowledge. We hope that it will aid and guide future efforts.

Robert Willette, Ph.D.
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CHAPTER II
SYNOPSIS

A. INTRODUCTION

This synopsis is organized into four major sections. The introductory section summarizes opening remarks to the panel by Dr. Willette and Dr. DuPont. The second section summarizes the "state-of-the-art" of current investigations presented by representatives of NIDA and the National Highway Traffic Safety Administration (NHTSA) of the U.S. Department of Transportation (DOT). The third section defines the issues raised by the panel. The fourth and concluding section contains recommendations developed by the panel for future governmental initiatives.

Dr. Willette directed the panelists to focus discussion on the effects of drugs on complex human behavior, particularly driving. He stipulated the need for an action plan based on the participants' review of the state-of-the-art in drugs and driving and recommendations for alternatives to be pursued by the government in this area.

Dr. DuPont presented some general information to the group. Three national data systems were briefly described: (1) the National Drug Abuse Treatment Systems (NDATS), which generate quarterly reports on the approximately 25,000 admissions that are made to drug programs each year; (2) the Drug Abuse Warning Network (DAWN), which concentrates on data from emergency rooms and medical examiners and reports on a monthly basis; and (3) annual national surveys, such as the 3-year followup survey of high school seniors.

Based on these data, Dr. DuPont expressed the need for public awareness of the dangers of driving under the influence of alcohol, marihuana, or a combination of the two, especially among the adolescent population. The mandate to the participants was to review the subject of drugs and their influence on human performance, and to specify the knowledge base of the impact of drugs on driving, from which alternative courses of action could be determined.

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B. PREVIOUS AND CURRENT NIDA-DOT RESEARCH

Studies sponsored by DOT have involved mainly alcohol and marihuana and have tested visual search, decisionmaking and risk-taking with respect to driving behavior. Lane-shifting frequency and pedal-to-brake time are being evaluated as possible criteria by DOT researchers as measures of driving performance. However, it is difficult to correlate performance on visual search behavior and risk-taking decisions with various drugs.

DOT studies that focus on specific drugs include drugs that improve driving performance in general as well as prescribed medication taken to alleviate certain health conditions of drivers. Ramifications of such cases for punitive legislative action are included within the scope of these studies. Among the ramifications are: (1) DOT studies have shown no deterioration of driving performance of subjects on methadone maintenance compared to a nonmethadone using control group. However, these findings may be due to the fact that the subjects had been in treatment for 6 weeks and had developed tolerance to the effects of methadone. (2) Studies of heroin users indicate that these individuals drove better than similar controls, but this finding might be attributable to overcompensation based on the users' fear of being stopped by police.

There have been no studies that have concentrated entirely on amphetamine usage, due partly to the lack of adequate detection assay techniques. There are no reliable studies of the effects of previous amphetamine use on subsequent driving performance. Most studies of this drug have relied on self-reporting and driving records and the results indicate that amphetamine users are slightly more accident-prone than users of other drugs. However, these studies are not well controlled and therefore are not necessarily reliable indicators of the influence of this drug on driving performance.

Studies on the involvement of drugs in fatally injured drivers are going to be continued. Up to 2,000 samples have been obtained over the past 2 years and analyzed for 60 drugs. Attempts have been made to analyze samples from matching controls, but failure to obtain adequate cooperation from living drivers continues to hamper interpretation of data from these studies.

Most studies of the relationships of drugs and driving must overcome problems of assessing the presence of drugs in the body. The most sensitive measures of the presence of drugs are still only obtainable from laboratory assays since there are as yet no portable means of detection. NIDA and DOT are developing instrumentation for the detection and quantification of marihuana from blood, breath and saliva. This instrumentation may hold some promise for roadside testing in the future. The possibility of obtaining samples immediately after a collision at the scene of the accident or traffic stop and analyzing them later in the laboratory is also being explored.

At the present time NIDA is sponsoring research, partly in collaboration with DOT, to detect marihuana consumption through measures of the concentration of THC (the active ingredient of marihuana) in body fluids such as saliva. These tests show, however, that marihuana is not easily detected after 1 hour. Several tests are being developed using immunoassay analysis, mass spectroscopy, and gas chromatography. However, the overriding question of whether and how the levels of drugs in the body correlate with performance needs to be determined and is being actively investigated.

At the present time NIDA, in collaboration with DOT, is involved in a 3-year pharmacokinetic study of nine drugs and their effects on basic behavior. The objective is to study, in simulated realistic settings, basic behavioral measures while determining drug levels in body fluids. Once these correlations of behavioral measures to drug levels are considered established, other findings will become more meaningful and may help establish some basic methodological procedures for future research. Multiple approaches are being used to determine the relationships between the time of drug taking and driving, dose levels, and drug typology.

Other NIDA-sponsored efforts are being carried out with cannabinoids (detecting THC and derivatives via mass spectroscopy), diazepam, methadone, amphetamines, benzadrine, cocaine and its metabolites, PCP, LSD, and other drugs. Almost all of these efforts deal with plasma assays. One of the goals of these efforts is the development of a handbook and procedural manual to increase familiarity and use of mass spectroscopy methods. Plasma assay studies are also being conducted by other institutions under contract to NIDA and DOT. Similarly, proficiency testing regulations for urinalysis and toxicology laboratories are being developed to increase the accuracy and reliability of assays for drug presence.

C. ISSUES

The panel identified four major categories of issues: epidemiology, laboratory studies, assay development, and legal questions. The substance of each category provided the context within which recommendations for future studies were developed.

1. Epidemiology

Current epidemiological studies of drugs and driving are frequently characterized by poor sampling procedures and result in making inappropriate inferences to the population of interest. For example, only limited data are available on the differences in drug use or abuse between the accident population and the total driving population. The sample design of studies in which observations are restricted to fatally injured drivers in hospital emergency rooms leads to overreporting of alcohol consumption from accident records, if these consumption patterns are assumed to be indicative of those of the total driving population. For another example, the sample

design of a study with observations restricted primarily to accidents that occur in the evening fails to detect the number of accidents attributable to the use of tranquilizers by the middle-aged female population, which does most of its driving during the day. In addition, users of illicit drugs, especially opiates, constitute a difficult population to study because of problems of locating them by conventional survey methods.

Epidemiological studies are also frequently characterized by the lack of an appropriate control group. For example, epidemiological studies with individuals on methadone maintenance have shown that, because tolerance develops rapidly from the time dosage is established, methadone maintenance shows little effect on task performance. Some of these studies included the use of control groups such as drug abstainers and hospital patients. However, these may not be the most appropriate controls. Differences observed between these groups and individuals on methadone maintenance may be due to different lifestyles or environmental conditions--such as those found in hospitals compared to the methadone subculture--rather than simply to drug conditions.

Procedures for collecting data for these studies are sometimes inappropriate. For example, these studies frequently use self-report data. Heavy drinkers usually tend to underreport both the quantity and frequency of drinking patterns. In addition, self-report data are sometimes characterized by only "yes" and "no" responses that fail to provide details of drinking episodes. Data obtained through studies that develop records contained in systematic drinking diaries were suggested as a potentially more accurate and successful technique for data collection.

A final shortcoming of epidemiological studies is often the failure to include appropriate qualifications in the analyses of study results. The factors of race, sex, and ethnicity may be important to consider in these analyses, since different groups display varying levels of ethanol tolerance. Other important variables for research consideration include age, duration of drug effect, and fatigue level of the subject. The importance of including sex as a variable in these analyses is underscored by the facts that previous studies have indicated that the driving performance for females is impaired at lower blood concentration levels than it is for males and that visual vigilance among females is impaired significantly by alcohol more quickly than among males.

2. Laboratory Studies

Experimental studies of the relationships between drug usage and performance decrements, conducted primarily in a laboratory setting, are also frequently characterized by problems of poor subject selection. Anxiety levels in laboratory subjects, generated by concern about experimental procedures, have a direct influence on changes in performance, as previous studies have indicated that the

degree of drug-induced impairment may be directly related to the level of anxiety in the subject.

Further, restrictions concerning the use of female subjects in the childbearing age group in experimental drug studies are an additional factor that limits selection of subjects for this type of study. These restrictions may constitute an impediment in developing tests for male-female differences in drug response.

More specific operational definitions of performance decrements in the laboratory setting should be developed. With respect to driving performance, a clear specification of how vigilance should be operationally defined should be prepared. One example indication of vigilance is the frequency of checking side and rear-view mirrors in a simulated driving situation within the laboratory.

A clear specification of hypotheses suitable for testing in a laboratory setting is needed. This need is important in assessing the relationship between the degree of drug-caused impairment and time of drug ingestion. For example, there are no systematic studies of the relationships between the use of sedatives and changes in performance skills over a period of 10 to 14 hours after ingestion. Hypotheses should be carefully developed and tested to determine whether performance capacity could be decreased by aftereffects, even when performance levels initially increase, as is the case with stimulants. Further, initial improvement in performance could decrease or change to impairment with chronic use of drugs.

Polydrug use introduces additional complications in developing and testing these hypotheses. These include the fact that the kind as well as the degree of impairment caused by a combination of drugs may differ markedly from that caused by either drug alone. The respective impairments are not necessarily additive.

Reliable evidence of the effects of drug and alcohol use on human performance is not presently available from laboratory studies. In laboratory studies of some 2,000 subjects at different drug levels, the pharmacokinetics of drug use were found to be different from alcohol and differed from each other, since these drugs have different kinds of distribution throughout the body, metabolize differently, and reach equilibrium levels at different rates. Thus, less straightforward correlations and greater variation can be expected for the results of studies of drugs other than alcohol, with the consequence that the results of these studies are difficult to interpret. These problems can be addressed by developing statistically valid experimental designs that include these intervening variables so that the relationships between different drugs and human performance will become clearer. In addition, *awareness of impairment* from drug use may induce overcompensation that actually improves performance (over controls) and this factor should be studied.

The most realistic information on the effects of drugs on complex human performance is acquired through analyses of drug-influenced subjects in actual performance situations, such as driving. But studies of this type are rarely possible and the very complexity of a performance such as driving makes results difficult to assess. Thus, it is desirable that the experimental studies conducted in more controlled laboratory settings test a broad range of less complex behavioral responses that can be related to responses involved in realistic performance situations. These studies should include an assessment of the effects of different dosage levels of various types and combinations of drugs. However, the usefulness of the results of these experimental studies will continue to be somewhat limited until specific behavioral responses studied in the laboratory can be plausibly linked and correlated to complex performance in the real world.

3. Drug Assays

There are major differences in the methods required to detect and measure the presence of alcohol and drugs in the body. There is a strong need for the development of improved detection techniques, given the current analytical capabilities of most laboratories. Since only a few drugs are found in high concentrations in the blood, these techniques should be developed for breath as well as for other body fluids. These detection tests are particularly important for use among individuals involved in accidents and should be developed for use in autopsies as well as among nonfatalities.

Increased emphasis is needed on the study of threshold effects, controlled for body weight and drug concentration. The determination of the relationship between drug levels and blood concentrations has significant implications for the legal problem of adjudicating accident liability. Currently, chemical analysis alone cannot be used reliably for legal action, since individual variations in tolerance and thresholds for performance decrements differ widely.

The reliability and suitability of urinalysis as an appropriate detection technique to be used in establishing the effects of drug use on performance are as yet unknown but concentration studies might be helpful, even when conducted with dead subjects. However, the results of these studies should be interpreted with caution. For instance, methadone has been shown to be present in urine up to a week after intake and propoxyphene up to 18 hours, presumably far too long a time period for these substances to affect performance.

4. Legal

Efforts should concentrate on determining the effects of each drug's use on performance and the role of various intervening variables such as body weight, sex, age, dosage, time since

ingestion, etc., in this relationship, rather than on addressing legal issues with respect to the effects of drugs on performance, particularly driving performance. The problem of impaired driving caused by the influence of drugs should be taken one step at a time, beginning with a determination of the actual effects of various drugs on behavioral reactions and then investigating the relation of these impaired reactions to actual driving behavior. This phased approach is particularly appropriate in view of the nature of the relationship of the dosage of certain drugs to performance, since small amounts of ethanol or stimulants may improve performance while increased dosages, depending on body weight, may be detrimental.

Although various law enforcement measures have not been notably successful in reducing the effects of alcohol on driving behavior, they should be reexamined to determine if they might be useful in the case of other drug abuse. At a minimum, the medical profession should be encouraged to develop effective standards for prescribing drugs and increase public awareness of the possible detrimental effects of drugs on driving performance.

D. RECOMMENDATIONS

Recommendations were developed in three major categories: (1) drug categories to be studied, (2) methodological issues, and (3) prevention strategies.

Panel members reached a consensus concerning these recommendations. They were able to place priorities on the drug categories to which future studies should be directed, but did not do so for methodological issues or prevention strategies. Therefore, the materials in the final two subsections only summarize the recommendations of the panel members.

1. Drug Categories

a. The first level of priority for further study is alcohol. Alcohol causes the greatest problems in impairment of complex human performance, due to its frequency and quantity of use. Studies of the detrimental effects of alcohol on human performance should focus on blood alcohol concentration levels of 0.10 percent and greater. The primary goals of studies within this priority category should be to determine with greater precision the frequency and quantity of use by people engaged in complex performance, to assess the frequency of use of alcohol by these individuals as against that of marihuana and cigarettes, and to determine how much the impairment caused varies with the frequency and quantity of use. In addition, the effects of alcohol in combination with other drugs should be assessed more thoroughly. (However, unlike the panelists, DOT spokesmen felt that levels *below* 0.10 should receive greater attention, since legal definitions at these levels are still vague).

b. The second level of priority for study is cannabis and diazepam (Valium) and their derivatives. The panel members agreed that because of differing patterns of usage, studies of cannabis and its derivatives should be restricted primarily to younger members of the population while studies of diazepam and its analogs should be restricted primarily to older members of the population. The primary goals of studies within this priority category should be to determine the frequency of use of these drugs by people engaged in complex performance, to obtain more complete laboratory evidence of the drugs' behavioral effects, to assess the degree of impairment caused and/or directly related to drug intake, to determine the relationship between this impairment and the traffic accident probability, and to develop improved techniques for detecting and recording concentration levels of these drugs in various body fluids.

c. The third level of priority of drugs for study is sedatives and hypnotics. As in the case of the two higher priority categories, a principal goal of studies of drugs in this category is to determine more precisely the relationship between their use and the impairment of complex human performance. Other goals of studies of these drugs include the development of more accurate and realistic assays for detecting the presence and level of these drugs in the body, and improved techniques for detecting changes in the use of drugs in this priority category--for example, by comparing information on sales and prescription figures for these drugs to levels of abuse among the population.

2. Methodological Issues

Panel members suggested a number of methodological topics that should be the focus of future studies, but did not rank them. A summary of these methodological topics is provided in the following paragraphs.

a. Epidemiological Studies. A major focus of future research should continue to be epidemiological studies. But the usefulness of these in the past has been limited because the target populations are recent imbibers of various types of drugs in different amounts who have had driving accidents (or shown other evidence of performance decrements). An adequate "fix" on these populations is hard to come by without assays for detecting drug concentration levels. Drug concentration levels have been obtained from studies involving alcohol and also for certain other drugs. Current DOT epidemiological studies have obtained data from both fatal and living drivers and drug concentrations for drugs such as those falling under the heading barbiturates. Methods for detecting marihuana concentrations in urine, plasma, saliva and breath are now being developed.

Research topics include: (1) establishing correlations between people exhibiting drug-induced performance decrements and

accident probabilities, (2) cost-benefit analyses of various countermeasures such as public education to alert and perhaps mitigate performance decrements, (3) analyses of the relationships between multiple drug use and accident probabilities, and (4) comparing the nature and severity of accidents to types of drug use. Future epidemiological studies should use information from appropriately designed samples to avoid improper generalization from small sample sizes or inadvertant over/underrepresentation of a particular population.

Increased emphasis should be placed on studies of injuries in an industrial setting, since detrimental effects of drugs on job performance may be as serious a problem as on driving performance. Studies currently underway to assess the extent of drug use in industrial settings could be expanded to include an assessment of the relationship between drug use and performance decrements.

An important source of data for future studies may be hospitals. In the future, better accident data may be collected from emergency rooms (ER) and medical centers since accident victims are being brought more frequently to these facilities where better medical care is available. Investigators might achieve better cooperation from ER personnel for these studies by stressing their importance in the overall strategy to assess the relationship between the use of drugs and alcohol and accidents and injuries that require hospitalization.

But epidemiological studies that rely on data collected in a hospital setting present problems. These include the need to obtain data from an appropriate control group, the difficulty in establishing causality in an accident investigation, and the previously cited problem of potential overrepresentation of drug users among accident victims.

b. Laboratory Studies. Two principal reasons dictate continued emphasis on laboratory studies. First, most reliable available information on drug-induced performance decrements has been obtained from laboratory studies. Second, studies should focus on the causal relationship between changes in body chemistry that occur as a result of drug ingestion and changes in specific behavioral components rather than on trying to link drug use directly to changes in complex performance such as driving and flying. Laboratory studies are obviously an appropriate approach for assessing these chemical-behavioral component relationships. Furthermore, "real life" actual performance studies will always be characterized by difficulties in establishing the causal relationships between drug usage and performance decrements, due to the presence of large numbers of noncontrollable intervening factors.

Future laboratory studies should include development of a battery of psychomotor tests to detect the presence of certain side

effects of drug use, such as changes in risk-taking, and the development of procedures to assess the magnitude of these side effects.

c. Drug Assays. Improved techniques for drug assays are needed because frequently the reliability of the assay report is uncertain and laboratory procedures are not controlled. In addition, relatively few laboratories in the United States are capable of producing reliable results for a sufficiently wide spectrum of drug assays. Of these laboratories, an even smaller number are aware of and have implemented rigorous quality control procedures.

A battery of tests to measure impairment as a function of dose is needed. So also are improved analytical methods of measuring blood concentration levels. Development of each of these measures is needed to specify more precisely the possibly nonlinear relationships between levels of drug concentration in the blood and the degree of impairment.

Drug assays should establish lethal levels of drugs such as barbiturates and aid in the selection of appropriate countermeasures and prevention strategies. Countermeasures are frequently conceived in terms of punitive legislative initiatives that are often relatively ineffective in altering drug utilization. An alternative countermeasure might be a decision to issue warnings of detrimental side effects of usage.

3. Prevention Strategies

In order to provide a basis for an overall drug prevention strategy, studies of unnecessary usage of tranquilizing drugs in the United States should be undertaken. These studies should include a followup of persons found to be using these drugs unnecessarily, to determine the effects of withdrawal from drugs. Methodologies for conducting these types of studies are currently underway in Canada and should be relatively easily transferred to similar studies in the United States.

Law enforcement officials should be educated to focus more on erratic driving behavior itself rather than on the causes of such behavior. Drivers should be arrested for "driving erratically" rather than for "under the influence," as present detection methods for the presence of drugs in the body are not sufficiently developed for determining the causal relationship between drug use and erratic driving behavior.

Other prevention strategies are expanded labeling and education programs. The former would provide information on drug labels concerning the length of a safe time span from drug intake to safe driving. The education program should focus on individuals who frequently dispense drugs, such as doctors and pharmacists,

and should provide them with information concerning the detrimental effects of drug usage on human performance. At present, drug companies are including warning messages on packages of a large number of drugs, with the consequence that the information content of these messages may be extremely low. This problem can be overcome by defining a certain level of risk associated with the drug use that warrants the development of warning labels. These levels of risk can be derived from the recommended epidemiological and laboratory studies and from the drug assays.

CHAPTER III
SUMMARY OF POSITION PAPERS

In the course of considering the many issues surrounding the identification and definition of the effects of drugs on driving performance, several problem areas and unanswered questions have been identified. They fall into six major categories: epidemiology, experimental design and performance measures, the relationship of drug levels to performance (pharmacokinetics), subject variables, drug selection, and legal and prevention concerns.

Epidemiology

At best, any epidemiology study presents difficulties and the driving area is particularly complicated. At present, it is felt that insufficient information is available to confirm that a drugs-and-driving problem exists. Common sense suggests some risk is likely. Studies in the past have concentrated on fatally injured drivers and greater attention must be placed on nonfatal accidents, accident-involved pedestrians and passengers. We know relatively little about how often drug users get into accidents, what type of accidents they get into, and how often and where these accidents occur. There is a strong need to pinpoint populations at risk and establish the magnitude of the increased risk to them from driving under the influence of drugs. And finally, there is a significant lack of information about the relationship between drug levels and accident frequency.

In an effort to minimize the need for carrying out the costly and difficult epidemiology studies, numerous laboratory or experimental studies have been conducted to identify drugs that can impair driving performance. The experimental design of these performance measures are exceedingly important and often fall short of producing the desired result. Several observations and suggestions are in order.

1. Good driving performance should be measured objectively and numerical values assigned to various driving behavior components. Measuring effects of drugs on particular components rather than on some vague general competence called "good driving" would provide a more meaningful test.

2. Drugs may alter performance but other variables such as physical state of the driver, road conditions, vehicle condition, may be more important determinants of performance failure. These factors should be taken into account.

3. Tests should be developed which would assess the likelihood that people drive or operate machinery after taking drugs. This would help establish the size of the problem.

4. One should compare simulator performance with real performance to establish the validity of the former in predicting the latter.

5. Subjects should be tested under actual driving conditions with validated real performance tests and also under simulator conditions with behavioral tests of driving skills having a face-valid relation to real performance tests. Such test results would help link these levels of testing so that eventually a few simple psychomotor tests might be acceptable, valid indicators of real driving competence.

6. Dose-effect functions of a drug should be compared on several behavioral tasks which tap components of "real" driving performance to establish a profile. Once such sensitivity profiles are established, the ability of various behavioral tasks to predict performance tasks could be determined. This approach would establish predictive potential and behavioral mechanisms necessary for driving skills.

Experimental Design and Performance Measures

Attention should be paid to the following facts: Drug-performance level relationships are inadequately defined because drivers differ in their skills prior to taking drugs; some drivers may be tolerant to drugs from chronic use; drivers may be able to compensate for drug effects when motivated. Baseline standards should be established against which subjects can be measured and evaluated. More emphasis must be placed upon tests of perception. Visual tests, in particular vigilance tasks, are essential to include in any battery of performance tests. Specific types of studies should include tests of vigilance performance, drugs interaction studies using sedatives, tolerance-behavioral impairment and cross-tolerance behavioral impairment studies. Length of training is important since some drugs may improve skills of (inexperienced) subjects while these same drugs may produce deterioration in experienced subjects. Motivation must be considered and controlled in any studies conducted.

Dose response studies are more useful than single dose for single-drug studies. Further, these should be administered under blind and double-blind conditions in a crossover design to assess contributions of suggestibility to drug impairment.

Many believe that the best studies are derived from measured driving performance conducted in closed driving courses. Possibly two or three simple, rapid, controlled laboratory measures can be agreed upon as relevant indicators of driving performance to acquire valid data for public policy purposes. Others believe that although used for safety, closed courses are inadequate for testing drug effects because driving skill interacts with a variety of vehicles, road and environmental factors which produce more natural driving situations. Simulators also are only part-task devices, since only some of the necessary skills are measured. Thus, the contention is, rather than attempt to measure total driving performance inadequately by closed courses or simulators, it is more useful to break up the notion of driving performance into plausible indicator behaviors and then measure them for drug impairment.

It has been difficult to establish a representative sample of required behaviors involved in driving performance, demonstrated by the low correlation between driving test evaluation and accident histories. The tasks selected in a testing program should be specified in terms of the behavioral demands made on the subject and this should be the basis of comparison between tasks. The selection of tasks to examine could be skills most highly correlated with driver performance and those performance skills whose lack is most frequently reported as the basis for accidents by groups performing intensive onsite investigations of auto accidents. Systematic determination of what behaviors are affected by a drug is the necessary direction for the field to take.

The Relationship of Drug Levels to Performance

There is a serious question whether definite, dangerous performance decrements due to drugs can be identified to set legally unacceptable drug levels for drivers as has been done for alcohol. Efforts towards answers to this question have long been stymied by the lack of suitable analytical methods for the determination of drug levels, either in the laboratory or especially at the roadside. This lack of a device comparable to the breathalyzer for drugs has hampered the necessary acquisition of such information. Now, as methodology has been developed, work is proceeding towards studying the pharmacokinetics, that is the relationship between drug levels, time and effects, of a variety of drugs. Some problem issues remain. The experimental design of such studies must take into account the duration of action of these drugs and the influence of many factors, including the presence of other drugs and disease states, both on the levels of the drug and its effects.

Subject Variables

As epidemiological studies will by necessity cover a wide range of subjects or victims, it is necessary to include a variety of subjects in any set of controlled studies. Too often such studies are carried out on healthy volunteers, whereas a large percentage of drug users, taking drugs on prescription or over-the-counter, are in various disease states. It is important to determine if such people drive better with drugs that might impair normal subjects. Studies should include older subjects, females, and less experienced, or perhaps younger drivers. Large sample sizes are necessary to measure individual differences.

Drug Selection

Sufficient data exist to narrow down the selection of the most likely candidates of drugs warranting concentrated attention. Some obvious choices are dictated by such factors as basic pharmacology, frequency and volume of consumption, and known incidence in driving accidents. Marihuana in younger people and diazepam and other sedative drugs such as flurazepam in older people are prime targets. Several other examples of widely prescribed drugs with CNS depressant actions, such as propoxyphene, codeine, anti-histamines, barbiturates and tranquilizers are also suspect.

Legal and Prevention Concerns

A cycle of information flow and decision making occurs in balancing the direction of research initiatives with prevention strategies or countermeasures. Consideration of which prevention approaches are most likely to succeed and which have poor previous records is important in making research priorities. Likewise, information from research studies is essential in establishing the validity of any countermeasure taken. For example, laws (driving under the incluence, drunken driving) prescribing legal sanctions for driving/alcohol levels have at best only somewhat lowered the death rate from drunken drivers. It is problematic whether establishing similar levels for drugs would do better, even if this complex determination could be made. Enforcement of such limits would also depend on availability of roadside techniques. Education campaigns aimed at users and prescribing physicians have often proved unsuccessful. Before serious consideration is given to such measures as invalidating a driver's lisence for "driving under the influence of an impairing drug", or setting any level of drug use as legally impermissible, it would be necessary to assess the drug's socially acceptable risk/benefit. In order to do this the actual risks would have to be defined and that returns us to GO.

CHAPTER IV
DRUG IMPAIRMENT REVIEWS

ANESTHETICS AND FOREIGN TRANQUILIZERS

Markku Linnoila, M.D.

SUMMARIES

STUDY: Doenicke, A., J. Kugler, M. Laub. Evaluation of Recovery and "Street Fitness" by E.E.G. and Psychodiagnostic Tests After Anaesthesia. Can. Anaes. Soc. J., 14:567-583. 1967. (This study has been conducted in West Germany, but the address of the authors is not indicated in the reference.)

Subjects: The total number of subjects is not evident but it must be above 200. Eighty-one subjects completed the psychomotor test battery. Demographic data on the subjects and descriptions of their health or drug use prior to the study are not given. They are, however, described as healthy volunteers.

Method: This is an experimental study conducted in a clinical laboratory. The drugs administered as a single dose were thiobutabarbital (500 mg), methohexital (150 mg), and propanidid and C1-581 in doses which are not reported. Some subjects received repeated anesthesia but their number is not reported, nor is the order of or the interval between the anesthesias. Some subjects also received halothane, diethylether, or nitrous oxide after propanidid. Halothane was administered for 15 minutes. None of the concentrations of the inhalation anesthetics are reported in the text.

EEG was continuously recorded for 12 or 24 hours from the time of anesthesia. Several psychomotor tests, such as Track tracer, Chapuis' labyrinth, down counting, simple and choice reaction time and accuracy, and mental concentration ability tests were administered to the subjects up to 8 hours after anesthesia. No description of the exact test times can be found in the text. From figure 8, one can conclude that the tests were probably given at 1, 2, and 4 hours after anesthesia. No statements concerning preexperimental training of the subjects are available. Certain cardiac and circulatory functions were continuously recorded during the experiment. Their exact nature, however, is not specified in the text.

Drugs: Some subjects received alcohol in addition to the above treatments. The dose was calculated to induce a blood alcohol concentration of 0.08 percent. Additional subject groups of unknown size received propanidid (7 mg/kg) or methohexital (2 mg/kg)

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in combination with alcohol. The exact time of the alcohol administration remains unclear, even though in the legend for figure 14 a statement can be found that alcohol was administered "one-half hour before beginning test."

Dependent variables: Scores of the psychomotor tests and manually scored EEG's were the dependent variables. However, it remains obscure to the reader how the results of the psychomotor tests were really scored. Even though there are statistically significant differences among the results of the psychomotor tests after different treatments, no statement is made how these were obtained. In 20 subjects, the blood barbiturate levels were measured as well. However, no correlations between the blood levels and performance effects of the drugs have been computed.

Results: The authors sum up their results by stating that drowsiness lasting for 12 hours was observed after barbiturates or ether anesthesia, but not after propanidid and halothane. This was confirmed by both psychodiagnostic tests and EEG. The authors suggest that after propanidid, street fitness should be regained within 2 hours. They stress the importance of the simultaneous measurement of psychodiagnostic and psychophysiological variables in the evaluation of street fitness after anesthesia.

Comment: This report concerns one of the first large-scale human experimental studies investigating the "hangover" effects after anesthesia. The writing is regrettably fussy and in many respects obscure, as indicated above. It is therefore, impossible for the reader to evaluate the conclusions of the authors based on the text per se. However, a comparison of these conclusions with more recent experiments reveals that they are valid. The necessity of recording EEG in measuring late sedation and its co, comitants after anesthesia has not been confirmed in later experiments.

STUDY: Schuel, H., C. Shienle, G. Reinhardt. Vergleichende Untersuchungen Über die Strassen Verkehrstauglichkeit Nach Kurznarkosen und Unter Alkoholeinfluss. Anaesthesist, 17:131-134. 1968.

Site: Department of Dental Surgery and Department of Forensic Medicine, University of Erlanger, Nurnberg, West Germany.

Subjects: The 78 subjects were dental patients aged between 17 and 58 years, and healthy except for their dental problems. They were divided into the experimental groups without selection; this is an obvious drawback, taking into account their wide age distribution. No statements are available concerning the sex distribution of the subjects.

Method: The present study can be classified as a controlled clinical experiment as to the administration of the drugs. However, no statements are made concerning the quality of the operations and their distribution among the experimental groups. If their painfulness varied among groups, as one is led to believe, uncontrolling this variable among groups could reduce the reliability of the

results. The psychomotor tests included Mierke's Determinationsgerat, Tachistoscope, Fallstab, as well as an attention test, a combined tapping-coordination test, and a projective personality test. The recorded variables included cumulative reaction times, accuracy of reactions in a choice reaction test, speed of comprehension, concentration ability, eye-hand coordination, and certain personality characteristics. BAL was measured according to the Widmark method. The tests were repeated 30, 45, 60, 90, 120, and 240 minutes after the anesthesia, and 30, 90, and 150 minutes after the ingestion of alcohol.

Dosage: Atropin (0.5 mg, intramuscularly) was used as a premedication 30 minutes before the anesthesia. Propanidid (500 mg), which was repeated in 10 patients, and thiobarbital (0.8 to 1.0 g) were the anesthetics investigated.

Dependent variables: The variables mentioned above were measured, but no statistical treatments were computed to correlate the drug effects with BAL or to compare the effects of the drugs with each other.

Results: After propanidid (500 mg), driving skills were regained in 60 minutes. The effect of thiobarbital lasted for a longer period of time; however, this period has not been defined. The effect of alcohol has been used as control for the late sedation after anesthesia.

Conclusions: The authors conclude that driving for 4 hours after propanidid should be prohibited. They recommend this period because of the lack of knowledge of other potentially harmful postoperative effects of propanidid.

Comment: The subject material has not been well controlled, and therefore the results are somewhat questionable. The followup period after anesthesia is much too short. That is why the authors are unable to demonstrate the period required to abstain from driving after thiobarbital. The results from the group ingesting alcohol are of little benefit. No comparisons of the sensitivities of the different tests in detecting the late sedation after anesthesia have been made. On the other hand, the results concerning the length of the late sedation after propanidid agree well with literature.

STUDY: Healy, T.E.J., H. Lautch, N. Hall, P.J. Tomlin, M.D. Vickers. Interdisciplinary Study of Diazepam Sedation for Outpatient Dentistry. Brit. Med. J., 3:13-17. 1970.

Site: Department of Clinical Investigation and Research, Dudley Road Hospital, Birmingham 18, Great Britain.

Subjects: Forty-four anxious dental patients were subjected to a total of 54 courses of treatment. Their ages ranged from 15 to 54 years. Before the tests, the patients completed the Eysenck

personality inventory. They were observed to resemble the original group of Eysenck's neurotic subjects as to their anxiety.

Method: This study can be characterized as a partially controlled clinical experiment. The duration of the operation and presumably its painfulness, as well, varied from patient to patient. This must have increased the variability of the results. Body sway, auditory flutter fusion, visual reaction time, memory functions, and coordination in the form of writing and manual dexterity were measured between 45 and 165 minutes after anesthesia. The measurements were repeated eight times, except for the handwriting and memory tests, which were measured only three times, at 60 and 90 minutes after anesthesia and a week later. Several vital functions and blood chemistry were monitored during and immediately after the anesthesia, but these measurements are not important to the present topic.

Dosage: Diazepam (0.2 mg/kg) was administered intravenously. This sedation was supplemented with 2% lidocaine plus adrenaline (1/80,000) locally to the site of operation. The dose of the local anesthetic was not standardized but adjusted according to the individual needs. These doses must have varied considerably, since the duration of the operations was anywhere from 5 to 115 minutes.

Dependent variables: The maximum body sway during 15 seconds after a 5-second adjustment period was recorded. Reaction times were recorded with an accuracy of 1/100 second. Elements of discrimination, decisionmaking, and coordination were required in the choice reaction task. The auditory flutter-fusion frequency threshold was taken to be the pulsation rate at which the sound seemed continuous as the frequency was increased. At each test time, six practice stimuli were given in the choice reaction task and three practice runs were allowed in the flutter-fusion task.

Results: Body sway and reaction time measurements returned to normal within 2 hours, and it took 2.5 hours for the flutter-fusion performance to return to normality in all patients. Manual dexterity was regained within 90 minutes in all patients and no retrograde amnesia was observed after diazepam. All patients experienced anterograde amnesia; for visual stimuli, it lasted for an average of 15 minutes, and for verbal stimuli, for 25 minutes.

Comment: In the discussion the authors mention one patient who needed a higher dose of diazepam for equivalent sedation. In such cases, they recommend that a longer time be allowed for the recovery of the patient before driving or controlling machinery.

Critique: Nothing is mentioned about the length of training of the subjects on the apparatuses. Therefore, the short recovery periods observed after diazepam may include a significant learning effect. By the time of this experiment, the recurrence of sedation several hours after diazepam was not known and no measurements were conducted later than 165 minutes after the drug. The wide age range of the subjects as well as the varying lengths of operations and

doses of local anesthetic render the results of this study hard to interpret. It appears that due to the factors mentioned above, the estimated recovery periods after diazepam sedation are too short.

STUDY: Hannington-Kiff, J.G. Measurement of Recovery From Outpatient General Anesthesia With a Simple Ocular Test. Brit. Med. J., 3:132-135. 1970.

Site: Department of Anaesthetics, Farnham Group of Hospitals, Farnham, Great Britain.

Subjects: Sixty-five of 80 dental patients who were able to cooperate in using the test apparatus participated in the study. The age of the subjects varied considerably, from 5 to 64 years. Care was taken to keep the female/male ratio constant between the experimental groups receiving different treatments. No other demographic data of the subjects are available. No statements concerning the general health of the patients were made.

Method: The study can be classified as a controlled clinical experiment. Methohexital, propanidid, and thiopental were given intravenously. Anesthesia was maintained by NO_2 or halothane inhalation. Halothane (0.5 to 1.0%) was administered to subjects who needed a deeper anesthesia than that obtained with NO_2. The operation times varied very little--between 3 to 11 minutes. The only test used was Maddox wing, which measures mainly the muscle tone of the medial rectal extraocular muscles. It is pointed out in the introduction that Maddox wing, when used as in the present experiment, is not very sensitive to the changes in accomodative power induced by general anesthesia.

Dosage: The patients received methohexital (1.2 mg/kg), propanidid (4.0 mg/kg), or thiopental (3.6 mg/kg). No premedication was given. One group of patients received an entirely inhalational anesthetic which consisted of a 2:1 mixture of NO_2 and oxygen with the addition of halothane (1-2%).

Results: In the measurements that were repeated every 5 minutes for a 30 minute period, it became evident that a full recovery appeared in 50 percent of the patients 4.5 minutes after the cessation of the operation in the halothane group, 12.5 minutes after the operation in the methohexital group, and 16.3 minutes after the operation in the propanidid group. However, 30 minutes postoperatively extraocular imbalance was still present in 30 percent of patients after methohexital, 30 percent after propanidid, and 70 percent after thiopental.

Comment: The experimental method measures only one aspect of the drug-induced late impairment after anesthesia--muscle relaxation. Even though this method is a very sensitive indicator of the ability of drugs to induce muscle relaxation, it is inadequate in assessing late sedation after anesthesia. The time of ocular imbalance is much shorter than the time necessary for recovery when

skills such as eye-hand coordination and choice reaction performance are measured. The large age variation of the subjects should have enabled the author to compute correlation between drug effects and age. However, this opportunity was not taken.

STUDY: Baird, E.S. and D.M. Hailey. Delayed Recovery From a Sedative: Correlation of the Plasma Levels of Diazepam With Clinical Effects After Oral and Intravenous Administration. Brit. J. Anaesth., 44:803-808. 1972.

Site: Royal Dental Hospital of London, London WC2, Great Britain.

Subjects: Healthy male volunteers, aged between 30 to 23 years, participated in the experiments. In part one, 29 subjects were used; in part two, 5 subjects received a high dose of diazepam.

Method: The experiment can be classified as a controlled clinical experiment. Single doses of diazepam were used. Seven subjects received diazepam orally, and venous blood samples were taken at intervals of 0.25, 0.50, 1.0, 1.5, 2.0, and 2.5 hours after drug administration. Twenty-two subjects received diazepam intravenously. Venous blood samples were collected 3, 5, 10, 15, 30, and 60 minutes after drug administration. The subjects were followed clinically and they were asked to report their drowsiness to the investigators. In this part, the benzodiazepines were analyzed after hydrolysis. In the second part the volunteers received diazepam intravenously and venous blood samples were drawn for 48 hours. This time the glc-procedure for the analysis was a direct one without hydrolysis of the agents. Again the subjects were asked to report feeling drowsy during the experiment.

Dosage: In part one, the oral dose of diazepam was 10 mg, and the intravenous ones were 10 and 20 mg. In the second part, the intravenous dose of diazepam was again 20 mg.

Dependent variables: The investigators were interested in the plasma diazepam, and N-desmethyldiazepam concentrations as a function of time after drug administration. They assessed the relationship between the feeling of drowsiness, the plasma levels of diazepam, and N-desmethyldiazepam as well.

Results: A late increase in the plasma diazepam concentration was observed. In four out of five subjects, the plasma diazepam concentration increased about 6 hours after the drug administration. Plasma N-desmethyldiazepam levels increased throughout the experiment. The subjects showing an increased plasma diazepam concentration at 6 hours reported an increased feeling of drowsiness as well.

Conclusions: The authors discuss the role of a possible enterohepatic cycle of diazepam in the late drowsiness and elevation of plasma diazepam concentrations after intravenously diazepam.

Comment: No objective measurements were used to quantitate possible impairments of performance concomitant to the subjective feeling of drowsiness. Therefore, no conclusions concerning the importance of this finding to driving and controlling machinery can be made. Since this study, it has become evident that no significant enterohepatic cycling of diazepam occurs in man.

STUDY: Dixon, R.A. and J.A. Thornton. Tests of Recovery From Anaesthesia and Sedation: Intravenous Diazepam in Dentistry. Brit. J. Anaesth., 45:207-215. 1973.

Site: Departments of Community Medicine and Anaesthesiology, the University of Sheffield, S10 2TN, Great Britain.

Subjects: Seventy-eight dental patients received diazepam, and 70 control patients received only local anesthesia. No data concerning the ages and the state of general health of the subjects are available.

Method: Two paper and pencil tests were administered to the subjects, one 5 and the other 25 minutes after the patient left the chair. The order of the tests was alternated from patient to patient. The tests were the deletion of p's test and the maze test. In the deletion of p's test, the subjects had to delete all p's from a foolscap (16" x 13") sheet containing 58 lines, each with 38 closely spaced letters of the alphabet. They had to work systematically from left to right down the page. In the maze test, the patients traced around a number of adjacent mazes printed on a single sheet of foolscap. The subjects were allotted to the treatment groups and to the groups taking the tests in the different orders, so that the types of dental treatments, sex, and the time from the administration of the local anesthetic to leaving the dental chair were balanced between them.

Dosage: Patients were given diazepam at a rate of 5 mg/min until signs of sedation followed. The mean dose was 0.23 mg/kg (range 0.12 to 0.32 mg/kg).

Dependent variables: The number of lines completed in 180 seconds and the number of errors were counted in the deletion of p's test. The number of mazes completed and the number of errors, i.e., the number of times the line drawn with pencil touched a "hedge" during the 60 second experimental period, were recorded.

Results: The exact way of conducting the statistical analysis is not indicated in the text. The patients receiving diazepam were significantly unrecovered, i.e., their performances were substantially impaired at both test times. No effects of the local anesthetics were documented by the tests. By appropriately combining the results of the two tests, the authors claim an accuracy of 82 percent in detecting psychomotor impairment after diazepam sedation.

Conclusions: The authors conclude that patients receiving intravenous diazepam in the same dose range they used should not drive for 24 hours after the operation.

Comment: The times of measurement are too close to the actual operation. The tests should have been administered several times during a much longer period in order to test their real reliability. They appear not to be very sensitive, since they do not demonstrate any effect of the local anesthetic used. In later studies, such an effect has been demonstrated to occur within the first hour after the administration of these agents.

STUDY: Trieger, N., W.J. Loskota, A. W. Jacobs, M.G. Newman. Nitrous Oxide - A Study of Physiological and Psychomotor Effects. J. A. D. A., 82: 142-150. 1971.

Site: Division of Oral Surgery, School of Dentistry, University of California at Los Angeles.

Subjects: Twenty white male UCLA dental students volunteered for the study. No other data concerning the subjects are available.

Method: This experiment is a controlled clinical study. The subjects received three different combinations of NO_2 and oxygen in a fixed order with the highest NO_2 concentration in the middle. An interim period of 7 days was allowed between each administration. Psychomotor tests were performed according to the following schedule: a test after 1 minute of 100% O_2, a test after 1 minute of NO_2 and O_2 at the prescribed concentration, two tests at 2-minute intervals immediately thereafter, a test 30 seconds after the anesthetic had been discontinued and while the subject breathed 100% O_2, and two tests at 2-minute intervals immediately thereafter, with the subjects breathing only room air.

The psychomotor test was a modification of a drawing test from the Bender Motor Gestalt Test. It consists of a series of dots spaced approximately 1 mm apart in a geometric figure that, when drawn, measures psychomotor function and coordination.

Several physiological parameters and possible alterations in the pain threshold were also measured during the experimental sessions as well. However, their relevance to the present problem is minor.

Dosage: Doses of 25, 50, and 75% NO_2 in combination with O_2 were given. The anesthetic was administered for 6 minutes, with an administration of 100% O_2 immediately preceding and following the anesthetic.

Dependent variables: The number of dots missed and the deviations of the pencil line from a straight one were counted and added to give a single score.

Results: At the highest dose of NO_2, many students were unresponsive to verbal commands. In each instance, however, a complete psychomotor recovery was achieved within 5 minutes, as measured by the above-mentioned test. With the lower concentrations of NO_2, a complete recovery became evident within 3 minutes.

Conclusions: The authors note that local anesthesia in addition to NO_2 has to be used for dental procedures.

Comment: The conclusions of the authors concerning psychomotor recovery after NO_2 intake are based on results obtained in healthy young volunteers. In addition, only one test of eye-hand coordination was used. One must therefore be more careful in generalizing the results than the authors are, particularly, since later studies have shown that NO_2 may indeed have longer after effects on psychomotor skills than those mentioned above.

STUDY: Tetsch, P., E. Esser, A. Stumborg. Verkehrsmedizinische Probleme bei Operativen Eingriffen in Lokalanaesthesie Unter B-Receptorenblockade. Anaesthesist, 22:251-254. 1973.

Site: Abteilung fur Mund- und Keiferchirurgie, der Westf. Wilhelms-Universität, Münster, West Germany.

Subjects: One hundred and fifty-nine dental patients were divided unevenly in five experimental groups. No other data concerning the patients are available.

Method: This study can be classified as a partially controlled clinical experiment. The test apparatus was a choice reaction machine delivering alternatively three different visual stimuli (lights with different colors), and a sound. The subjects had to respond to the stimuli by pressing a lever, one for each type of stimulus, as soon as possible after the stimulus appeared. The total number of stimuli in every experiment was 30. Only reaction times were recorded. The subjects were trained on the apparatuses in order to reach a stable pretest performance. Whether the allocation was random does not appear in the text. The first group received a local anesthetic, the second group received a local anesthetic and a beta-receptor blocking drug (Betadrenol R), the third group received the beta-receptor blocking agent 20 minutes before the local anesthetic, the fourth group received 10 mg of diazepam orally as premedication, and the fifth group received .5 mg atropin intramuscularly 30 minutes before the operation. The choice reaction test was completed twice, 10 and 30 minutes after the operation.

Dosage: The average dose of the local anesthetic was 3 ml of 0.05% solution and that of the beta-receptor blocking drug was 1.5 mg.

Dependent variables: The dependent variable was the average reaction time in the choice reaction test. The students' t-test was used for the statistical treatment of the data.

Results: The average choice reaction times were shorter in all groups receiving premedication. In all groups, the test completed immediately before the medications for the operation demonstrated prolonged reaction times. This was interpreted to be due to the stress caused by awareness of the operation.

Conclusions: The authors discuss the euphoria-inducing effect of diazepam, and stress this as an extra risk factor in traffic. However, no such effect was demonstrated in the experiment.

Comment: There is a considerable variation in the average choice reaction times between the groups; this leads one to believe that there were considerable differences among the groups of subjects. Since a shortening of choice reaction times was demonstrated after diazepam as a clear central effect of the drug, and because it is known that such effects are often accompanied by impairments (e.g., in coordination), one should be more cautious drawing conclusions than were the authors. The conclusions should not be based on results of a single psychomotor test. The lack of data concerning the number of mistakes in the choice reaction test is suspicious.

STUDY: Korttila, K. Outpatient Anaesthesia in Finland: Drugs Used and Postoperative Care of Patients. Ann. Chir. Gyn. Fenn., 64. 1975.

Site: Department of Anaesthesia, University Central Hospital, Haartmaninkatu 4, SF-00290 Helsinki 29, Finland.

Method: In this study, the author mailed a questionnaire concerning the drugs used in outpatient anesthesia to the physicians responsible for their administration in 126 medical facilities in Finland. Eighty-one of them responded. The time of hospital stay and the time the patients were advised not to drive after anesthesia were reported as well.

Results: Drugs most commonly used were diazepam, propanidid, thiopental, NO_2, diazepam plus meperidine, halothane, divinyl ether, diethyl ether, methohexital, and droperidol, in that order. The intravenous dose ranges for propanidid, thiopental, diazepam, and methohexitone were 200-1,500, 125-1,000, 3-35, and 75-200 mg, respectively. The ranges of the time the subjects were not allowed to drive after the same drugs were 2-27, 10-24, 6-24, and 6-36 hours, respectively.

Conclusions: The author concludes that the highest doses of the intravenous agents propanidid and thiopental, in particular, are dangerous. According to him, droperidol should not be used at all due to the very later recovery it causes and the common extrapyramidal symptoms after it. The rapidity of recovery after propanidid or halothane with NO_2 has not been generally appreciated.

Comment: There are no attempts in the article to compare the length of the recommended recovery periods with the doses of

anaesthetics used in different hospitals. It is not apparent whether high doses were associated with prolonged times of recommended avoidance of driving and vice versa.

STUDIES: 1. Korttila, K. Psychomotor Skills Related to Driving After IntraMuscular Lidocaine. Acta Anaesth. Scand., 18:290-206. 1974.

2. Korttila, K., S. Hakkinen, M. Linnoila. Side Effects and Skills Related to Driving After Intramuscular Administration of Bupivacaine and Etidocaine. Acta Anaesth. Scand., 19:384-391. 1975.

Site: Department of Anaesthesia and Pharmacology, University of Helsinki, Helsinki, Finland, and Department of Industrial Psychology, Institute of Technology, Espoo, Finland.

These two experimental, clinical studies are reviewed together because the methodology in them is essentially the same, and the main problem in both is the effect of intramuscularly administered local anaesthetics on psychomotor skills related to driving.

Subjects: Thirty healthy student volunteers, 20 to 25 years of age, participated in study number 1. The subjects were of normal weight as to their height, ± 10 percent (according to Home Economics Research Report, No 10, ARS, USDA). The three experimental groups were controlled as to their sex distribution as well. None of the subjects had a history of mental illness. They had not been on drugs for at least a month prior to the study. There were 24 males and 6 females in the whole group. Eleven subjects, nine men and two women sharing the characteristics of the subjects described above, participated in study number 2.

Method: A choice reaction test with three different coloured visual and two sound stimuli was used in these controlled clinical experiments. The total number of stimuli was 32. Two foot pedals were used for responding to the visual stimuli, and a button was pressed when responding to the sound stimuli. Total duration of this test was about 1 minute. Two tracking tasks were used to measure eye-hand coordination. In these tasks, the subjects had to keep a black dot on an illuminated track by means of a steering wheel. The track was driven once at a fixed speed and the subjects were allowed once to adjust their speed by means of an accelerator pedal. In an attention test, the subjects had to follow simultaneously four dials with revolving pointers. Every time a pointer in any dial passed a sign at the periphery of a dial the subject had to respond by pressing a key with his or her finger. There were four keys, one for every dial. The keys were in front of the sitting subject on a handrest in the same order as the respective dials. Two of the dials were in the center of the visual field, and two of them were symmetrically positioned in its periphery. The visual angel needed for the task was about 110 degrees.

Critical flicker fusion was used in study number 2. Artificial pupillae and a stable background illumination were used to eliminate the effect of drugs on ocular parameters that would interfere with the results. The frequency of flickering of a 3-mm-diameter red light source was increased gradually. The subjects had to report when they saw a continuous red light. The position of the subject's head was standardized at a distance of 90 cm from the light source. Threshold for discrimination, sensitivity to brightness, and visual discrimination ability in bright counterlight were recorded as well.

The subjects were trained for an hour on the tests before the experiments. The drugs were administered intramuscularly, double blind, and measures were taken not to inject intravenously or subcutaneously. Study number 1 was not crossover, whereas study number 2 was crossover and the design was balanced with a Latin square. One hour before the injection, the subjects were tested to produce the base line results. Additional tests were conducted 15, 80. and 170 minutes after the injection in study number 1, and 30, 120 and 240 minutes after the injection in study number 2. Immediately after the tests, venous blood samples were drawn for the measurement of the drug concentrations in plasma.

Dosage: In study number 1, 10 subjects received placebo, 10 received 200 mg of lidocaine, and 10 were given 500 mg of lidocaine with adrenaline. In study number 2, every subject received placebo, etidocaine (2.6 mg/kg), and bupivacaine (1.3 mg/kg) at 1-week intervals. The order of the treatments was randomized.

Dependent variables: Average cumulative reaction times and number of mistakes were recorded in the reaction test. Number of deviations from the track, and the length of these deviations as percentages of the total track length were recorded in the coordination tests. In coordination test II, which was driven at the free speed, the driving time was recorded as well. In the attention test, the numbers of correct responses were individually recorded for every dial during the 10-minute test period. The numbers during the first, fifth, and tenth minute were separately analyzed in order to detect possible deterioration of attention as a function of time. The two-way analysis of variance, student's t-test, and Fisher exact probability test were computed for the data analysis. Additivity and within-cell variances were checked before the analysis.

Results: Lidocaine prolonged reaction times at 25 minutes after its injections, whereas lidocaine and adrenaline improved attention 90 minutes after injection. No correlation was found between the blood concentrations of lidocaine and its effects. The author suggests that driving should not be allowed for 1 to 1.5 hours after local anesthesia with lidocaine. In study number 2, bupivacaine significantly impaired coordination and flicker fusion during the whole observation period, whereas etiodocaine impaired flicker fusion discrimination only. The authors conclude that driving should not be allowed for at least 2 hours after local

anesthesia with these agents. Again no clear correlation between the drug levels and performance was found.

Conclusions: The study number 1, the author concludes that the effect of lidocaine is mainly due to the parent compound and not due to its metabolites. The author discusses the generalizability of the results and point out that the effects of the drugs are probably most deleterious in patients who are old or who have liver disease.

Comment: In study number 2, the time of followup was too short; it should have been 8 hours at least. No dose response relationships were investigated. These studies, like a majority of those available concerning recovery after anesthesia, did not measure vigilance performance. Vigilance has recently been demonstrated to be very sensitive toward the effects of alcohol, and it may prove to be a good measure of late sedation, as well.

COMMENT: ANESTHETICS

The rapid increase of hospital expenses taking place in all western countries has forced the expansion of outpatient services. This trend has imposed new requirements on the methods used for anesthesia and sedation. Hospitals should use anesthetics which lack cardiovascular side effects and which allow for a rapid recovery after the medical procedure is over (1,2,3). This is of particular importance in countries such as the United States, where personal cars provide the most convenient transportation for local travel. Our knowledge concerning the recovery of psychomotor skills related to driving after anesthesia is increasing, but we are still far from the goal of being able to predict the duration of the aftereffects of an anesthetic on an individual patient.

There are several methods to choose for outpatient anesthesia, depending on the type of operation or procedure and the habits and preferences of the anesthetist. Local anesthetics can be suggested for outpatient use whenever possible. Lidocaine in high doses does not impair psychomotor performance for more than 2 hours (4), and combining the anesthetic with epinephrine can reduce the adverse psychomotor effects of the drug by slowing its absorption from the site of injection (4). Prilocaine has an even lower central-nervous-system toxicity than lidocaine (5). On the other hand, the more potent and toxic local anesthetics etidocaine and bupivacaine have adverse effects on skills related to driving for 2 hours at least (6). However, local anesthetics cannot be used in certain outpatient procedures as the only means of anesthesia, and overtly anxious patients generally need some kind of sedation in addition to the local anesthesia.

To reduce the side effects of anesthetics and the doses of these drugs, premedications are often used. Atropine alone has been recommended as a premedication for outpatient anesthesia (7), but intramuscular diazepam has its supporters as well (8). Atropine does not have prolonged adverse effects (9), but diazepam can

delay recovery (10). Narcotic analgesics cannot be recommended for outpatient practice because they delay recovery (11,12).

Intravenous sedation and anesthesia with such agents as diazepam, lorazepam, thiopental, methohexital, and other ultra-short-acting barbiturates produce delayed recovery, and the patients should generally be advised not to drive for 24 hours after taking the drugs (13,14,15). Young subjects (under 30 years) are generally able to drive 10 hours after taking diazepam (16). Alphadione impairs psychomotor skills for a shorter time (about 6 hours) than the above-mentioned agents, and the shortest recovery period after any intravenous anesthetic is that after propanidid (about 3 hours) (17).

The inhalation anesthetics--NO_2 and halothane, in particular--have not been thoroughly examined, but there is a widely accepted opinion that these agents do not cause a delayed recovery. This concept, however, may have to be modified, because during prolonged operations the amount of halothane accumulating in the body is substantial and both agents may induce adverse psychomotor effects in the personnel of operating theaters, who are exposed to low concentrations of these gases for prolonged periods of time (18,19). Diethylether can produce delayed recovery (20).

The above conclusions have been extracted from the most recent literature concerning outpatient anesthesia and driving, and they are based on the most reliable information that is available. Even though the recommendations are much more specific than those given in a review I wrote in 1974 concerning the same topic (21), there are still important aspects of outpatient anesthesia which have not been addressed in the studies published so far.

It is hard to determine what are equivipotent doses of different anesthetics, and, therefore, the comparisons between drugs are somewhat unreliable. When producing dose-response relationships concerning recovery periods after anesthesia, a generally accepted method should be used for testing analgesia during the anesthesia and amnesia after the procedure. This would guarantee that drugs doses of equal anesthetic power would be compared with each other. So far, very few studies concerning recovery have tested the depth of the anesthesia and the duration of amnesia.

A conspicuous feature of many studies in the field is that subjective feelings of drowsiness last longer than does actual impairment of skills, as measured by objective testing. Such a discrepancy is suggestive of inappropriate choice of variables in studies using only one or a few restricted variables to measure recovery. However, the subjective feeling of drowsiness lasting for a very long time can often be substantiated by EEG changes after anesthesia (20).

Because even complicated test batteries sometimes show results at variance with the EEG findings and with subjective feelings of performance, we may, as mentioned above, have overlooked in the

past certain important variables in choosing our test methods. One such variable may be visual vigilance, which has not been tested in studies concerning recovery after anesthesia. Dr. C. W. Erwin and I have recently demonstrated that ethanol has, against former belief, a profound deleterious effect on visual vigilance (22). Since ethanol has effects similar to general anesthetics, this finding suggests that visual vigilance should be tested in investigating recovery after anesthesia.

Another psychological function impaired by ethanol and not investigated after anesthesia is iconic memory (23), which may have a significant role in dense traffic. Decisionmaking and problem solving are also specific psychological functions that can be adversely affected by anesthetics and which have not been investigated.

The subjects in the studies concerning outpatient anesthesia have generally been either healthy volunteers or patients. Studies using healthy volunteers have generally controlled the background of the subjects fairly well, but the subjects have usually been students, which limits generalizing the data. Old and sick persons are probably more sensitive to the anesthetics than young and healthy ones. This sensitivity can be due both to central and peripheral factors such as increased end-organ sensitivity (24) and to delayed metabolism of the agents (25). Another factor that is excluded in the studies using healthy volunteers is postoperative pain. Pain of moderate intensity can antagonize the effects of ethanol (26). Therefore, a mild postoperative pain may, by increasing arousal, antagonize the delayed effects of an anesthetic. A severe pain, on the other hand, may per se impair driving ability and require additional medication. This additional medication, which in the case of outpatients is often ethanol, can increase the late, deleterious effects of anesthetics. Our knowledge concerning the combined effects of anesthetics, analgesics, and ethanol is fragmentary.

Since anxious patients may need higher than usual doses of anesthetics, their recovery might be longer than usual. However, the relationship between the anxiety of the patients and their recovery after anesthesia has not been systematically investigated.

To minimize the late effects of anesthesia, the anesthetists at the moment can use the lowest possible doses of the anesthetics for any particular operation. A fast injection rate of, for example, diazepam and the barbiturates causes a deeper anesthesia or amnesia than a slow one (27) and enables the use of low doses. Even the risk of thrombophlebitides associated with a fast injection rate of diazepam may be avoided after the development of a new vehicle for the drugs (28).

In a thorough review concerning recovery of skills after minor outpatient anesthesia (29), Dr. K. Korttila reccommended the following topics for future research:

1. Driving skills after taking inhalation agents should be thoroughly examined.
2. The effect of age on recovery from anesthesia should be evaluated.
3. Dose-response relationships after use of the most common drugs should be investigated.
4. Simple clinical tests having a correlation with the recovery of skills related to driving should be developed.
5. Well-controlled studies using patients of different ages should be undertaken.

These recommendations are valid, and combined with the suggestions provided above, should form a basis for the future studies.

COMMENT: TRANQUILIZERS

In this short review, the term tranquilizer is used for three classes of drugs: neuroleptics, antidepressants, and anxiolytics. Including the antidepressants under the term tranquilizer may seem controversial, but in the medical practice they are often used in the treatment of neurotic outpatients for indications similar to neuroleptics and anxiolytics.

From the epidemiological point of view, the role of tranquilizers in traffic is obscure at the moment (1). I have earlier pointed out in two reviews (1,2) that studies concerning the influence of tranquilizers on the numbers of fatal accidents do not demonstrate a clear overrepresentation of users of these drugs among the participants. However, the only hospital study available so far (which concerns the prevalence of diazepam, the most commonly used anxiolytic, among participants in personal injury accidents) demonstrates a clear overrepresentation of the drug users.

This seemingly controversial result may eventually appear quite logical when attention is paid to the populations represented in the two types of studies as related to the population of drug users. Participants in fatal accidents are mostly young males, who seldom use tranquilizers--at least for therapeutic purposes--whereas participants in personal injury accidents are more often from other groups of drivers. The fatal accidents often take place late on weekend nights, whereas the personal injury accidents are more evenly distributed throughout the week and often happen during the early hours of the evening. Tranquilizers are used mainly by elderly and middle-aged persons. Females use tranquilizers more often than males. As drivers, these persons are relatively seldom on the roads during the times when most fatal accidents occur. They may also be at a smaller risk of speeding and of driving under the influence of alcohol, two common features in fatal accidents.

Conclusions from the data above may not be very reliable, however, since the studies concerning the fatal accidents have mainly been conducted in the United States, and the hospital study was conducted in Oslo, Norway. Therefore, there is an obvious need for a series of epidemiological studies concerning the role of tranquilizers in

personal injury and property damage accidents. Such a series of studies should in an optimum case be conducted in several countries at the same time and under the guidelines of an international organization such as OECD or IDBRA. This would enable the comparison between different countries of the consumption statistics of these drugs as related to their role in traffic accidents. These figures also would reveal some aspects of the prescription habits of the physicians in these countries and, if used correctly, could modify these habits later on. After all, tranquilizers are prescription medications, and their use is under the control of the medical profession. If tranquilizers have a significant role in property damage and personal injury accidents, this role can be diminished only through a fruitful cooperation with the medical profession.

Most recent laboratory studies concerning tranquilizers and driving have been discussed by Dr. I. Saario in the summary of his M.D. thesis (3). Different kinds of impairments of psychomotor skills have been observed after use of the different classes of tranquilizers. This is as expected, when the pharmacology of the diverse drugs classified as tranquilizers is taken into account. Laboratory studies have indicated that the relationship between the levels of the drugs in biological specimens (such as blood, plasma, or urine) and their effects is much more complicated than that between blood alcohol levels and their effects. This is because most of the tranquilizers have multiple active metabolites, which may have a role in their adverse effects. The development of tolerance to the effects of tranquilizers is much stronger than that toward alcohol. The pharmacokinetics of the tranquilizers are also much more complicated than those of alcohol. Structurally, closely related tranquilizers may have major differences in their pharmacokinetics, depending on factors such as water solubility, pK_a, etc.

Taking into account the above discussion, it seems hard to develop legislation concerning tranquilizers and driving which would be equivalent to the present drinking and driving laws in the United States; i.e., any legal limits of plasma tranquilizer concentrations are extremely hard to define. What can be done in the future concerning tranquilizers and driving? The role of tranquilizers in traffic accidents has to be established, as suggested above. If a significant role is found, then studies should be directed in the following manner.

1. Controlled laboratory studies should be conducted to study the influence of the following factors on the effect of tranquilizers on psychomotor skills: age, sex, personality, and mental illness. The psychomotor skills measured should include choice reaction, coordination, divided attention, vigilance, and memory functions, as well as information sampling.
2. Best possible correlations between the pharmacokinetics of the drugs and their metabolites and psychomotor performance should be searched. In this context, a very important variable has turned out to be the duration of treatment.

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3. Simple clinical tests for the measurement of skills related to driving should be developed.
4. Tests concerning the effects of drugs on skills related to driving should be included in the premarketing testing of tranquilizers and certain other drugs that are going to be used mainly for the treatment of outpatients.
5. Use of tranquilizers should be limited to those patients who really need them. Present consumption statistics suggest that many relatively healthy persons use tranquilizers; fewer of these people should take them.
6. Since we have recently demonstrated a fairly strong state-dependent effect of diazepam (4), training the drug users in how to manage in traffic under the influence of the tranquilizers may become a useful means of reducing the possible accident risk caused by these drugs.

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GENERAL TRANQUILIZERS

Jane H. Speaker, Ph.D.

SUMMARY

Current methodology for determining plasma levels of diazepam and its active metabolites employs electron-capture gas chromatography and can measure 1- to 10-ng quantities (2,15).

When a group of people are administered diazepam at a particular dose, there is a wide range of plasma concentrations of diazepam (2,3,6,7,12,15). This range, in 13 subjects administered 15 mg of oral diazepam daily for a week or more, is 16 to 400 ng/ml (6,15). Garattini et al. (3) found a range of 10 to 250 ng/ml in 27 subjects given a single 15-mg oral dose. A half-life of 38 to 92 minutes has been measured by this group in five female subjects. Kleijn et al. (7) calculated a half-life of 20 to 42 hours after 10 mg three times a day, about 0.5 mg/kg/day orally in five subjects.

This great variability in plasma concentration is a major problem in interpreting drug effects on human performance. Perhaps the factors that influence plasma concentration curves can be identified and controlled. With seven subjects, Linnoila et al. (11) showed that ingestion of food increases plasma levels of diazepam 6,7, and 8 hours after intravenous administration of 0.3 mg of diazepam per kg. They suggest that enterohepatic recycling of diazepam is occurring. Kleijn et al. (7) had also suggested this mechanism.

The influence of ethanol on diazepam plasma levels was also studied. In both the Linnoila et al. study (12) and that of Haffner et al. (5) diazepam levels were higher when alcohol was also given. By contrast, Linnoila et al. (12) did not see significant alterations in chlordiazepoxide or thioridazine plasma concentrations after ethanol ingestion.

When diazepam dosage was administered on a body weight basis, great plasma concentration variations were still usually encountered (5,12,14). However, Linnoila et al. (11) found much closer agreement in the levels of their seven subjects when both body weight and food intake were controlled. Unfortunately, the individual values are not presented in this article, but their standard error appears from the table to be about $\pm$ 20 for values between 300 and 400 ng/ml.

The sampling time is important. The peak after oral absorption occurs 0.5 to 3 hours after administration (2).

Kanto et al. (6) suggest several reasons for believing that diazepam may induce its own metabolism to desmethyldiazepam in man. They point to the appearance of high levels of the N-desmethyl metabolite in the plasma of chronic diazepam users after a single diazepam dose and to the very low levels seen in control subjects given the same dose. They also demonstrated a marked drop in the N-desmethyl metabolite plasma response to a diazepam dose after abstinence from diazepam in a chronic user. They present evidence that patients who have been taking diazepam for periods of months or years have lower plasma levels than those who have been on diazepam a few weeks, and show in a series of eight patients that after 1 to 6 weeks on 15 mg/day orally, there is a fall in plasma diazepam levels. Enzyme induction cannot explain the great variations seen in plasma diazepam levels because the N-desmethyl metabolite concentrations vary as much or more than the diazepam levels and generally are higher when diazepam levels are higher and lower when diazepam levels are lower (6,7,15).

Diazepam binds to protein (7). Relatively little diazepam can be recovered from hemolyzed red blood cells (15). The proportion of a diazepam dose bound to tissue may be a critical factor in the variability of plasma levels. Interestingly, Zingales (15) finds low levels of the N-desmethyl metabolite in erythrocytes after cessation of diazepam administration and at a time when there is no longer a measurable plasma level of diazepam or its metabolites.

As with diazepam, a given dose of chlorpromazine produces a wide range of plasma levels (1). Ingestion of food may alter the chlorpromazine plasma concentration. Fasting may result in rapid attainment of high plasma levels when chlorpromazine is subsequently administered orally. Since this effect is not always obtained, the authors suggest that residual food from a previous meal may be interfering with rapid absorption of the drug. Curry et al. (3) also present evidence for phenobarbital induction of increased metabolism of chlorpromazine. They found, in addition, that only about 1 percent of a 1-g oral chlorpromazine dose was excreted in urine and feces. This study covers many ideas and presents a number of kinds of measurement. It suffers from a lack of numbers of subjects. In most cases the plasma levels represent measurements on only a single individual.

Gordon (4) reports that diazepam can produce the classic effects of addiction: tolerance, phychic dependence, and physical dependence. He presents only one case, but that is sufficient to demonstrate the matter.

Kleinknecht and Donaldson (8) review 23 articles which present data on the effects of diazepam on cognitive and psychomotor performance. They organize the many tests employed into groups according to the attributes they believe the tests to measure. They suggest that there is need to control and/or analyze for age, sex,

personality (e.g., introversion vs. extroversion), and subject population (e.g., student vs. mental patient). Three of the articles reviewed by Kleinknecht and Donaldson are represented in the present summary (5,9,14). Two additional articles dealing with the effects of tranquilizers and ethanol on simulated driving performance are added to the present survey (10,13).

Haffner et al. (5), Mørland et al. (14), Linnoila (10), and Loomis (13) have shown that diazepam (5,10,14), chlordiazepoxide (10), thioridazine (10), haloperidole (10), flupenthixole (10), chlorpromazine (13), secobarbital (13), and meprobamate (13) in therapeutic doses can impair human performance in complex tests like simulated driving. Similarly, alcohol can impair this performance. When tranquilizers and ethanol are administered to the same subject, complex performance is impaired to a greater degree (10,13,14). When separate elements of a complex task are looked at individually or tests for less complex behavior are administered, there is less consistency in the data (5,9,10,14). With ethanol and diazepam, performance on some elements of simulated driving was improved over that with placebo and lower doses of the same agent (10).

Lawton and Cahn (9) found only slight impairment with diazepam on three of five less complex psychomotor tests. Their oral dosage regimen was 5 mg three times a day for 3 days prior to testing and 5 mg just before testing on the morning of the fourth day. The 20 subjects also took 3 ounces of 100-proof vodka in grape juice or pure grape juice just before testing. Alcohol did not impair performance on these tests nor did it further increase the effect of diazepam. No drug concentrations were reported. The blood ethanol concentrations varied widely, from 68 to a surprising 140 mg/100 ml, and the change in concentration in 3 hours exceeded 60 mg/100 ml in every case. The average change was 82 mg/100 ml or over 27 mg/100 ml/hour, far too high to be consistent with values of 15 to 20 mg/100 ml/hour usually reported. There seems to have been a problem with the method of analysis, although other possibilities include improper storage before analysis and wide variations in sampling times.

COMMENT

It is difficult to interpret the relation of diazepam plasma levels to behavioral responses because of the great variation in concentrations achieved with any particular dose. Food and alcohol intake patterns contribute to the variation.

There are some problems with the entire group of five behavioral studies (5,9,10,13,14). All the subjects were healthy young males. No attempt was made to identify individuals suffering from anxiety. There seems to be great difficulty in designing or selecting tests for the mental and psychomotor elements of complex tasks. For instance, critical flicker-fusion frequency tests are very sensitive to diazepam effects, but the relationship of the test performance of complex human tasks is not obvious. In addition, either no

plasma levels of the tranquilizers were measured (9,10, 13) or large variations were reported among the subjects (5,14).

However, these are careful studies. Haffner et al. (5) and Mørland et al. (14) presented a large range of mental and psychomotor tests, and their use of two diazepam dose levels permits delineation of the threshold for drug effects. All of the papers reviewed here report the use of placebos, and in all but one (10), ethanol blood levels were measured. Different subjects were used for each test (10,13) or a randomized rotation procedure was used with at least a week between testing procedures (5,9,14).

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OPIATES
MINOR TRANQUILIZERS

Morton F. Mason, Ph.D.

SUMMARIES AND COMMENTS

STUDY: Gordon, N.B. Reaction Times of Methadone-Treated Heroin Addicts. Psychopharmacologia, 16:337-344. 1970.

Site: Rockefeller University and Yeshiva University, New York City, New York.

Subjects: The subjects were divided into six groups. Groups 1 and 3 both had been maintained for at least 1 year on methadone for the treatment of heroin addiction. Group 1 had 18 males whose average age was 32.5 years; group 3 had 9 females whose average age was 33.5 years. Group 2 consisted of 20 unpaid male volunteers who did not use drugs; they averaged 32.5 years. The participants in groups 4 and 5 had recently withdrawn from narcotic drugs. The 20 males in group 4 averaged 31.5 years and had withdrawn 14 days earlier. The 19 males in group 5 averaged 30 years and had withdrawn 4 days earlier. Group 6 consisted of 9 females whose average age was 23 years. They were paid volunteers from the nonprofessional hospital staff, and did not use drugs.

Method: Measurements were taken under controlled laboratory conditions; urines were tested (details were not given) for drugs to assure conformity to group. Variations of reaction time were tested in a button-pressing situation: (a) simple reaction time (one of six stimuli); (b) multiple discrimination/multiple response (one of six stimuli for one of six responses); (c) multiple discrimination/single response (one of six discrimination presented in random spatial and temporal order, with single response). A diagram of the instrument used was provided. The digit 1 readout was sequestered from the subject and a noise level was introduced to obscure instrumental sounds which might be used by the subject to his advantage.

Dosage: Subject group 1 (males) received 100 mg of methadone per subject per day for a year or more. Subject group 5 was composed of females, who also received 100 mg of methadone per subject per day for a year or more. The other subject groups received no drugs: group 2 had males who were not drug users; group 3 had persons withdrawn from drugs for 14 days; group 4 had males withdrawn from drugs 4 days prior to testing; and group 6 had females

who were not drug users--paid volunteers from nonprofessional hospital staff.

Results: The subjects receiving methadone had shorter reaction times than did the others to the tests administered. The results were statistically significant except in the cases of the 4-day and 14-day detoxified groups.

Comment: The findings would be much more significant if, following the original observations, closed- and/or open-course driving tests had been made along with simulator tests such as tracking, tests involving divided attention, etc.

STUDY: Kiplinger, G.F., G. Sokol, and B.E. Rodda. Effect of Combined Alcohol and Propoxyphene on Human Performance. Arch. Int. Pharmacodyn., 212: 175-180. 1974.

Site: Lilly Laboratory for Clinical Research, Marion County General Hospital and Indiana University School of Medicine, Indianapolis, Indiana.

Subjects: Eight medical and graduate students and others participated and were paid for their services. Essentially no information was provided regarding sex, age, size, driving history, and their general state of health and lifestyle was self-assessed.

Method: Subjects were asked to refrain from taking CNS-affectant drugs (except for tobacco) for 24 hours prior to testing. The purpose of the tests was explained to them and they fasted for 6 hours prior to drug administration. Combinations of alcohol, propoxyphene, and control placebos were administered in four treatment sequences that followed a randomized block design; each subject received all treatments in the course of the experiments. Testers used double-blind technique under controlled laboratory conditions. Parameters of measurement included: (a) four pursuit meter patterns (as described by Forney et al.); (b) four conditions of standing stability (described by Shipley and Harley); and nine verbal tests (using DAF measurements also described by Forney et al.).

Dosage: Mixed in an iced pineapple-grapefruit beverage, alcohol was given at 15 ml ethanol per 50 lb body weight, a dose designed to produce a concentration of about 0.05% v/v in 60 minutes when 30 minutes was taken for ingestion. The alcohol placebo was iced beverage alone. Subjects received propoxyphene as a 65-mg capsule, its placebo being starch and talc. The capsule was swallowed at the start of each experiment so that the peak plasma concentration could be expected to occur during the experimental period.

Results: The data were statistically evaluated. Very little difference was found between the modest impairing effects of ethanol and those of propoxyphene at the doses given. Dosage with both drugs produced moderate additive impairments. There was no evidence for interaction.

Comment: It would have helped to have studied doses considered "abuse" quantities. Also, closed-course driving might have yielded more evidence of significant impairments.

STUDY: Linnoila, M., and M.J. Mattila: Drug Interaction on Psychomotor Skills Related to Driving: Diazepam and Alcohol. Europ. J. Clin. Pharmacol., 5:186-194. 1973.

Site: Department of Pharmacology, University of Helsinki, Helsinki, Finland.

Subjects: The four hundred volunteers (371 males, 29 females) were comprised of medical students, technical students, and cadets. A brief history was taken to exclude subjects suffering from diseases or taking drugs. (Caffeine and tobacco were not specifically mentioned as being exclusionary, but coffee and "drugs" were stated as excluded "during the tests.") The mean age of the subjects was 22 years (S.D. = 2.8 years). The subjects were divided into 20 groups of 20 subjects each which were similar in sex, age, weight, educational level, and district of residence. Driving experience was not mentioned. Results of only 10 of the test groups are reported in this article.

Method: The research was experimental, under controlled laboratory conditions, using double-blind technique. Coding was changed daily, and 10 subjects were tested each day. Before any administration of drugs and drink, the subjects were instructed in the test procedures and apparatus by the same person in the same way. Each subject was tested 30, 90, and 150 minutes after taking capsules.

The groups tested were as follows:

No drug, no drink	Zero group
Placebo + capsule + placebo drink	Placebo group
Diazepam(5 mg) + placebo drink	D5 group
Diazepam(10 mg) + placebo drink	D10 group
Placebo capsule + alcohol(0.5 g/kg)	A5 group
Placebo capsule + alcohol(0.8 g/kg)	A8 group
Diazepam(5 mg) + alcohol(0.5 g/kg)	D5 A5 group
Diazepam(10 mg) + alcohol(0.5 g/kg)	D10 A5 group
Diazepam(5 mg) + alcohol(0.8 g/kg)	D5 A8 group
Diazepam(10 mg) + alcohol(0.8 g/kg)	D10 A8 group

Several parameters of measurement were employed, one being a commercially available choice reaction testing instrument. Subject reacted to three different light stimuli by pushing one or both of two foot pedals. They also had to push a button responding to a low pitched sound and not react to a higher pitched sound. The test totaled 36 stimuli normally requiring 54 seconds. Cumulative reaction time was recorded along with incorrect responses.

A commercially available coordination tester was used twice in each test, (I) at a fixed speed and (II) at an optimum speed

chosen by the subject. The test was a tracking task to keep a black ball on a track by means of a steering wheel. Coordination test I lasted 30 seconds; test II lasted 30 to 80 seconds depending on the subject. A cumulative mistake percentage of total track length was calculated for I. The driving time was recorded in II.

Subjective examinations included: (a) subjects grading their own performances on scale of 1 (very good) to 5 (very bad); and (b) subject statements of what treatment they believed they had received.

In another test, blood alcohol levels were determined by ADA and Widmark methods for 20 medical students not used in tests, after they ingested 0.5 g/kg alcohol (10 students) and 0.8 g/kg (10 students). Five of both groups also took 10 mg of diazepam and the other five received placebos.

The results for all tests were adequately evaluated statistically.

Dosage: Diazepam was administered in 5-mg capsules, with lactose capsules as placebos. Alcohol, a bitters solution containing 28 percent alcohol, was blended w/v with one-third volume of water, using nonalcoholic bitters as placebo. The amounts were adjusted to 0.5 g and 0.8 g/kg, and drinks were cooled to 8° to 10° C.

Results: The zero and placebo groups estimated their performances as slightly lower than normal. Psychomotor variables of the placebo group were slightly impaired compared to the zero group. Group A5 psychomotor variables were slightly improved compared to those of the zero group, but only the reaction time at 30 minutes was statistically significant. At 30 minutes, the A8 group reaction times were also slightly shorter than those for the zero group and statistically significant. The driving times of the A8 group were longer than those for the zero group.

Subjects in the A5 group considered their performances good, but actually were found to be slightly (but not significantly) impaired, except for a moderate prolongation of driving time. No significant difference was found between the D5 and A5 groups. The D10 group believed their performance was improved and they actually were slightly improved, although driving time was prolonged at 30 and 90 minutes. No significant difference was found between the D10 and A8 groups.

The D5 A5 group showed slight impairment in coordination test I and increased driving time compared to the zero group, and they were more impaired than the A5 or A8 groups. Subjects in the D10 A5 group were more impaired than those in the A5 group. The difference was greater between the D10 A5 and A8 groups, and the D10 A5 group members were more impaired than those in the D10 group.

The D5 A8 group was more impaired than either the zero group or the A8 group. Likewise the D5 A8 group was more impaired than the

D10 group. The D10 A8 group was also more impaired than the zero group or the A8 group. Comparison of D10 A8 with D10 showed greater impairment by the former group.

The discussion of these complex combinations of results indicated with diazepam alone, psychomotor test performances were somewhat improved after either 5- or 10-mg doses. Slight improvements were also noted after alcohol ingestion in the amounts given. Combinations of both drugs impaired psychomotor performance. It was also concluded (on the basis of unpublished data obtained by the authors) that alcohol accelerates the absorption of diazepam.

In a discussion of the relation of the findings to "real world" driving, the authors stated that coordination test I most strongly correlated with actual driving. Subjects in this test did not show improvement after single drug administration, and furthermore were the first to show impairment after taking drug combinations. It is likely that in "real world" driving, too, improvement does not occur after such single drug doses, and that psychomotor skills while driving would be impaired by the interaction of combined drugs, as they were in test I.

Comment: The detailed presentation and accompanying discussion indicates the complexities involved in studying the effects of alcohol and other drugs on driving, and their interactions. In this paper, minor impairments by combinations of diazepam and alcohol at modest dosages are demonstrated. Single drug effects showing improvement rather than impairment with 5- and 10-mg dosages are shown and then essentially discounted by the authors. From a medicolegal standpoint, initial studies involving obvious abuse-dosages of drugs would be of much greater value.

STUDY: Landauer, A.A., G. Milner, and J. Patman. Alcohol and Amitriptyline Effects on Skills Related to Driving Behavior, Science, 163:1467-1468. 1969.

Site: Department of Psychology, University of Western Australia, Nedlands, Western Australia and Mental Health Services of Western Australia, Claremont Hospital, Claremont, Western Australia.

Subjects: The subjects were healthy medical students (18 men, 3 women) with a mean age 22.1 years (S.D. = 1.15). None of the subjects were taking any medication and none had a recent illness. They were divided into three groups of six men and one woman each.

Method: Testing was performed under controlled laboratory conditions, double-blind. It began 2 hours after the second issue of tablets (see Dosage). After completion of first series of tests, subjects drank their preferred beverage over a period of 30 to 45 minutes in amounts calculated to bring their blood alcohol concentrations to 0.08% w/v. Fifteen minutes later, a Breathalyzer test was administered and the performance tests were repeated. After a meal, the subjects were medically examined,

filled out a questionnaire, and were taken home. All data were statistically evaluated by analysis of variances.

Parameters of measurement included a simulated driving test, a dot tracking test, and a pursuit rotor test. The simulated driving test employed the Gibbs variant of tracking, in which the subject is required, by means of a steering wheel, to move a pointer in line with one of five horizontal lights that flash on for 1.27 seconds in random order. The test lasts 12 minutes but only the last 150 seconds are scored, making it a good measure of fatigue. A one-way screen separates the subject from the recorder and observer. The proportion of errors to total recorded responses made is used to score the test.

In the dot tracking test, a continuous line must be drawn between dots arranged in an irregular spiral pattern. Scoring is based on number of dots tracked accurately. The pursuit rotor test allows 2 seconds for practice, then gives 10 trials of 10 seconds duration each, with a 28-second interval between trials. Responses are electrically recorded and scored on the basis of time on the target.

Dosage: Group A received amitriptyline (0.8 mg/kg) in tablet form on the night before the test and on the morning of next day prior to testing--i.e., at a 12- to 15-hour interval. Group B received a placebo at night and amitriptyline the next morning; and group C was given placebo tablets both the night before and the morning of testing.

Results: For simulated driving, when subjects were sober, there was no difference in performance among the three groups. With alcohol, there was no increase in errors by the double placebo group (group C) but errors were increased in groups A and B, which received amitriptyline. For dot tracking, essentially the same results were obtained. The improvement with practice was overcome by the presence of amitriptyline. There were similar decrements in performance in the presence of amitriptyline in the pursuit rotor task.

Comment: It had earlier been found that after several days on medication, driving skills were not significantly further decreased by interaction of amitriptyline with alcohol. Hazardous interaction may occur, however, during the first 2 days of medication with amitriptyline.

It would have been useful to have studied the interaction of the drugs at abuse dosages with alcohol; i.e., those leading to blood concentrations of 0.10 to 0.25% w/v.

STUDY: Clayton, A.B., T.A. Betts, and G.M. Mackay. A Study of the Effects of Certain Tranquilizers and Small Amounts of Alcohol on Driving Performance. European J. Toxicol., 5:254-257. 1972.

Site: Departments of Transportation, Environmental Planning, and Psychiatry, University of Birmingham, United Kingdom.

Subjects: The 50 males and 50 females were mostly students, the mean age being 28.1 years. Their driving experience varied, and none normally took prescribed psychotropic medications.

Method: Subjects performed closed-course driving tests under controlled conditions. They were generally tested in groups of six, using a fixed routine.

On Wednesday afternoon, subjects practiced for 1 hour on all driving tests at the driving site. They then received two unmarked bottles--one containg five drug tablets, the other five placebo tablets--along with directions of how and when to take them. (Both bottles used by the control group contained placebos.) One bottle was to be used first--one tablet Friday evening; three on Saturday (at intervals); and the fifth Sunday morning. Random double-blind administration techniques were used. On Sunday morning, subjects performed three runs on test 1, three runs on test 2, and five runs on test 3 (all described below). They received an objective assessment rating and answered a subjective questionnaire derived from Reisby and Theilgaard. After this they were given ethanol (0.5 g/kg) in flavored sugar base, to be drunk within 10 minutes. One hour later, the BAC was determined with a Breathalyzer and the testing procedures were repeated.

The following Wednesday, another practice session was held. From Friday to Sunday, subjects took the drugs in the second bottle, whereupon the testing cycle was repeated. Methods of scoring were accurately described.

Subjects drove a Ford "Escort Saloon," 2.98 meters long. Test 1 involved driving the vehicle around posts 5.97 meters apart in a straight line and then reversing back around the posts to the starting point. Test 2 required parking between two boards 5.97 meters apart and getting as close to the curb as possible. Test 3 measured gap estimation. Subjects were required to estimate a minimum distance between sets of posts through which they could drive and then to drive through the chosen gap.

Dosage: The drugs were administered in amounts approximately equal to the usual clinical doses: chlordiazepoxide, a benzodiazepine, 10 mg; amobarbital, a barbiturate, 30 mg; trifluoperazine, a phenothiazine, 2 mg; haloperidol, a butyrophenone, 0.5 mg; and alcohol, when given, 0.5 g/kg.

Results: Except for haloperidol, the drugs did affect driving performance. An analysis of results was done using a split-plot analysis of variance for each drug group for male and female subjects separately. Little evidence of alcohol-drug interaction was obtained, probably because of the low concentration of alcohol and chronic administration of drugs.

Some differences between men and women were found in tests in which skills were affected. The impairments were statistically significant, but were not detected by the subject or by objective clinical assessment. Physicians are advised to warn patients of these driving dangers, especially during early stages of medication.

Comment: This report is hard to follow, but its design seems acceptable. Insufficient information on statistical data analysis is supplied. Essentially, we are left with the statement that the ratio of significant results to nonsignificant results exceeded 1:20, and that all drugs (even haloperidol) showed at least one significant effect.

The work would have been much more useful if further data with much higher alcohol concentrations had been obtained.

STUDY: Betts, T.A., A.B. Clayton, and G.M. Mackay. Effects of Four Commonly Used Tranquilizers on Low Speed Driving Performance Tests. Brit. Med. J., 4:580-584. 1972.

Site: Departments of Psychiatry and Transportation and Environmental Planning, University of Birmingham, Birmingham, United Kingdom.

Subjects: There was a total of 113 volunteers, mostly students, the first 13 of whom were used in a pilot study testing vehicle handling techniques. They ranged in age from 18 to 30 years, and were free from medical or psychiatric problems. All had valid drivers licenses. Further information regarding driving experience was obtained during the testing.

Method: The 100 nonpilot subjects (50 men, 50 women) were divided into five groups for testing and data analysis: (1) chlordiazepoxide vs. placebo; (2) haliperidol vs. placebo; (3) amobarbital vs. placebo; (4) trifluoperazine vs. placebo; and (5) placebo vs. placebo.

The subjects were tested in groups of six every 2 weeks, with double-blind, randomized administrations. The fixed test procedure was to have the subjects who would be tested during a given fortnight come to a closed-course driving site on Wednesday afternoon. They were given (1) a visual screening test; (2) an Eysenck Personality Inventory; (3) a biographical and driving history questionnaire giving age, occupation, driving experience, mileage, accidents, convictions, and car ownerships; (4) a subjective feeling questionnaire, and (5) an objective assessment. Then, after a few minutes driving the vehicle to be used, they were given an instruction sheet and had a practice session: test 1, 6 runs; test 2, 4 runs; test 3, 3 runs; test 1, 6 runs (see below). At that point each subject was given two bottles containing the appropriate drugs, with instruction on how and when to take them.

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They returned to the driving site on Sunday morning, and after completing a subjective questionnaire and having an objective assessment, they completed the driving test: test 1, 3 runs; test 2, 3 runs; test 3, 5 runs. They were then given alcohol in a flavored sugar base, 0.5 g/kg. An hour later, they completed the subjective feeling questionnaire, again took the objective assessment test, and were tested on a Breathalyzer, whereupon the three driving tests were repeated.

The following Wednesday the original procedure was repeated, the second bottle of drugs was taken as directed, and on Sunday the rest of the entire procedure was repeated.

For the three road tests, subjects used a Ford Escort Saloon, 13 ft 0.6 in. long. Test 1 involved driving a zigzag course between five posts set one and one-half times the length of the car and then, in reverse, returning to original starting position. For test 2, subjects parked between two boards set across a curb at a distance from each other of one and one-half times the length of the car. Only three movements were permitted: forward, backward toward the curb, and forward to line up parallel with the curb. Test 3 was a gap estimation test. A gap created by movable posts was adjusted upon instruction from the driver to the minimum gap through which he thought he could drive the car.

Scoring of the measurements was adequately described, and the results were statistically evaluated. When alcohol was administered, the mean blood alcohol concentration achieved was close to 0.05% w/v.

Dosage: Each of four drugs--chlordiazepoxide, 10 mg; amobarbitol, 30 mg; trifluoperazine, 2 mg; and haloperidol, 0.5 mg--was given five times over a 36-hour period. All drugs and placebos were prepared as similar white tablets.

Results: All drugs except haloperidol significantly impaired response to one or more of the driving tests to a 5 percent significance level. There was no certain evidence for interaction with alcohol, perhaps because of the low blood alcohol concentrations reached. Objective assessment showed haloperidol had a significant depressing effect, whereas amobarbital caused a slight euphoria. In evaluating themselves, the subjects felt that none of the drugs had any effect. With alcohol, the subject taking haloperidol felt "worse," whereas those taking amobarbital had a subjective stimulating feeling.

Comment: The measurements made in tests 1, 2, and 3 are more relevant to real-world driving than are the frequently reported tests under controlled laboratory conditions. It would seem preferable to have made tests with subjects taking the drugs at true "abuse" levels, and when alcohol was administered to have some groups attain common "real-world" blood alcohol concentrations of the order of 0.1 to 0.25% w/v.

STUDY: Patman, J., A.A. Landauer, and G. Milner. The Combined Effect of Alcohol and Amitriptyline on Skills Similar to Motor Car Driving. Medical J. of Australia, 2:946-949. 1969.

Site: Department of Psychology, University of Western Australia and Claremont Hospital, Nedlands, Western Australia.

Subjects: Subjects were healthy volunteers over 21 years of age--12 men and 12 women whose mean age was 26.0 (S.D. about 6.0). They did not show histories of illnesses and were not on medication.

Method: Measurements were taken under controlled laboratory conditions, using double-blind techniques; results were evaluated by statistical analysis of variance. The subjects were divided into four equal groups and the individuals completed a battery of psychomotor tests on three consecutive mornings. Groups 1 and 2 were given the active drug and groups 3 and 4 received a placebo. The effects of alcohol were tested by giving groups 1 and 3 alcohol at the second testing session (fourth day of drug administration) and placebo alcohol at the third session (fifth day of drug administration). Groups 2 and 4 received their placebo alcohol at the second testing session and alcohol at the third testing session. The testing sessions for each subject were on the third, fourth, and fifth days of medication. Testing sessions involving alcohol were given to half the subjects on the fourth day and the other half on the fifth day.

The tasks consisted of a short clerical test (ACER, 1967); a dot tracking test; a pursuit rotor test; and a simulated driving test. The latter three are described in the other Landauer et al. study reviewed earlier in this report.

Dosage: Each subject received tablets every day for five days. The tablets for groups 1 and 2 were amitriptyline; those for groups 3 and 4 were placebo. On day 1, the dosage was two tablets. Subjects each received four tablets, spaced, on days 2, 3, and 4. On day 5, the dosage was again two tablets. In addition, each group was given both alcohol and placebo: group 1 - alcohol on day 4, placebo on day 5; group 2 - placebo on day 4, alcohol on day 5; group 3 - alcohol on day 4, placebo on day 5; and group 4 - placebo on day 4, alcohol on day 5.

Results: Amitriptyline caused no effects on performance. Some decrement of performance was found due to alcohol in the pursuit rotor and simulated driving tests. No evidence for interaction with amitriptyline was found.

Comment: The findings support earlier ones that impairment from interaction of alcohol with amitriptyline is more apt to be observed during the first 2 days of administration, and that the impairment decreases with time. It would have been worthwhile to have had data in which the alcohol and drug doses were increased to "abuse" quantities, to see if their interaction persisted.

STUDY: Seppala, T., M. Linnoila, E. Elonen, M.J. Matilla, and M. Maki. Effect of Tricyclic Antidepressants and Alcohol on Psychomotor Skills Related to Driving. Clin. Pharm. Therap., 17:515-522. 1975.

Site: Department of Pharmacology, University of Helsinki, Helsinki, Finland.

Subjects: The 40 student volunteers were of normal weight, 20 to 25 years old. All used alcohol occasionally; none had a history of mental disorder.

Method: The experiments were laboratory controlled, with double-blind, cross over arrangements. Test groups were coded as follows. For trial I--dosage daily for 2 weeks:

Placebo drug, placebo drink	P Group
Placebo drug, alcohol	A Group
Amitriptyline, placebo drink	AMI group
Amitriptyline, alcohol	AMI-A group
Doxepin, placebo drink	D group
D epin, alcohol	D-A group.

For trial II--dosage daily for 2 weeks:

Placebo drug, placebo drink	P group
Placebo drug, alcohol	A group
Chlorimipramine, placebo drink	CIP group
Chlorimipramine, alcohol	CIP-A group
Nortriptyline, placebo drink	N group
Nortriptyline, alcohol	N-A group.

Testing sessions were on the 7th and 14th days of treatment. Measurement parameters consisted of: (1) subjective assessments; (2) psychomotor tests at 30, 90, and 150 minutes after ingestion of the drug and beverage; (3) a tyramine pressor test initially and on 14th day of every treatment; (4) a choice reaction test; (5) two coordination tests; and (6) an attention test (not described). Measurements (1), (4), and (5) were the same as those described in the Linnoila and Mattila study reviewed earlier in this report.

Dosage: Gelatin capsules, lactose placebo, amitriptyline, doxepin, and nortriptyline, 10 mg each, were administered three times per day for 7 days. The doses of chlorimipramine were 10 mg three times per day for 7 days and 25 mg three times a day for the next 7 days.

Alcohol was administered in an alcoholic bitters solution (placebo being bitters without alcohol) before psychomotor testing, at a dose of 0.5 g alcohol/kg body wt.

Results: The tyramine test showed a decreased response with time, indicating an antityramine effect from antidepressants. None of the drugs alone importantly impaired psychomotor skills. When combined with alcohol, doxepin and amitriptyline exhibited some interaction, but no clear-cut interaction was demonstrated with nortriptyline or chlorimpramine.

Comment: The results do not seem to support the statement in the abstract that doxepin and amitriptyline, at the dosages given in combination with 0.5 g/kg alcohol, may be especially dangerous in driving. The effects actually appear to be slight. It would help if tests were also made at abuse dosages of the drugs, and especially with abuse concentrations of alcohol. In the United States, persons charged with driving while intoxicated rarely have blood alcohol concentrations indicating that their alcohol dosage had been on the order of 0.5 g/kg.

STUDY: Huffman, W.J., A.E. Florio, J.L. Payne, and F.E. Bays. The Influence of Two Selected Tranquilizers on Driving Skills. Amer. J. Psychiatry, 119:885-886. 1963.

Site: Department of Health and Safety Education, University of Illinois, Urbana, Illinois.

Subjects: Twenty-five young adults participated--15 men, with a mean age of 22.5 years, and 10 women, whose mean age was 20.5 years. They had normal health histories, possessed valid drivers licenses, and were familiarized with the test procedures.

Method: This study consisted of a controlled laboratory experiment and three driving tests, all double blind and counterbalanced in design. Each subject served as his own control. Hydroxyphenamate ("Listica") and meprobamate were compared with a placebo. For Phase I, subjects were tested after "normal" doses of the two drugs vs. placebos. Phase II occurred when, after about a month, the subjects were again tested, this time with double the dosage of drugs.

Sixteen measurements were made on each subject on six separate occasions: the first two after placebo; the third after hydroxyphenamate, 200 mg; the fourth after hydroxyphenamate, 400 mg; the fifth after meprobamate, 400 mg; and the sixth after meprobamate, 800 mg.

Subjects were tested for (1) reaction time; (2) hand steadiness; (3) visual acuity (both eyes); (4) acuity, right eye; (5) acuity, left eye; (6) stereo (depth) perception; (7) color perception; (8) vertical deviation; (9) lateral deviation; (10) near visual acuity, both eyes; (11) near acuity, right eye; (12) near acuity, left eye; (13) near lateral deviation; (14) reaction time distance; (15) braking distance; and (16) total stopping distance. The last three tests involved use of an automobile. Data significance was assessed by means of t tests.

Dosage: The Phase I dosage was 200 mg of hydroxyphenamate and 400 mg of meprobamate; for Phase II, dosages doubled. The tablets were administered 1 hour before testing and tests were completed by 2 hours. (No interaction with alcohol was studied.)

Results: The 96 tests showed five significant effects. In Phase I, visual acuity of the right eye improved after hydroxyphenamate compared to placebo; visual acuity in the left eye improved after hydroxyphenamate compared to meprobamate. In Phase II, reaction time increased after meprobamate compared to placebo. Acuity (both eyes) diminished after hydroxyphenamate compared to placebo, and near acuity (both eyes) diminished after meprobamate compared with placebo.

Comment: The data seem clear-cut and are very simply presented, as compared to many other reports. The relevance of the 16 measurements to real-world driving, however, is questionable. In any event, one would surmise that in other tests of the effects of these two drugs at the two dosages given, there would not be much impairment.

STUDY: Landauer, A.A., and G. Milner. Desipramine and Imipramine Alone and Together with Alcohol in Relation to Driving Safety. Pharmacopsychiatric Neuropsychopharmakologia, 4:265-275. 1971.

Site: Department of Psychology, University of Western Australia, and Mental Health Services of Western Australia.

Subjects: Twenty-seven medical students served as paid experimental subjects. Their mean age was 23.1 years (S.D. = 1.5), and mean weight was 73.7 kg (S.D. = 8.7).

Method: In this controlled laboratory study, the subjects were randomly divided into three groups of nine each. The three groups received either imipramine, desipramine, or placebo, the drugs being administered in tablet form, one at night before the experiment and the second on the morning of the experimental day--i.e., at a 12- to 14-hour interval. Alcohol was diluted with lime juice, syrup, and water and had to be drunk in less than 15 minutes.

Subjects were required not to drink alcoholic beverages on the day before the test. On test day, after a light breakfast, a medical examination, and the second tablet dose, they were asked to complete a questionnaire rating themselves on their present state, and on anything felt or experienced since taking the first tablet. When 25 minutes had elapsed (for absorption) they were given motor skill tests in random order.

These tasks consisted of a tapping test, a dot tracking test, a pursuit rotor test, and a driving simulator test. Both the tests and methods of scoring them are described in the study by Patman et al. reviewed earlier in this report. When the test battery was completed, alcohol (or placebo) was given and then 30 minutes after stopping drinking a Breathalyzer test was administered.

The same test battery and Breathalyzer test were repeated. After having a meal and remaining under observation until appearing entirely sober, the subjects filled out a second questionnaire, rating themselves on their recent intoxication and on symptoms. A medical examination was performed and they were taken to their houses, with a warning not to drink or drive for 24 hours.

Dosage: Imipramine, desipramine, and placebo each took the form of one tablet, 0.8 mg/kg body weight. Alcohol and placebo alcohol doses were 0.8 ml/kg body weight, prepared as described above.

Results: All data except the present rotor test were scored before the drug key was known. The mean blood alcohol level attained was 0.074% w/v (S.D. = 0.009% w/v). The results were statistically evaluated by analysis of variance.

Only the first questionnaire showed any significant differences. The placebo group members rated themselves higher on having a stuffy nose and on frequency of headaches ($P < 0.05$).

The laboratory tests failed to show any significant impairments at the dosages given of either imipramine or desipramine and there was no evidence for interaction of these drugs with alcohol. Alcohol at 0.07% w/v blood alcohol content significantly impaired performance of most tests, but improved the "transformed scores" (see original article) of the driving simulator test.

Comment: The findings are another example of alcohol being the dominant impairing agent when drug dosages close to "therapeutic" quantities are taken with alcohol. This is more clearly seen in these experiments because the dose of alcohol used produced a mean blood alcohol content of 0.07%, a concentration at which most people begin to be objectively affected in the eyes of a careful observer.

The paper does not confine itself to simply reporting the hard data, but also contains useful discussion of review material on drugs and driving, the chemistry and pharmacology of tricyclic antidepressants, previous work on antidepressant-alcohol interaction, clinical trials of desipramine and imipramine, stimulant effects of antidepressants, and methodological difficulties encountered in studies of alcohol-drug interactions in humans.

STUDY: Linnoila, M., I. Saario, and M. Maki. Effect of Treatment With Diazepam or Lithium and Alcohol on Psychomotor Skills Related to Driving. European J. of Clinical Pharm., 7:337-342. 1974.

Site: Department of Pharmacology, University of Helsinki, Helsinki, Finland.

Subjects: Twenty male students, 20 to 23 years old, volunteered. All used alcohol occasionally, none was obese, took drugs, or had any psychiatric disorders.

Method: The double-blind, crossover, 2-week studies under controlled laboratory conditions measured the subacute effects of diazepam alone and in combination with alcohol, and those of lithium alone and in combination with alcohol. The test groups were coded as follows:

Placebo drug, placebo drink	P group
Diazepam, placebo drink	D group
Lithium, placebo drink	L group
Placebo drug, alcohol	A5 group
Diazepam, alcohol	DA5 group
Lithium, alcohol	LA5 group.

Testing took place on 7th and 14th days of the treatments. Effects of learning were excluded by allocating subjects at random according to Latin square design. Subjects were trained on apparatus used before the experiments. Each testing period consisted of three sets of tests 30, 90, and 150 minutes after administration of the drug or drink. At each session, half the subjects received alcohol and half, the placebo drink. Changeover of the drinks was done between each session.

Measurements: The subjects assessed their own performance by completing a rating scale that included guessing of the present treatment modality. Psychomotor tests included a choice reaction test, two coordination tests, and an attention test. Blood samples taken at the end of each session were analyzed for lithium (serum, by flame photometry); for diazepam and N-desmethyldiazepam (serum, by electron capture gas chromatography); and for alcohol (blood, method not stated). Test results were treated by a modification (by Fischer) of the analysis of variance using two- and three-factor designs. The attention test results were also examined by the student's t-test. The three-factor analysis revealed no significant differences among any treatments at the 7th and 14th days; hence, the two-factor analysis was used for presentation.

Subjective assessments: The P and L groups considered themselves normal on the 7th day but impaired on the 14th day during the 15-minute test. Alcohol produced slight subjective impairment at 30 and 90 minutes. Diazepam had no effect. The combined effects of alcohol and diazepam or lithium caused subjective impression of impairment, especially on the 14th day.

On the 7th day, 30 percent of the P group and on 14th day, 50 percent of P group thought they had received a tranquilizer. More than 80 percent of the D group thought their treatment was with a tranquilizer. On the 7th day, 30 percent of the A5 group thought their drink was a placebo and 70 percent of the P group thought they had received alcohol. At the end of the trial (14 days), estimates were 90 percent correct.

Psychomotor measurements: For the choice reaction test, there was no difference between the P and A5 groups. The D group had shorter

reaction times and fewer mistakes. The DA5 group was impaired compared to the P group, especially at 30 minutes. Lithium prolonged reaction time and increased mistakes. The LA5 group showed short reaction time and accurate responses at all times.

In coordination test I, alcohol increased the number of mistakes. D subjects had only a slightly increased mistake percentage compared to the P group. The DA5 group had the largest number of mistakes but their percentage of mistakes was of the same order as that for the A5 group. These mistakes increased from 30 to 150 minutes. L subjects had an increased number of mistakes but a low mistake percentage, whereas the LA5 group had a small number of mistakes but an increased mistake percentage.

For coordination test II, the P group had shorter driving times and lower mistake percentages than other groups but their mistake numbers were high. The A5 group showed a lower number of mistakes but an increased mistake percentage and prolonged driving time compared to the P group. At 30 minutes, the results of the P and D groups were similar but at 90 and 150 minutes the mistake percentage of group D increased and their driving time was prolonged. The mistake percentage and driving times were increased in the DA5 group at 30 minutes compared to the P group, but thereafter the DA5 group decreased its mistake percentage and increased its speed. Lithium increased the mistake percentage and prolonged driving times at 150 minutes. The LA5 group showed impairment at every test time compared to the P group.

In the attention test, several groups showed some impairment after alcohol ingestion compared to the P group. The D group did not, but the DA5 group showed impairment at 30 and 90 minutes, the LA5 group showed impairment at 30 minutes, and the L group was generally impaired compared to the P group.

The blood alcohol concentrations of the tested subjects ranged from 0.40 to 0.60 mg/ml, with the highest values being at 90 minutes.

Dosage: Five mg of diazepam were administered three times daily in gelatin capsules; and lithium carbonate tablets were given with dosage adjusted to produce serum concentrations of 0.75 meq/1. Placebos were administered as capsules or tablets identical in appearance to the real items. Alcohol was given in bitters at a dose of 0.5 g/kg; the placebo bitters had the same volume.

Results: The experiments show very little effect of diazepam alone at the chronic dosage given. Alcohol alone caused only a small amount of impairment. The combination of alcohol and diazepam enhanced impairment; interaction may therefore be presumed. Lithium alone caused some impairment, especially in information retrieval, and when combined with alcohol produced a slight antagonism of effects.

Comment: The information is useful but it would be very helpful if experiments with real-world abuse doses of the drugs and alcohol were undertaken first, to be followed by such work as reported here, where the results are quantitatively unimpressive and of uncertain significance with respect to real-world complex performance.

SEDATIVES

Satanand Sharma, Ph.D.

SUMMARY AND COMMENTS

An assessment of the relationship between sedatives and driving accidents requires the survey of literature dealing with: (1) the effects of sedatives on actual driving behaviors, (2) the epidemiological studies of sedatives and traffic accidents, and (3) the physiological, psychological, and behavioral effects of sedatives on factors related to driving.

Only a few studies have tested the effects of sedatives either in a simulator or in the field. Loomis and West (1) tested eight subjects in a driving simulator from 1 to 6 hours after they were given various drugs. The simulator consisted of an automobile steering wheel and brake accelerator pedals arranged as in a standard automobile. The steering wheel operated a model car placed on a moving belt 150 ft. long and 30 in. wide with an opaque 1-in. strip running down it lengthwise, which simulated the road bed. The strip was shifted randomly, moving smoothly from side to side as the belt advanced. Accelerator and brake pedals actuated and controlled the rate of belt movement, and the steering wheel controlled the position of the model car. A light source placed 14 in. above the car was capable of producing an amber, red, or green light. The subject was required to keep the car centered on the road bed and to respond to the lights by depressing the accelerator pedal when the green light appeared, releasing the pedal when an amber light appeared, and depressing the brake pedal to stop the belt when a red light appeared.

Response measures included braking time following the appearance of a red light, time required to release foot pressure on the accelerator pedal at the appearance of an amber light, and a steering score, which measured the cumulative time during which the car was not "centered on the road."

The experimenters describe the procedure as follows. "Tests were performed at 1 (trial #1) and 2 (trial #2) hours after the administration of the drug. At 2½ to 3 hours after the initial medication, standard lunch . . . was consumed. One hour later the driving test was conducted following which the second dose of medication was taken by mouth . . . The five drugs were: placebo (cornstarch) 200mgm; secobarbital sodium 100mgm; chlorpromazine hydrochloride (Thorazine) 50mgm; meprobamate (Equanil) 400mgm; and

phenaglycodol (Ultran) 300mgm." It is not clear from this description whether the drug amounts cited were the sum of the first and second doses or whether this amount was given at each of the two drug administration times.

Secobarbital, chlorpromazine, and meprobamate produced impairment on the tests. The decrease under secobarbital was the largest, with a 115.6 percent decrement apparent at the fifth hour after initial drug administration. However, it is not clear whether this occurred after 200 mg (a high dose) or after 100 mg of secobarbital.

The Loomis-West simulator represents a part-task simulator in that it measures only some of the tasks related to driving. The simulator does represent some of the demands of driving in that it requires the subject to perform multiple acts simultaneously.

Another study which was carried out on a closed course was conducted by Betts et al. (2). They examined the effects of 150 mg sodium amytal on three vehicle-handling tasks. These were a weaving test, a parking test, and a gap estimation test requiring subjects to estimate the gap between two traffic cones through which they could drive. Fifty men and 50 women served as subjects. The results indicated that the male subjects increased their failures in gap estimations under the barbiturate, and the women decreased their distances from the curb in the parking test, but increased their successes in gap estimations. The qualitative difference in performance between men and women on the gap estimation may indicate a heightened risk-taking attitude in men and a lowered risk-taking attitude in women under the drug condition.

This is a typical closed-course study designed to determine the effects of drugs on driving behavior. The results are suggestive of impairment in certain areas, but they cannot be extended to real world driving situations. The closed course lacks all of the environmental stimuli which place demands on driving. Closed courses are necessary for conducting safe tests, but they reduce the validity of the results.

Flying simulators have also been used to determine the effects of sedatives on complex behavioral tasks. One such study is by Harper and Kidera (3). The authors tested 30 pilots in a twin turbojet flight simulator. The measures included the following parameters: (1) airspeed, (2) altitude, and (3) ILS glide slope and localizer indicator. In addition, an observer scored the subject on "procedures and techniques." The subjects also filled out a questionnaire which was designed to measure feelings of alertness, fatigue, and quality and soundness of sleep the previous night.

The 30 subjects were divided into three groups, with each group receiving one of the three treatments: (1) placebo, (2) glutethimide (500 mg), or (3) flurazepam (30 mg). The subjects were trained for 4 hours, and then 1½ hours of performance data were recorded as a baseline. These data were compared to those obtained after the subjects were given the dosages for two consecutive nights.

The tests were given approximately 12 hours after the second dose. The simulator observations were presented only as improvement, decrement, or no change, as compared to the baseline data. No quantitative scores were provided. Six of the ten subjects under glutethimide and four of the subjects under flurazepam showed decrements. No subjects showed no change, and five showed improvement. The results from the subjective questionnaire for glutethimide indicated seven subjects to be feeling worse than they did when their baselines were recorded. Three under placebo reported their feelings to be worse than their baseline days. The flight data were scored in the same way as the simulator observer data. Four subjects under glutethimide, three under flurazepam, and four under placebo showed "decrement" performance in their final approach.

The authors' summary statement is, "Using flight recorder data as the objective measurement, flurazepam (30 mg) and glutethimide (500 mg), after two nights' dosage, had no apparent effect on flight performance twelve hours after use." This is based largely on the lack of differences between the drug and placebo groups. However, this conclusion may be unwarranted since the study does suffer from some methodological problems. The apparent lack of quantification does not indicate what the various degrees of impairment were in the different groups; and the use of the simulator observer and the subjective rating scale does not allow a clear-cut determination of the drugs' performance effects per se.

Two other studies with flying simulators which did not contain these shortcomings were conducted by McKenzie and Elliott (4) and Hartman and McKenzie (5). In the first study, subjects were tested under 200 mg secobarbital on a flying simulator. The simulator required division of attention and placed multiple monitoring demands on the subject. This is analogous to the driving situation, in which it is necessary to keep the car centered in a lane and simultaneously monitor other environmental signals that may occur. This simulator, therefore, did require use of some skills necessary for driving. It consisted of a cockpit-like console with stick, rudder, and throttle controls. A panel containing four instruments for airspeed, turn, bank, and engine rpm was mounted in front of the subject. The dial needles were programmed to run independently, but simultaneously. The subjects were required to monitor the dials and use the controls to keep the needles in the center position.

The testing occurred 10 hours after ingestion of the drug and lasted for 12 additional hours, with 15-second rest periods following each minute of operation. The results clearly indicated that multiple tracking was degraded 10 hours after ingestion and performance impairment continued to show for the remaining 12 hours.

It is interesting to note that the impairment lasted well beyond the peak pharmacological effect of the drug. From this study it is apparent that the behavioral impairment does not linearly follow

the blood levels of secobarbital. In assessing the effects of drugs on driving behavior, it is valuable to keep this in mind.

The second study, by Hartman and McKenzie, used a similar flying simulator and tested four subjects 10 hours after drug administration. The test lasted for 4 hours and was performed under 200 mg, 100 mg, or placebo doses. Performance was degraded under the high dose, but not the low dose. One interesting aspect of the study was the enhancement of performance under placebo. This was accompanied by the subjects' subjective reports to the effect that they slept as well after receiving placebos as after receiving 200 mg secobarbital. This indicates a strong placebo effect and raises questions regarding the reliability of subjective reports.

It is important to note that the impairment was sustained for 14 hours after drug administration. These residual or "hangover" effects are important for driving. If impairment is exerted for a considerable period of time, then the likelihood of involvement in accidents is increased, even though the blood levels of the drug may not be high. The hangover effect is also evident in other studies.

One example of this hangover effect is a study by Walters and Lader (6). They administered 100 and 200 mg of sodium butabarbitone and 5 and 10 mg of nitrazepam to 10 subjects in a balanced double-blind design. The tests included EEG recordings at rest and also during an auditory reaction time task, a key-tapping rate test, a digit symbol substitution task, and a subjective ratings test for alertness. Testing took place 12 hours after drug administration. The results showed that "many tests were affected significantly by the drugs." This indicates that drug effects are demonstrable for extended periods of time. As the authors stated, " . . . we must remain aware that, although these hypnotics lessen the distress of insomniac patients, psychological impairment and electrophysiological changes are inevitably left the next morning. Indeed, it is unrealistic to expect any adequate hypnotic drug to be devoid of pharmacological effects on wakening." These residual effects are factors which must be faced in research related to drugs and driving.

While the above simulator studies are important in yielding information regarding the effects of drugs, the extension of the results to the real world has to be done with caution. A simulator only partially taps the demands of operating a real vehicle in real situations. The differences between drug effects on simulator performance and on flying an airplane are shown in the study by Billings et al. (7).

In this experiment, five highly experienced pilots were tested under 0, 100, and 200 mg secobarbital, both in a Cessna Model 172 airplane and in a Link-Singer GAT-1 simulator. Before testing, each subject was permitted "to familiarize himself with the vehicle and to practice instrument approaches until he was satisfied with his performance." On test days, the pilots conducted two instrument

flights after ingesting the secobarbital. After the flights, duplicate studies were performed on the same pilots under similar conditions using the simulator. The responses recorded were tracking performance in two axes and airspeed control. The average decrement at the 100- and 200-mg doses, as compared to the placebo, were 17 percent and 26 percent in the simulator and 2 percent and 14 percent in the airplane. The manual control decrement at the 100-mg dose in the airplane was not different from placebo. At the higher dose level, little difference was observed for tracking in the first flight, but significant differences were observed in the second flight. The differences were significant for both flights at both doses in the simulator. The paper does not state clearly at what time interval after the administration of the drug the testing took place. Also, the total time of testing is not specified. It appears that testing may have taken place immediately after administration, in which case the peak pharmacological effects may not have been reached during testing.

However, it is clear from the results that there are differences in performance between the simulator and the airplane. 'This study serves as a reminder that a simulator--and this may be true of most simulators--is not an airplane. 'Flying' it demands a different strategy than that utilized in flying the airplane for which it is a surrogate, and proficiency in the one vehicle does not imply equal proficiency in the other." A similar statement can be extended to driving and driving simulators.

The literature on epidemiological evidence which implicates sedatives with driving accident involvement is scant. It deals largely with coroners' reports, and published materials generally only indicate the number of driving fatalities which have occurred under the drug's influence or report the number of persons with drugs present while they were driving.

A typical study dealing with sedatives is one by Gupta and Kofoed (8), in which they assayed urine and blood samples from persons cited for driving while under the influence of drugs. They report the number of persons showing the presence of barbiturates and no alcohol. (For 1964, 18 such cases were cited in Ontario, Canada.)

There are a number of problems in using such data to implicate sedatives in causing driving accidents. The numbers of drivers apprehended under drugs do not indicate the nature of the relationship between the drugs and accident involvement. To determine this, it is essential to know (1) the number of drivers involved in accidents under the influence of sedatives and (2) the number of individuals who drive under sedatives in the location where the accident took place at the same time of day, but who are not involved in accidents. Only a comparison of the accident-involved drivers and the at-risk population will yield an index that implicates sedatives in causing driving accidents. Such studies are available for alcohol, but are sorely lacking for sedatives. Further, the Gupta and Kofoed study did not indicate what the drug blood levels were. It is important to know what the relationship

is between drug levels and apprehension or accident involvement. It has been mentioned earlier that impairment under barbiturates is sustained for long periods of time. Thus, it is important to relate the residual effects of the drugs to driving accident causation. The existing epidemiological studies on sedatives suffer from many methodological problems, ranging from the populations sampled to the lack of quantitative data on drugs in body fluids.

The data from studies of the effects of sedatives on driving-related skills also provide information regarding drug involvement in traffic accidents. Such behavioral studies can focus on various aspects of driving skills. Driving itself is a complex task requiring acquisition of information, processing of information, and the execution of responses based on that information. These stages require the performance of such tasks as monitoring the environment for signals; tracking, or keeping the car on the road; and responding to the stimuli by braking, accelerating, or steering. There are a number of papers which deal with aspects of these driving-related skills.

Drugs could affect sensory mechanisms, which in turn could produce deleterious effects on driving behavior. There is a lack of literature on the effects of sedatives on visual functions. However, there are a number of papers dealing with the effect of sedatives on oculomotor functions, such as the one by Holzman et al. (9). They examined the effects of single doses of chlorpromazine (0.667 and 1.33 mg/kg body weight), Valium (0.071, 0.142, and 0.284 mg/kg body weight), and secobarbital (100 mg) on smooth-pursuit eye tracking. Five male subjects (four for the barbiturate) were required to follow a pendulum that moved with a frequency of 0.4 Hz. The horizontal eye movements were measured by silver-silver chloride skin electrodes applied to the outer canthus of each eye and recorded on a dynograph. The scoring procedure required two scorers to independently classify the tracking as qualitatively "normal" or "deviant." One quantification of the scores was the number of times the eyes stopped their pursuit of the target.

The results showed that only secobarbital disrupted eye-tracking performance. Two of the four subjects under the barbiturate replaced their ocular pursuit with saccades. One of the subjects who showed no qualitative disruption of his tracking pattern was given the higher dose of 130 mg of secobarbital. This dose was found to produce eye-tracking disruption which lasted 24 hours.

These results are suggestive of disruption of higher order processes. However, the study does contain some methodological problems. The number of subjects is too small to allow generalizations about the results. Also, the qualitative measures relied on the judgment of scorers, and even the quantitative measures used in the study are inadequate for describing the deviation of eye movements from smooth pursuit. Manual inspection of the data is, of course, time-consuming and limits the size of the study.

There are several studies dealing with the effects of sedatives on vigilance behavior. Vigilance is important in the operation of machinery or automobiles. Any unchanging environment can produce impairment in skills performance. Kopřiva et al. (10) tested 90 professional drivers under 150 mg/70 kg body weight pentobarbital. Auditory signals were presented to the subjects at irregular intervals via earphones, such that the signals differed in spatial location (left, right, and midline). The subjects were asked to ignore the midline stimuli (50 percent of the presentations) and to depress a button when the other two kinds of stimuli occurred. Each subject "was also informed that the course of physiological functions after drug application permits to determine . . . whether the drug has any effect or not and that this information would be transmitted to him by a light signal in time, so that he would be prepared to counteract any disturbing effect of the drug." Pentobarbital increased the number of misses, and the cue did not affect performance, but false alarms increased with the cue condition under this drug. The authors noted that this may be related to a shift in discrimination criteria. However, due to the lack of signal detection analyses, it is not clear whether the poorer performance under the drug is related to set or criterion shifts. It is nevertheless clear that pentobarbital affects signal detectability.

Psychomotor performance under sedatives has been studied by various investigators. One such study is by Goodnow et al. (11). They tested 30 male subjects on placebo and 100 mg pentobarbital, using a crossover design. The test battery contained a number of tests including: (1) tapping speed, using a telegraph key; (2) auditory reaction time, in which the subject was required to depress a key at the presentation of an auditory stimulus; (3) naming of opposites, in which the time required to name the opposite of a common word was recorded; and (4) memory for digits, which was simply measurement of backward digit span. the pentobarbital degraded performance on all four of the tests 4 hours after administration. There was a trend toward poorer performance (not statistically significant) 14 hours after the drug dose.

This study represents a sound experiment, in that the design controlled for many sources of variance. Learning effects were controlled by performing the statistical analyses on the differences between the before and after tests for the placebo and drug treatments.

As has been mentioned earlier, driving is essentially a dual-task function, requiring the detection of environmental signals and tracking to keep the car on the road. Two examples of papers on tracking under sedatives are those by Borland and Nicholson (12) and Shroeder et al. (13).

Borland and Nicholson tested seven subjects under placebo and 200, 300, and 400 mg of heptabarbitone on a tracking task. This required subjects to position a spot inside a randomly moving circle displayed on an oscilloscope. An error signal proportional to the distance between the spot and the center of the circle controlled

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the difficulty of the task by modulating the mean amplitude of the movement of the circle. Each trial lasted 10 minutes with only the last 500 seconds used as the performance measure. Each subject was trained until a plateau level was reached. Predrug trials were run, and post-drug trials were run at various intervals after administration. The various drug doses were administered in random order.

The results showed that heptabarbitone produced decrements in performance at 10 hours after the 200-mg dose, at 10- and 13-hour intervals after the 300-mg dose, and at 10-, 13-, 16- and 19-hour intervals after the 400-mg dose. The performance impairment was dose related. It is interesting to note that blood levels of heptabarbitone did not correlate with individual performance.

The study by Schroeder et al. tested the effect of placebo, secobarbital (100 mg) and d-amphetamine (10 mg) on tracking performance. Ten subjects were tested in each of the drug groups. The tracking performance was tested under two conditions: (1) while the subject sat stationary and (2) while the subject underwent angular motion. The tracking test consisted of an aircraft localizer/glide-slope indicator with the vertical needle being deflected to the right or left of center by a sinusoidal forcing function. The subject was required to keep the needle in the center by compensatory movements of a joy stick. After the subjects were trained on the task, there was a predrug test, and three post-drug sessions were conducted at 1, 2, and 4 hours after administration of the drugs. The response measures included tracking errors under both static and dynamic conditions and the number of nystagmic eye movements during the dynamic condition. During the static condition, secobarbital did not affect tracking scores. Amphetamine was found to improve scores over control for the 2- and 4-hour post-drug sessions. During angular acceleration, secobarbital produced more tracking errors and increased vestibular nystagmus as compared to both the control and amphetamine groups for all post-drug sessions.

Both of the above studies give examples of deleterious effects of sedatives on tracking performance. The second study did not demonstrate any effects under the stationary condition, but it would be worthwhile to examine the effects of the drug at more delayed intervals after drug administration.

Since alcohol is to a large extent consumed in conjunction with other drugs, it is important to evaluate the combined effects of sedatives and alcohol on driving skills performance.

Examples of this kind of investigation are presented in papers by Sellers et al. (14) and by Mould et al. (15). In the first study, Sellers et al. tested the effects of placebo, alcohol, and chloral hydrate, singly and in combination, on changes in heart rate, arterial pressure, skin temperature, simple and complex reaction times, a tracking task, and a vigilance task. Five male subjects were tested under the following drug conditions: (1) placebo; (2) alcohol (0.5 g/kg body weight); (3) alcohol (0.5 mg/kg body weight) given ½ hour after chloral hydrate (15 mg/kg body weight);

(4) chloral hydrate (15 mg/kg body weight); and (5) alcohol (0.5 g/kg body weight) after prior treatment with chloral hydrate (15 mg/kg body weight) for 7 days, with the last sedative dose being given 12 hours before alcohol.

Compared to the control conditions, alcohol was found to increase heart rate between ½ and 1 hour after administration. Chloral hydrate combined with alcohol increased the cardiac rate at ½ hour after administration more than did alcohol given alone or chloral hydrate given alone. Chloral hydrate followed by alcohol caused greater increases in skin temperatures than the other treatments. There was no drug effect on the reaction time tasks. Alcohol was found to degrade the tracking and vigilance tasks, but chloral hydrate given alone had no effect on these tasks. The decrement was pronounced (and larger than for alcohol alone) when chloral hydrate was given in combination with alcohol on both the tracking and vigilance tasks.

There are a number of methodological problems with this study. For example, the size of the sample is too small and the specifics of the experimental design are not clear. However, it is clear that alcohol and chloral hydrate in combination do cause greater performance deficits than does either substance taken alone.

Mould et al. tested six subjects on the effects of glutethimide (250 mg) alone and in combination with alcohol on reaction time, tracking, and a finger-tapping task. Glutethimide alone was found to affect all the behavioral tests. Glutethimide consumed simultaneously with 100 ml of vodka was found to increase the reaction time responses, but did not affect the other tests (nor did alcohol alone). This is in contrast to the previous study, where chloral hydrate in combination with alcohol had no effect on reaction time tests, but did affect the tracking task.

One interesting finding was that, when chloral hydrate and alcohol were given simultaneously, blood alcohol concentration was significantly higher (11 percent) at 105, 135, and 165 minutes after drug administration than when the alcohol was ingested alone. In contrast, a second experiment which was part of the same study tested phenobarbital (60 mg) given in combination with alcohol (50 ml vodka). A decrease in the blood alcohol concentration was shown at 30 and 90 minutes after administration. This study also suffers from the use of a small sample size and an ambiguous experimental design.

An example of a study which investigated the effects of drugs in combination (other than alcohol) on behavioral performance is one conducted by Dalton et al. (16). They tested 12 subjects under marihuana (25 mg THC/kg body weight) and secobarbital (150 mg/70 kg body weight), alone and in combination, on a complex tracking task, a stability test, a tapping test, and mental performance tests. Marihuana alone was found to impair stability of stance and performance on the tracking and mental performance tests, but did not affect the tapping task. Secobarbital degraded performance on all

the tests, except the stability of stance test. The combination of secobarbital and marihuana evidenced performance deficits on the pursuit, stability, and mental performance tests beyond those experienced under either drug alone, suggesting additivity of the component effects.

This study is an example of degraded performance when drugs are used in combination; it suggests a need to explore this area further.

Finally, the history of drug-taking can have differential effects under sedatives. Metabolic rates are known to be accelerated for certain drugs by other drugs (e.g., tolbutamide by alcohol) and other types of physiological changes may be induced by the use of some drugs which could modify the effects of yet other drugs. A study by Raft et al. (17) provides an example of the differences in responses to sedatives between light and heavy alcohol drinkers. They tested 12 heavy drinkers and 12 light drinkers, either under placebo or 200 mg of pentobarbital. One hour after drug administration, the experimenter subjectively evaluated the subjects' impairment of memory, concentration, and "physiological signs," including nystagmus. The heavy alcohol drinkers were found to be "resistant" to the effects of pentobarbital. The "low alcohol users exhibited significantly more signs of intoxication then did high alcohol users."

The authors did not report the blood pentobarbital levels at the time of evaluation. The results, of course, have to be interpreted cautiously, since they are subjective impressions and not objective data. However, they are suggestive of behavioral tolerance buildup caused by the use of other drugs. Whether such tolerance lowers impairment under sedatives is left to further study. There is clearly a need for more research in this area.

It is clear from the above examples of research on sedatives that there are several areas dealing with sedatives and driving that require further investigation. These include: (1) the epidemiological evidence of relationship between sedative use and driving accident involvement; (2) the extended duration of action of sedatives; (3) vigilance performance under sedatives; (4) the interaction of sedatives and other drugs, including alcohol; and (5) physiological and behavioral tolerance buildup to sedatives as well as cross-tolerance between sedatives and other drugs.

There are many methodological problems inherent in epidemiological data collection for sedatives and driving. In addition, simulator and closed-course studies yield little data which provide information about either accident causation or mechanisms of sedative actions leading to driving accidents. The one area which clearly will provide much information about sedative use and driving is research dealing with the behavioral mechanisms affected by sedatives. It is suggested that further studies be performed which would systematically investigate the behavioral impairment experienced under sedatives.

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STIMULANTS

Robert Forney, Ph.D.

SUMMARY

Leake (1) philosophizes concerning the sleepy driver and his involvement in traffic accidents. He suggests that physicians should take an active interest in their patients' driving habits, warning about the effects of drug and alcohol use.

Many disease states may complicate driving prowess. Drugs--e.g., caffeine, amphetamine--may be used to combat fatigue. No definitive data are presented. The suggestions and discussion are interesting but not novel.

Rutenfranz and Jansen (2) studied the effects of caffeine or Pervitin (methamphetamine) using two subjects (age or sex not reported) and a driving simulator. The alcohol dose was either 0.5 g or 1.0 g/kg. Either 0.2 g of caffeine or 9 mg methamphetamine were injected. Either alcohol dose deteriorated performance. Methamphetamine reversed this effect with the low dose of alcohol and partially with the high dose. The subjects claimed not to feel the alcohol effect when their blood concentration was 0.06 percent. Caffeine also reversed the alcohol effect but was less potent.

The study was poorly controlled, and too few subjects were used. The results have not been confirmed by others.

Kraft (3) has reviewed a series of case histories to emphasize the possibility of central stimulating drug involvement in driving performance. The driving errors were not documented as having been influenced by drugs, but that possibility was raised, considering the pharmacological properties of commonly used drugs. The fact that alcohol disappearance was not altered by this class of compounds is not surprising. The paper serves to reemphasize the problem but offers no solution.

Hurst (4) has studied the effect of d-amphetamine on risk taking based on the observation that it is a mood elevator. Heightened optimism contributes to self-confidence and increased risk taking. Little data had been published to indicate that amphetamines had behavioral or judgmental effects. Studies bearing on this possibility were so structured as to be insensitive to mood changes. Gambling was chosen as the test measure. Twenty-nine male penitentiary inmates were the subjects. The dose of d-amphetamine was 10

mg. Risk taking increased with drug treatment. The change was not dramatic and the subjects were very special. The dose of d-amphetamine was modest, especially for nonprescription use.

Wilson et al. (5) studied the combined effect of ethanol (1.2 g/kg) and amphetamine (15 mg/kg) on performance using 32 medical and pharmacy students, sex presumed to be male but not stated. No difference was shown between ethanol-amphetamine and ethanol-lactose on performance of balance, skipping, Minnesota manipulation, Purdue Peg board, Maudsley Personality Inventory, pursuit rotor, or digit span. During testing, blood alcohol values ranged from 0.06 to 0.08 percent (Breathalyzer). Minor changes were noted with other test parameters. No placebo controls were used. The testing devices were likely insensitive. No dramatic data were obtained. No information to relate amphetamine and/or amphetamine-ethanol use in driving was provided.

Laties and Weiss (6) summarized published information relative to the effect of amphetamines on enhancing performance. The work was a 5-year update of a previous analysis of the question. They reaffirmed that amphetamines do improve performance on a wide variety of tasks. They suggest that greater improvement can be achieved by manipulating the variables controlling the tasks. Introducing an element of variety may increase attention to and interest in performance, but how this could be utilized in a driving situation was not discussed. Any device to increase driver motivation and/or attention has great potential for good. Suggestions for such an innovation were not made but should be considered.

Livingood et al. (7) have studied the effects of d-amphetamine (15 mg), caffeine citrate (500 mg) and high temperature (125.6° F) on human performance. Twenty-four young males were subjects. Strength task data, heart rate, rectal temperature, and evaporating water loss were observed, although the data are considered irrelevant to driving performance. Improvement in mental performance was noted in subjects dosed with amphetamine and in a high-temperature area. The improvement, however, was at a low level of significance which would be unimportant in driving skills.

Hurst et al. (8) studied the effect of amphetamines on judgment and decisionmaking by evaluating published studies (including their own, reviewed here) which have shown that drugs improve mood and lessen fatigue. Increased risk taking may be a reflection of these effects. The complicated explanation of the results obtained in the experiments reviewed has little relevance to a driving situation and adds nothing of importance.

Hurst (9) further examined the effects of amphetamines upon judgments and decisions. At this time he reported that, despite published data to the contrary, the belief that amphetamine affected judgment was widely held. Either d-amphetamine or diamphetamine in doses of 15 mg/kg was given to 93 students of mixed sex. A mathematical reasonsing test with self-appraisal and a reward for good performance was given. Performance was not affected.

Positive self-appraisal was effected by either drug treatment, with d-amphetamine, as expected, being more potent. Improved self-appraisal may be a reflection of mood elevation. Whether impaired performance in a motor car would attend this was not discussed and is certainly not apparent.

Hurst et al. (10) have investigated the effect of ethanol and d-amphetamine upon mood and volition. Seventy male subjects were used. The parameters of risk taking (gambling), verbal production on an assigned subject, and mood were measured. Even the authors did not suggest what significance verbal production changes would or did mean. The increase in confidence with alcohol or amphetamine was not expected. The modest increase in mood or risk taking may be attributed to the modest doses of either drug (15 mg d-amphetmine, 45 g ethyl alcohol). Nothing definitive or applicable to the problem of these drug combinations in drivers was presented.

Wagner (11) responded to a question-and-answer section of the medical journal concerning elderly people who doze when driving. He suggested that a medical condition may be responsible and recommmended caffeine or amphetamine for mild stimulation. No data are presented and the medical opinion is not helpful.

Bye et al. (12) have compared the effects of 1-benzylpiperazine, a compound having some activity similar to dexamphetamine in mice and rats, with dexamphetamine on human performance. Two groups of normal subjects were tested; the first group had 9 men and 3 women and the second had 7 men and 5 women. The age range was 21 to 46 in group 1 and 21 to 47 for group 2. Significant improvement ($p < 0.05$) occurred in an auditory vigilance test after either drug. In the short-duration tests (i.e., tapping rate, hand steadiness, and arithmetic) significant changes were not seen. The conclusions of the study are interesting but have little relevance to performance in motor vehicle operation. A relationship may exist between improved auditory signal detecting and automobile driving; the authors unfortunately did not discuss it.

Frank et al. (13) measured the effect of caffeine (300 mg/kg) alone and in combination with ethanol (75 mg/kg) on 68 students of both sexes. Tests measured cognitive, perceptual, and motor functions. The battery consisted of standing steadiness, simple and complex reaction time, manual dexterity, numerical reasoning, perceptual speed, and verbal fluency. A placebo control was used. The peak plasma ethanol concentration of 92 ± 4 mg percent was not altered by caffeine. Caffeine did not antagonize the ethanol-induced performance decrement except in reaction time tests, in which caffeine antagonized complex reaction time impairment induced by ethanol. The authors agree that no clear pattern of ethanol antagonism occurred with the doses of caffeine used. The suggested hazard of a driver feeling more alert with caffeine after drinking yet having a performance decrement is a conjecture unsupported by their data. The evidence is that ordinary amounts of caffeine do not practically antidote ethanol-induced impairment.

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MARIHUANA
GENERAL HALLUCINOGENS

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SUMMARY: MARIHUANA

The following group of studies involving the administration of either marihuana or a hallucinogenic drug has been concerned primarily with the conclusions that one can derive from possible changes in the dependent behavioral methodological issues in drugs studies attempting to examine skills performance.

The experimental literature on marihuana offers an excellent survey of the techniques commonly used to investigate the effects of drugs on skills performance. These range from studies done with actual cars in real driving situations to laboratory studies of components of behavior assumed to be important for driving.

The experiment with perhaps the most face validity for a real driving situation was performed by Klonoff (1). He utilized 64 subjects, some studied in a closed driving course and some studied while on the streets of Vancouver. Active treatments were dosages of 4.9 and 8.4 mg delta-9 THC administered by smoking. The subjects on the closed course went through a slalom, two tunnels of different widths, a funnel, a stop-and-back-up maneuver, a corner, an emergency stop, and a risk-taking situation involving gap estimation.

Scoring was generally unambiguous, being based on the number of cones hit, except for risk taking. Scoring for the traffic driving situation, however, was less definitive as it involved subjective estimations of performance by examiners from the State Department of Motor Vehicles. No evidence was given for the reliability of these subjective judgments, and this may be the source of the large variability found in performance under marihuana. Some subjects exhibited improved performance. In the 11 scales of subjective judgments, such as cooperation, attitude, irritability, care while driving, speed, confidence, tension, judgments, etc., that were used in the study, only 3 appeared to be significantly affected--judgment, care while driving, and concentration. The objective scores on the closed course revealed no significant impairment at the low dose, but did at the high dose, on all but the backup and corner tasks.

If one can accept the validity of the subjective measures used by the traffic examiners in the open traffic driving situations,

their scoring suggests that marihuana impairs some aspects of driving skills which might be examined in a more objective experimental situation. The subjective variables themselves give little insight into the nature of the pharmacological actions which might be affecting driving. Clearly, the closed course situation with its more objective measurements provides greater certainty that marihuana had impaired driving skills performance. The study attempts to determine whether the skills utilized in driving are affected by the use of a particular drug. The variables (e.g., number of cones hit, etc.) have not been related to any behavioral variables; therefore, the nature of the deficit produced by marihuana cannot be understood.

Typical of the simulator studies performed under the influence of marihuana is a study by Rafaelsen et al. (2). Subjects in the simulator performed two major behavioral tasks--tracking and responding to various signals. The tracking task required following a simple outline of a road, which moved in a circular track; the recognition task required responding with the brake to stoplight signals and with the accelerator to start-light signals. Speed and number of gear changes were also recorded in this manual transmission-equipped car. Marihuana was orally administered in doses of 8, 12, and 16 mg delta-9 THC.

The two larger marihuana doses primarily affected the speed of responding to signals, either from the start or stop lights. At no dose level was the frequency of gear changes or the mean speed affected. In comparison with road driving, the simulator has more objective measures for components of driving.

This study suggests that marihuana has a greater effect on sensory or perceptual aspects of car control than upon motor aspects. While deficits occurred in the latency of responses to signals, none appeared in tasks involving motor responses, such as gear changes or speed. In comparing two methodologies of actual car driving versus simulator studies, the one advantage of the simulator has been its ability thus far to differentiate aspects of behavior more clearly than has been possible by actually driving cars. This is not a theoretical necessity, but merely a consequence of the limited range of responses that have been available in most instrumented cars. It should be noted, though, that the Department of Transportation has recently developed an instrumented car with considerable capacities for analysis of tracking behavior.

Another example of the manner in which simulators have been employed to examine specific behavioral characteristics is their use in studying the effect of marihuana on risk taking. Dott (3) used the closed-loop simulator built by the U.S. Public Health Service in Providence, Rhode Island, to develop a passing-task situation. This simulator uses a single-beam optical projection system with model cars on two belts. The two belts represent two road lanes, and can be moved at different speeds relative to each other. In the study, the subject was required to pass a car in his lane before a car approached in the opposite direction in the other

lane, which was to be used for passing. The study was complicated by a requirement for aborting the passing maneuver or, conversely, for attempting a rapid completion when various light signals were presented.

Twelve subjects were examined under two active treatments and one placebo treatment, the active treatments being 11-1/4 and 22-1/2 mg delta-9 THC. The results indicated that subjects made fewer attempts to pass under marihuana. When the warning signal occurred, the subjects were placed under stress for a quick decision to pass or not to pass. Despite a reward for successful passing, the subjects under marihuana were more likely to abort the attempt to pass and thus adopt a more conservative set of behaviors. Objectively, there were no differences in the paths traversed under the different doses and treatments for the passing maneuver. The author thus concluded that marihuana produced a decreased willingness to take a risk.

The only negative finding regarding the effect of marihuana was that the length of time necessary to decide whether to pass when an opportunity to do so was presented increased under marihuana. An interesting aspect of the latter finding was that the passing situation was presented under two conditions. One condition was not considered to be an emergency and one was presented as an emergency with a warning signal demanding a rapid response. The increased decision time only occurred when it was a nonemergency situation. If a warning signal occurred, there was no difference in decision time from that when not under marihuana. Apparently, the stress of the situation helped compensate for part of the negative effect of marihuana upon decisionmaking. Methodologically, this study of drug effects with a simulator had the advantage that its design permitted a separate examination of a risk-taking behavioral function. Rather than merely producing a yes-no comment on whether marihuana was or was not impairing, it was able to examine drug effects on a behavioral function.

Most marihuana research has taken place in behavioral laboratories, where attempts have been made to isolate specific behavioral functions for further analysis. Typical of such studies is one by Manno et al. (4). The authors examined what they called motor performance, utilizing the pursuit tracking test at four levels of difficulty, a delayed auditory feedback task, and a variety of other psychological and subjective measures. The 12 subjects were given doses of either 0, 2-1/2, or 5 mg delta-9 THC. Pursuit tracking involves two stimuli, typically two dots or bars on an oscilloscope screen. One of the stimuli is under the influence of a forcing function, and the other is controlled by the subject. The subject's task is to track the first dot with his dot so as to minimize the distance, or error, between them. The differences between the four pursuit tracking conditions in this situation would be directly related to the forcing function's complexity.

Both marihuana doses seriously impaired performance on the tracking test, with no difference between the two dose levels. Since

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tracking is an important component of driving, this is clearly an important finding. The finding is limited only by (1) its inability at this time to relate the difficulty level of the tracking task in the laboratory to that of the tracking task in an actual driving situation, and (2) its inability to determine what behavioral functions are involved in performing a tracking task.

Manno et al. also examined performance on delayed auditory feedback, which is described as a measure of mental performance. This skill was also impaired by marihuana. However, no comment will be made on this measure, as it is not clear how it relates to skills performance. This study also examined the effects of alcohol, and alcohol and marihuana in combination, on these behavioral variables. There was a clear additive effect of greater impairment. This suggests a need for further investigation of the interaction between drugs and alcohol, since they are frequently used together.

As it became clear that tracking tests were sensitive to the influence of marihuana, other investigators utilized tracking tasks to evaluate the influence of marihuana upon further behavioral variables. For example, Roth et al. (5) examined the effect of marihuana on tracking performance using a paced contour tracking test. This is a pursuit tracking task in which the subject has a moment-by-moment preview of the demands of the task, and is closely akin to the tracking demands of real driving, in which we can see the road ahead. The study examined two issues--whether marihuana would be sensitive to such a pursuit tracking task, and whether taking samples of tracking performance at 15-sec time intervals would produce evidence that marihuana effects fluctuate during short time periods. Nineteen subjects received placebos and 18 subjects received oral doses of 20 mg of delta-9 THC.

No evidence was found which suggests that marihuana effects fluctuate in short time periods. However, tracking task performance was significantly impaired by marihuana, although the deficit did not appear proportionately as great as that found in the Manno et al. study perviously cited. This could be due to the differences in the forcing functions rather than the differences in the type of pursuit tracking tasks used in the two studies.

One of the difficulties in interpreting these studies is that it is not clear which behavioral characteristics are important for tracking performance. There is evidence that both perceptual and central cognitive aspects, as well as motor skills, are important in tracking. In recent years there has been considerable interest in a more analytical evaluation of the nature of tracking performance, and among engineers attempts have been made to apply linear mathematical models, known as describing functions, to describe the human operator. These techniques will become increasingly important as soon as there is greater agreement on the meaning of the various elements of those linear differential equations, in terms of behavioral characteristics. There is a growing literature designed to elucidate precisely this issue.

An example of this methodology in drug research is a study by Reid et al. (6), which examines alcohol and marihuana effects on compensatory tracking using a spectral analysis of tracking responses. Three subjects received the low dose of 21 mg delta-9 THC/kg body weight, and three subjects received the high dose of 88 mg delta-9 THC/kg body weight. While alcohol affected several parameters of the tracking describing function, only the high dose of marihuana had any effect, a small increase in the random error term in the describing function. Unpublished work from other laboratories suggests that there is a greater effect than that demonstrated in this study, possibly because the forcing function selected was inadequately difficult. The study does have merit, however, in that it indicates a method of examining tracking performance in which changes in tracking performance can be broken down into components related to the behavioral aspects affected by the drug.

Such an analytical method is more satisfactory than using the pursuit rotor task, as in the study by Weil et al. (7). Using doses of 4.5 and 18 mg delta-9 THC, Weil et al. found that naive subjects were significantly affected at both doses on the pursuit rotor tracking test, but that chronic users were not. While the study is valuable in demonstrating a tolerance effect, which should be taken into account when evaluating other performance skills under the effects of marihuana, the pursuit rotor has failed to demonstrate that it utilizes behavioral components that are characteristic of tracking tasks in industry or driving. It also fails to indicate which behavioral components are involved in this task so that we can at least make some statements regarding the nature of marihuana's effect on significant psychological variables.

Drug researchers often select response variables for which interpretations in terms of skills performance are unknown. For attempting to assess drug effects in relationship to industry or to driving, it is important that the response variables be appropriate.

In a study by Milstein et al. (8), several variables were examined under the influence of marihuana: these included a hand-maze test, moving a stylus in a vertical or horizontal groove, and tests of the speed of finger and toe tapping. This study compared the performance on these variables of 16 experienced male and female marihuana users with the performance of 16 subjects who had never taken marihuana. All subjects in this crossover design received 7.8 mg delta-9 THC by smoking. There were significant decrements in the vertical and horizontal groove task, the maze, and hand steadiness, although there were no effects on the finger tapping and toe tapping.

The authors found that the decrement in performance on the maze and hand steadiness test was significantly greater for the experienced smokers than the inexperienced smokers. This contradicts the report by Weil et al. as well as other data in the literature. Perhaps the difference is that most prior reports have dealt with

heavy users vs. infrequent users. This study seems to be comparing moderate users with naive subjects who had never previously used the substance. While the data may have merit in showing the differential effect in terms of usage, it would appear to have limited value for documenting the effects of marihuana on more complex skills performance.

Casswell and Marks (9) provide an example of the examination of marihuana's effects on a more complex function which a variety of studies have shown to be highly important for skills performance. The ability referred to is the simultaneous performance of two tasks, or division of attention. In recent years, research in skills performance has emphasized the importance of higher cognitive skills, with the ability to divide attention as a prime example. Driving is intrinsically a situation in which one is required to divide attention between a tracking task and a search and recognition task for environmental dangers.

In the Casswell and Marks study, 10 naive subjects and 10 experienced subjects were compared at doses of 0, 3.3, and 6.3 mg delta-9 THC. Subjects were required to indicate whenever a break occurred in the sequence of light flashes appearing at the center of a visual arc. They were also asked to detect the random flashing of a series of lights on the periphery of the visual arc. Under both doses of marihuana, there were clear deficits in the perception of changes for both central and peripheral lights. While the differences between the naive and the experienced users were not statistically significant, the trend appeared to be for a greater decrement in the naive users.

As noted earlier, this study is important because it involved a response variable which is important for driving skills. The major criticism of the study, which is unrelated to the previous point, is that a deficit shown in tests that measure division of attention can be due to (1) interference with the specific skill of performing divided attention, (2) to impairment of continuous attention, or (3) to a decrement in the ability to monitor the situation due to sensory input failure. Because there were no controls for the variables required for dividing attention, we are unable to pinpoint the nature of the reason for the deficit in division of attention. However, as mentioned above, it is noteworthy that this study selected a variable shown to be of great significance for driving.

An increasing number of studies are being published which are designed to examine in greater detail the nature of deficits in variables already known to be impaired by marihuana. One example is the study by Dittrich et al. (10), in which 17 subjects were examined after an orally administered dose of 15 mg delta-9 THC to determine aspects of marihuana's effects on memory, attention, and subjective states.

The essence of the study was the correlation between the effects of marihuana on an attention test and on a memory test, both

presented to subjects in the same session. Testing showed impairment of both attention and memory, and the decrement in attention was found to be correlated with the decrease in input into long-term memory storage. These results emphasized the importance of the role of attention as a variable influenced by the drug in explaining some of the other effects of marihuana on performance. While the variable examined here, memory, is probably not of great importance in driving and other skilled performance situations, the attempt to examine the relationship among more complex variables in order to understand the nature of the deficit makes the study valuable.

In addition to complex cognitive variables, skills performance is affected by changes in simple sensory input functions such as the thresholds for detection of auditory and visual signals. One early study on sensory skills under marihuana was published by Caldwell et al. (11). They examined auditory and visual thresholds in 20 experienced subjects before and after smoking marihuana. The amount of marihuana administered was not calibrated, but was determined by the subjects' reporting the point at which they experienced a "high." Marihuana had no effect on the visual brightness test, on the auditory frequency threshold test, or on differences between frequencies. There was a small effect on detection of differences between auditory intensity thresholds. In general, the evidence suggested that marihuana had little effect on auditory and visual thresholds.

The importance of studying simple sensory phenomena in the laboratory is twofold. On the one hand, it is clear that such simple sensory functions are of importance for driving and the performance of other skills, and on the other, it is necessary if we are to find the locus of the perceptual performance impairment under marihuana that has been exhibited in experiments involving more complex response tasks.

Users of marihuana have often reported the subjective, emotional influences it has on their feelings and, potentially, their behavior. These aspects of the effects of marihuana have been elusive in laboratory examination as compared to sensory, perceptual, or motor skills effects. It is important that these behavioral elements be examined, however, since they could affect the likelihood of accidents as much as deficits in visual or motor skills could.

Subjective elements are frequently examined for drug influence by self-reported scales filled out before and after a drug is administered. The study by Waskow et al. (12) is typical of this method. In this case, the chief measure was the Subjective Drug Effects Questionnaire (SDEQ), which examines changes in thinking, feeling, perception, and somatic areas influenced by drugs. Sixteen subjects received a dose of 20 mg of delta-9 THC and were compared with 16 subjects who received a placebo. Half the subjects under each drug treatment performed while music was being played.

This was designed to examine the influence of variables that are typically met in a social context.

In addition to the subjects rating themselves, observers rate the subjects on a standard observation form based on the Clyde Mood Scale. The main effect shown by the Mood Scale was that subjects under THC appeared more sleepy and less lucid to observers. The prime result on the subjective self-report scale was that subjects under marihuana felt that their thinking was fuzzy, their movements slow, and that they were losing their sense of time. They also reported perceptual changes, such as blurred eyesight and seeing images with eyes closed. Subjects reported feeling sleepy and "high," and also reported a fair amount of somatic discomfort with feelings of body heaviness and unsteadiness, and experiences of impaired cognition.

Some studies have indicated a discrepancy between subjective reports and objective performance changes; because of this, self-reports are often difficult to interpret. They can provide important clues as to marihuana's effects, but may not be completely accurate. In the study by Moskowitz and McGlothlin (13) on auditory signal detection, subjects receiving placebo treatments, for example, reported a "high" and various changes appeared on the Subjective Drug Effects Questionnaire, but there was no change in performance on the objective detection task.

An examination of social influences on drug effects was performed by Jones (14) in which 9 mg of delta-9 THC were administered to subjects who smoked in social group settings of four individuals, and also to subjects who smoked in a solitary setting. The response measure was again the Subjective Drug Effects Questionnaire (SDEQ), and the findings were similar to those in the paper by Katz et al. However, the subjects who used the marihuana in a group setting reported far greater perceptual and thought changes than those in the solitary setting, and also perceived the experience as far more euphoric with far fewer elements of dysphoria.

Clearly, as far as the "high" is concerned, the "drug effect" is much greater in a social setting. This finding for marihuana is similar to reports for narcotics. It indicates that the environment in which the drug is used strongly affects the subjective experience. In none of these studies, however, is there a comparison between subjective and objective measures.

A study by Pliner et al. (15) presents an interesting attempt to get around the problem of basing one's conclusions on individual self-reports. In this case, videotapes were made of subjects' behavior at two similar parties--one in which they were served alcohol and one in which they were served marihuana--with experimenter-participants leading the conversation to similar topics. The videotapes were edited to remove all references to the substances being utilized, and then presented to observers who had no prior knowledge of the drug used. These observers were asked to rate the behavior they observed on a series of Mood Scales,

the Nowlis-Green Mood Adjective Check List, and several semantic differential scales. The tapes were observed by individuals who were merely asked to describe how the behavior of the individuals they were viewing fell on the various Mood Scales. Since the situation was that of a party, the quantities of drugs used were determined by the subjects. On an average, the marihuana subjects smoked three cigarettes, each containing 8 mg delta-9 THC. Examination of the Mood Scale indicated that the groups intoxicated on marihuana were rated as appearing less active and more fatigued than subjects in the alcohol study group. Subjects under the influence of alcohol were rated as more tenacious, excitable, dissonant, tense, unfriendly, anxious, and aggressive than subjects on marihuana.

This study lends support to subjective self-reports of behavior changes made by individuals under the influence of marihuana. Observers were able to detect such changes without being aware of the drug's presence. This experiment would have been even more illuminating if subjects had also been examined. However, as a step toward describing highly complex patterns of social interaction which may in turn influence skills impairment under drugs, the study represents a step forward in methodology.

To summarize the situation with regard to marihuana, it is clear from the study examined, plus others, that the preponderance of evidence indicates that marihuana does impair skills performance, perceptual processes, attention, and tracking behavior. All important components of driving and skills performance were thus clearly affected.

The behavioral sites of marihuana's pharmacological action are less clear. That is, we do not know which behavioral mechanisms or functions are being affected to cause the decrements in the behavioral responses we are measuring.

While most studies on sensation of thresholds (e.g., the preceding discussion by Caldwell et al.) have found no evidence for impairment, a recent study by Hill et al. (16) found that marihuana decreased the pain threshold. The study used 20 subjects in the marihuana group and 6 in the placebo group. Subjects received approximately 12 mg delta-9 THC. Subjects under the influence of marihuana exhibited increased sensitivity, that is, lower thresholds, to electrical stimulation applied to the subjects' fingers. This was true for both painful and nonpainful stimulation. These results for electrical stimulation are at variance with results from the majority of studies on sensory thresholds for visual and auditory sensations. It would have been better to have a design which separated out such factors as the set or criterion effects from the actual sensitivity effects.

If signal detection theory had been utilized in the experimental design and in analysis of the results, we would have been able to determine whether marihuana affected sensitivity per se or whether bias was changed. Certainly, these results raise questions with regard to what is the proper pharmacological category into which

marihuana should be placed. At minimum, they make clear that we still lack knowledge about the nature of the behavioral mechanisms affected by marihuana.

SUMMARY: HALLUCINOGENS

The marihuana studies reviewed above have illustrated the wide range of techniques which have been applied to examine the effects of that drug on skills performance. Unfortunately, few such studies are available for the hallucinogens. While a large number of papers were examined on hallucinogens, the overwhelming majority of them were concerned with subjective reports of subjective states.

One of the better examples of these was the one done by Katz et al. (17). Twenty-four subjects were administered 50 µg of LSD and their responses to a series of rating scales, such as the Clyde Mood Scale and the Subjective Drug Effects Questionnaire, a picture rating scale, and a verbal and vocal behavior scale, were recorded. The subjects were compared with other subjects receiving 15 mg of amphetamine, 50 mg of chlorpromazine, or placebo treatment. It should be noted that the subjects were studied in prison, since there might well be an interaction between the nature of the environment and the drug.

Subjects under the influence of LSD reported the occurrence of very strong emotional reactions, without any apparent stimulation from the outside. They also reported feeling unable to control their emotions and thoughts, feeling detached from the real world, perceiving the real world as having an unreal quality and, finally, feeling generally suspicious about their perceptions. Such reports, while suggesting possible difficulties while driving, certainly would make it hard to predict how the drug would influence actual performance.

Woody (18) reported on three cases of patients who had experienced episodes of visual disturbance while driving. Subjects were active hallucinogenic drug abusers, although none had taken any of the substances within the preceding 10 hours. The episodes appeared to have been flashbacks, which can be described as either hallucinations or prolonged after-images. What is important is the fact that the subjects reported reacting to these visual disturbances as though they were real, either by stopping the car immediately or by driving off the road.

The experimental studies that we found on the effects of hallucinogens using objective measures were not performed on measures that could be easily related to skills performance. Thus, for example, there is the study by Hebbard and Fischer (19) which examined the effects of psilocybin, LSD, and mescaline, as compared to the effects of alcohol, on small, involuntary eye movements. The eye movements concerned are those microsaccades which occur while trying to maintain a fixation on a small target. Essentially, it was a physiological nystagmus that was studied. In all cases, the three hallucinogenic drugs, plus alcohol, increased both the fre-

quency and amplitude of these involuntary eye movements. The oscillographic records of these eye movements were very similar for the three hallucinogenic drugs, i.e., a microsaccade would occur with a rapid transition to a new point which was held steady, and then another saccade would occur very rapidly to another maintained position.

These records appear as a series of square waves. Alcohol showed a series of saw-toothed patterns in which, after the saccade had occurred, there was an extensive continued drift of position. The records indicate that the ocular motor control system is differentially affected by hallucinogenic drugs and alcohol. This particular measure of ocular motor control has no apparent relationship to the subject's performance. The major conclusion one can offer after examining a considerable number of papers (not reported) discussing hallucinogenic drugs, is the surprising lack of research examining objective skills performance under hallucinogenic drugs.

COMMENT

Many researchers have set their sights upon determining whether a particular skill is affected by a drug, whereas others have been concerned with how that skill is affected, i.e., what behavioral mechanisms are specifically influenced by the drug to produce the skills decrement. I suggest that, in general, the second view is the better for both theoretical and practical reasons.

Certainly only by determining which behavioral mechanisms are affected by specific drugs will we be capable in the long run of understanding the relationship between the alterations in physiology produced by drugs and behavioral changes. Also, only by determining the specific behaviors affected by a drug will we be in a position to specify possible countermeasures to the safety-reducing side effects. Many therapeutic drugs will remain in use despite their effects on skills performance. By understanding what behaviors they influence, we could possibly suggest effective countermeasures.

In addition to examining behaviors which suggest the nature of the drug effect rather than studying merely whether behavior is affected, one must face a major empirical problem with behavioral studies that aim solely to determine whether a particular skill is affected. This problem is that for few skills are we in a position to say that any study has obtained a representative sample of the behaviors required for that skill.

While it would be desirable to have a behavioral test which represents all the major requirements of driving, no such test currently exists. The behavioral demands are quite diverse, complex, and inadequately specified.

It might be thought that one could sample the necessary skills by placing subjects under drugs in an actual car on the road. Such an approach is inadequate, since the potential for danger from drug

use involves an interaction with a host of vehicle, road, and environmental factors which cannot be easily sampled in a short time span. Moreover, for safety, actual vehicle examination of driving behavior usually takes place on closed courses. These are quite unreal in the environmental demands they make on the subject.

It might be thought that a driving simulator could adequately sample the demands of driving. However, all existing and currently conceivable simulators are essentially part-task simulators. Some subsample of the total demands of driving is examined, with the demand character of the simulator and resulting dependent experimental measures being determined by the theoretical position of the simulator developer.

Moreover, many of the more complex simulators have difficulty specifying the nature of the behavioral demands placed upon the subjects driving them. It is better to test subjects on clearly specified behavioral skills involved in driving rather than to use devices with face validity but with little evidence to specify the nature of the behavioral demands involved.

Since any current testing program can only examine some subset of all the behavioral demands of driving, it is important that the tasks selected for testing be adequately specified in terms of their behavioral demands upon the subject. If this is done, information acquired can be compared with what is currently known and with knowledge that will be acquired in the future about the behavioral aspects of driving.

The selection of which performance tasks to examine could initially be based on literature from two sources: (1) skills tasks performance most highly correlated with adequacy in job (such as driver) performance and (2) those performance skills tasks most frequently reported, by their absence, as the basis of accidents by groups performing intensive on-site investigations of driving accidents. It is interesting to note that both sources of information suggest the same factors as being of prime importance in complex skills performance.

Correlations with long-term safety records and examinations of the immediate proximal causes of accidents suggest that the most important behavioral factors involved in accidents are perception, attention, and information processing.

The above areas to investigate are a good place to begin due to their obvious importance for skills performance. However, this is not completely adequate, since a particular drug could produce a deficit in a behavior normally assumed to have little correlation with skills performance because of its small variation range in normal adults. For instance, the range of visual acuity in the driving public is little correlated with driving accidents, but a drug which reduced acuity to 20/600 might well produce greater probabilities of accidents. Therefore, beyond the behaviors most highly correlated with skills performance, an adequate survey of

the possible effects of drugs on safety must examine functions which appear to show only small correlations with skills performance but which a logical analysis of the skills suggests are necessary component capabilities.

The above discussion has concerned which behavioral variables to investigate. An equally important issue is the nature of the experimental design and data analysis. In this regard, it is important to use the latest analytical psychological techniques which fractionate the behavioral area into psychologically significant variables. Thus, for example, one can investigate perception with classical techniques or using signal detection theory, a technique by which one can separate out changes in perception caused by sensitivity changes from those caused by changes in subject's criterion. Similarly analysis of tracking can utilize the newer techniques of describing functions which attempt to fractionate changes in tracking behavior into elements primarily related to such factors as basic reaction time, attitudes, and sensitivity.

To summarize, the study of the relationship between drugs and skills performance requires an understanding of how drugs affect various behavior components which are required in skills performance. Attempting to determine if any particular skill situation is liable to drug impairment is empirically difficult with any single test and may well be misleading. For the long run development of the field of behavioral drug studies as well as for the empirical needs of determining the potential hazards associated with a drug, systematic determination of what behaviors are affected by a drug are necessary.

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MARIHUANA
OTHER DRUGS

Arthur McBay, Ph.D.

SUMMARY: MARIHUANA

Marihuana has been smoked by 30 million Americans and it is estimated that 13 million smoke it rather frequently. Many must operate motor vehicles following the smoking of the drug. It has not been established that marihuana causes hazardous changes in driving ability. Until marihuana concentrations in drivers responsible for crashes are compared with marihuana concentrations in drivers not responsible for crashes, other less satisfactory studies will have to be used to shed some light on the potential problem.

Studies have examined the effects of marihuana on sensory-perceptual skills.

Moskowitz, Sharma, and Schapero (1) compared the effects of marihuana and alcohol on visual functions. Their 12 male subjects smoked marihuana cigarettes which allegedly delivered 0 or 200 µg of THC per kg. It was found that marihuana produced a significant decrement in peripheral signal detection under all conditions of central visual information processing, including the condition where no central information processing is required. A similar study on subjects who were given up to 0.8 g of alcohol per kg revealed that there was significant impairment of peripheral vision when central vision transmits material requiring information processing by the brain but not when central vision does not require information processing by the brain. The subjects who smoked marihuana showed significant increases in apparent movement of light (autokinesis) whereas the alcohol-influenced subjects did not. Neither drug impaired light adaptation or visual acuity. Both drugs produced an impairment of ocular motor control.

Moskowitz, Sharma, and McGlothlin (2) reported that marihuana impaired detection of peripheral light stimuli and that the decrement was linearly related to dose. This report is similar to that of the preceding report except that the marihuana smoked was alleged to deliver 0, 50, 100, or 200 µg of THC per kg.

Moskowitz and McGlothlin (3) studied the effects of marihuana on auditory signal detection. Their 23 male subjects each smoked marihuana cigarettes containing 0, 50, 100, or 200 µg of THC per kg. Their data indicated that marihuana produced significant decrements in auditory signal detection under concentrated and

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divided attention conditions. Alcohol at a dose of 0.69 g/kg produced impairment under conditions of divided attention but not when attention was concentrated. They concluded that alcohol impairment appeared to be related to the requirement that information be processed from two simultaneous sources. They also concluded that marihuana impairs single as well as two-source information processing and that the degree of impairment by marihuana is greater under more complex demands of divided attention.

Moskowitz, Shea, and Burns (4) examined the effect of marihuana on the psychological refractory period by measuring the reaction times to an auditory stimulus and a subsequent visual stimulus. Their 12 male subjects each smoked two marihuana cigarettes such that their dose levels were 0, 100, or 200 µg of THC per kg. They found that the reaction time to an auditory stimulus was delayed by the 100- and 200-µg doses, essentially the same amount, and that the reaction time to the visual stimulus was delayed approximately twice as much by the larger dose as compared to the smaller dose.

Another attempt at testing the deterioration of driving performance was through the use of the driving simulator. Moskowitz, Hulbert, and McGlothlin (5) reported on the effects of marihuana on simulated driving performance. Their subjects, 24 male college volunteers, smoked marihuana cigarettes which allegedly delivered doses of 0, 50, 100, or 200 µg of THC per kg. Marihuana smoking did not create significant deviations from the norm in car control and tracking aspects of the driving simulator.

The authors conclude that the data provide no evidence that marihuana significantly affects car control performance as measured by the driving simulator. There was not a statistically significant within-subject increase in reaction time as the marihuana dose was increased. The data did indicate a statistically significant dose-related impairment of reaction times to the subsidiary tasks of responses to light signals.

Rafaelsen and others (6) tested the effects of marihuana and alcohol on simulated car driving. Their subjects were eight volunteers from the Danish Civil Defense Corps. Cannabis resin was baked in small brown cakes each of which contained 0, 8, 12, or 16 mg of THC. The cakes were eaten. Drinks with alcohol were prepared by mixing 70 g of 96% ethanol with fruit juice. When ingested, blood alcohol concentrations of about 0.10 percent resulted. Fruit juice with no alcohol was used as a placebo. Alternating between ethanol, various strengths of cannabis, and placebos, each subject was allowed to serve as his own control. Cannabis in doses which contained 12 and 16 mg of THC and alcohol significantly increased brake time. Only cannabis in doses which contained 16 mg of THC significantly increased start time. The number of gear changes increased with alcohol and decreased with cannabis. Pulse rates increased with alcohol and cannabis. Neither drug affected the actual mean speed.

Crancer and others (7) studied the effects of marihuana and alcohol on simulated driving performance. Their subjects, 7 females and 29 males, each smoked two marijuana cigarettes which weighed a total of 1.7 g of 1.3% THC. The subjects ingested enough 95% alcohol in orange or tomato juice to produce 0.10 percent blood alcohol concentration. Following smoking marihuana, pulse rates increased and there was an increase in speedometer errors but there were no significant deviations from the norm in accelerator, brake, signal, steering, and total errors. The same subjects under the influence of alcohol accumulated significantly more accelerator, brake, signal, speedometer, and total errors than under control conditions. There were significant increases in steering errors. No increase in impairment was noted because of inexperience with marihuana or when marihuana dosage was increased. About half the subjects showed improvement in individual error scores following marihuana smoking.

In 1972, Dott (8) tested the effect of marihuana on risk acceptance in a simulated passing task. His 12 male subjects each smoked two marihuana cigarettes which allegedly delivered 0, 11.25, or 22.5 mg of THC. The mean plasma concentration was about 70 ng of THC per ml for samples taken following the 11.25- and 22.5-mg THC doses. Risk-taking behavior was measured by attempts, completed passes, and accidents. It appears that the subject under the influence of marihuana was less likely to accept the increased risk of attempting to complete the passes that were more hazardous. Marihuana did not significantly affect the number of attempted passes or the number of accidents; nor did it significantly affect the emergency decision-reaction time or the decision-reaction time or the lateral control of the vehicle. The drug did prolong the decision-reaction time during the nonabort of the passing situation. In a prior study, 16 subjects whose mean alcohol concentration was 0.09 percent attempted and completed more passes and had more accidents than those who smoked marihuana. Alcohol also affected the lateral position of the vehicle and the tracking range during passes; marihuana did not.

Klonoff (9) examined the effects of marihuana on driving in real-life situations. The marihuana was administered by having 64 volunteers smoke cigarettes containing 0, 4.9, or 8.4 mg of THC. Smoking was standardized and a double-blind procedure was used. Duel-control automobiles with an observer in the front seat were operated on a driving course and on downtown streets during peak traffic. Eleven behavioral components were used as measures of driving skills. Marihuana impeded learning; the rate of decline was dose related. Braking distance was not specifically affected. The results indicated a significant deterioration of performance by some subjects and improvement by others on the driving course and on city streets. The deterioration was greater than the improvement following marihuana usage. The deterioration was also greater following high marihuana usage than after low marihuana usage, and during street driving than in course driving. Marihuana appeared to significantly affect judgment, care, and concentration. The ambivalent effects of the drug on driving became apparent when no

significant change was found in 21 to 43 percent of the subjects and when 14 to 32 percent showed significant improvement after smoking marihuana.

Moskowitz in 1976 (10) reported on the effects of alcohol and marihuana on visual search behavior when viewing driving scenes. In the alcohol experiment, 27 male heavy drinkers were given enough alcohol to produce blood alcohol concentrations of 0.0, 0.075, or 0.15 percent. Blood alcohol concentrations were measured. Significant changes in visual search behavior including increased dwell duration, decreased dwell frequency, and increased pursuit duration and frequency were found in those under the influence of alcohol. The authors conclude that a person under the influence of alcohol can examine fewer events or examine the same event fewer times. He tends to pursue moving objects more often and for a longer time, further limiting the opportunity for simultaneously concentrating on different events.

In the marihuana experiment, 10 male social marihuana users smoked cigarettes containing mixtures of detoxified marihuana and marihuana containing 2.45% THC to give doses of 0, 50, or 200 µg of THC per kg. Not a single visual search or subsidiary task measure was affected to any degree by this rather heavy marihuana treatment.

Janowsky (11) reported on the effects of marihuana on simulated flying ability. Their subjects, 10 certified pilots, smoked a placebo and marihuana in pipes. The marihuana which contained 2.1% THC was presumably administered in a dose of 0.09 mg of THC per kg, using randomized double-blind crossover design. Average data for the entire group of pilots were presented rather than data for individual performance, which changed considerably from pilot to pilot and from variable to variable. The results indicate that when experienced pilots smoked marihuana in doses used "socially," significant deterioration occurs in simulated instrument flying ability within 30 minutes. The effect probably peaks for 2 hours and is gone within 4 hours. It appears that marihuana affects short-term memory and sense of time. It also appears to create alterations in concentration and attending behavior, generating concentration on one variable to the exclusion of others.

SUMMARY: OTHER DRUGS - DRIVING

Korttila and Linnoila (12) tested skills related to driving after intravenous diazepam, flunitrazepam, and droperidol. Their subjects, 62 students whose skills related to driving and the ability to discriminate the fusion of flickering light, were measured double blind. Intravenous injections of diazepam (0.3 mg/kg), flunitrazepam (0.03 mg/kg), and droperidol (5 mg) were given alone or in combination with pethidine (1 mg/kg) or fentenyl (0.2 mg). The doses of diazapam and flunitrazepam were halved in those subjects given pethidine but the dose of droperidol was the same with and without fentanyl. Droperidol proved more deleterious than the benzodiazepines. Flicker fusion discrimination and coordination

was impaired for up to 10 hours by flunitrazepam and up to 6 hours by diazepam. The doses of narcotic analgesics did not enhance the effects of other drugs. The authors were helpful by including blood concentrations of diazepam and flunitrazepam. They concluded that patients should not drive or operate machinery for 10 hours after injection of diazepam and 24 hours after flunitrazepam and droperidol.

Korttila and Linnoila (13) studied the recovery and skills related to driving after intravenous injection of diazepam. Their 34 subjects, whose skills related to driving, the ability to discriminate the fusion of flickering light, and hand and foot proprioception, were measured double blind. The effects of diazepam were not harmful to coordination. Coordinative skills were significantly impaired for up to 2.6 and 8 hours by 0.15 mg/kg, 0.30 mg/ kg, and 0.45 mg/kg of diazepam, respectively. Blood concentrations of diazepam were given. The authors concluded that patients should not drive or operate machinery for 6 hours after 0.15 mg/kg of intravenous diazepam or 10 hours after 0.30 and 0.45 mg/kg.

Korttila and Linnoila (14) examined skills related to driving after intramuscular injection of diazepam and meperidine. Their 11 subjects, whose skills again related to driving and the ability to discriminate the fusion of flickering light, were measured double blind, crossover fashion. The drugs were used in doses of 10 mg for diazepam and 75 mg for meperidine. Diazepam significantly impaired the coordinative and reactive skills for as long as 5 hours. Meperidine impaired reactive skills for up to 3 hours and flicker-fusion discrimination and coordinative skills for up to 12 hours. The authors concluded that patients should not drive or operate machinery for 7 hours after receiving meperidine intramuscularly. Serum concentrations of the drugs are given.

Korttila, Linnoila, and others (15) reported on recovery and simulated driving after intravenous anesthesia with thiopental, methohexital, propanidid, and alphadione. Skills of their 40 subjects were tested using a driving simulator. The intravenous anesthesia used was thiopental (6 mg/kg), methohexital (2 mg/ kg), propanidid (6.6 mg/kg), or alphadione (µl/kg). Driving performances were significantly deteriorated for 6 hours after thiopental, for 8 hours after methohexital, and for 6 hours after alphadione. Propanidid produced no impairment of driving skills.

Finkle (16) studied 2,500 cases in which drugs were involved in drinking drivers. The subjects were 2,559 of the 10,436 drivers arrested in Santa Clara County, California, during the years 1966, 1967, and 1968. The 2,559 cases in which drug involvement was reported were determined by the arresting officer questioning the driver, or by chemical analysis. It appears that some of the drugs were discovered because the police officers requested the analyses. Others were found because of drug analyses undertaken on subjects who had blood alcohol concentrations of less than 0.15 percent and who were exhibiting overt signs of intoxication. Seven hundred drug analyses were performed; 159 (22 percent) were positive. It

appears that there were 213 occurrences of 24 different drugs. One hundred and sixty occurrences were in subjects whose blood contained 0.10 percent alcohol or less, and it appears that the deterioration of performance in these cases were attributed to the various drugs. No mention is made as to whether some subjects had more than one drug or whether the concentration of the drug was considered sufficient to influence the operator. In any event, 160 represents 1.5 percent of the 10,436 drivers arrested. Three-fourths of the drugs involved were barbiturates. Data in this study thus reveal that a relatively small percentage of operators were detected whose driving appeared affected by drugs other than alcohol.

Garriott and Latman (17) reported on the detection of drugs in arrests for "driving under the influence." Since some of their data cover the last half of 1973 and all of 1974, and other data cover all of 1973 and 1974, this summary will deal only with 1974 data. In 1974, there were 6,047 driving under the influence arrests and 71 driving under the influence of drugs arrests in Dallas County, Texas. Drug-related arrests amounted to 1 percent of the total. In 13 of the 71 cases, alcohol was the only drug found. Alcohol concentrations of 0.10 percent or more were found in six cases where more than one drug was found. Neither alcohol nor any other drug was found in seven more cases. It appears that the drug charge was substantiated by scientific evidence in 45 (63 percent) of the cases. The principal drugs detected were barbiturates, methaqualone, and diazepam. No comments were made about what concentrations of these drugs are thought to effect the driver.

COMMENT: MARIHUANA

The studies of Moskowitz were based on visual and auditory stimuli and reaction times. Standardized marihuana cigarettes were smoked but no blood determinations were made. Blood concentration studies have revealed that tetrahydrocannibinol peaks in about 10 minutes after smoking and drops rapidly to about 5 percent of this concentration in an hour. The activities of any metabolites have not been firmly established. It would be interesting to know if any individual subjects were not affected by marihuana or whether some improved. His results were averaged. Moskowitz also used a driving simulator to study the effects of the drug. The above comments apply to this study also.

Rafaelsen used a driving simulator but he administered marihuana orally from baked cakes containing the drug. Crancer also used a driving simulator but his subjects smoked. In both these studies, no blood determinations are reported.

Dott used a rather sophisticated driving simulator. His subjects smoked marihuana, and plasma concentrations of THC were reported. Marihuana appeared to improve performance in a risk-taking passing situation.

Klonoff allowed drivers to smoke marihuana and drive on a course and on city streets. The ambivalence of the effects of marihuana

was demonstrated by those whose driving performance did not significantly change and those who had a significant improvement. No blood determinations were made.

Janowsky allowed pilots to smoke marihuana and tested their ability to fly a simulator. He averaged data because individual performance varied considerably. No blood determinations were made.

The effects of marihuana as determined by these studies are subtle. Complex testing would be required to detect deviations from skills from normal. The drug appears to affect the sensory-perceptual skills, judgment, and performance. Performance decrement appears when the subject is faced with unexpected and random events where constant attention is needed or where information must be stored and retrieved. The loss of motor control of vehicles is unlikely. There appears to be no effect on depth perception, visual brightness threshold, adaptation to darkness, and visual acuity. Marihuana seems to make subjects less aggressive and less likely to take a risk.

It is realized that the quantitation of THC in blood is a relatively recent practice, for which data are not readily available. Until performance is related to blood concentrations or until blood concentrations of accident-free drivers are compared with those who have accidents, it will not be possible to claim that performance is sufficiently affected to cause crashes and deaths. It will not be possible to justifiably charge a person with driving under the influence of marihuana until it can be shown that marihuana use, in itself, has a detrimental effect on driving. At the present time there is no evidence that marihuana is a significant public safety problem or is about to become one. The effects of marihuana reported in these studies are such that it is highly unlikely that a person driving erratically and recklessly would do so because of the influence of the drug.

People should be advised not to operate a motor vehicle or other machinery following the ingestion of any drug which could possibly cause any deterioration of performance. The effects of marihuana on driving should be compared with those of alcohol, barbiturates, aspirin, propoxyphene, caffeine, tobacco, and other drugs. The average operator can relate to some of these.

COMMENT: OTHER DRUGS

Korttila and Linnoila commented on the effects on driving of some drugs which may be used intravenously or intramuscularly on some ambulatory patients. The drugs were diazepam, flunitrazepam, droperidol, meperidine, thiopental, methohexital, propanidid, and alphadione. Blood concentrations for most of these were given. The authors' warnings about not driving for various times after the administration of these drugs are helpful.

Finkle's study reaffirmed the few studies made of drugs and actual driving. These studies in general have shown that drugs other than

alcohol are found in less than 5 percent of the cases. Of the drugs that were found, some have been shown to cause no deterioration in performance or to be present in concentrations too small to cause deterioration.

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OTHER DRUGS — GENERAL

Reginald Smart, Ph.D.

SUMMARY

Milner (1) reported on a study made in Perth, West Australia, of adults attending eight general practitioners, two psychiatrists, and two psychiatric hospital departments. There were 564 patients attending psychiatrists and 4,020 seeing general practitioners. Questions were asked about demographic characteristics, drugs prescribed, driving, and drinking.

It was found that 57 percent of the male and 35 percent of the female patients given psychotropic drugs "might" also drink and drive. Phenothiazines and other tranquilizers were prescribed for 45 percent of the patients, sedatives were next most common, followed by antianxiety preparations (Librium, Valium). A negligible amount of amphetamines and MAO inhibitors were prescribed. More than one drug was prescribed for 33 percent of patients. Of those given psychotropics, 85 percent of the men drank, 66 percent were licensed to drive, and 57 percent were at risk of drinking and driving while on a psychotropic. For women, the figures were 71 percent, 42 percent, and 35 percent, respectively.

It was concluded that:

1. A large proportion of patients drink alcohol and are licensed to drive.
2. As psychotropics are long acting, dangerous driving behavior may result from their use.
3. Warnings should be given to patients on such drugs.

The paper presented data only for conclusion 1.

Crancer and Quiring (2) studied the driving records of 628 persons in the State of Washington. They were sampled from the Seattle Police Department records and the entire list of active narcotic users in King County as supplied by the U.S. Bureau of Narcotics. Each was placed into one of three groups: (1) narcotic users, except marihuana (n = 198); (2) dangerous drug (amphetamines, barbiturates, and hallucinogens) users (n = 270); and (3) marihuana users (n = 160). Of these, 51 percent were licensed at some time in the previous 6 years. Only 302 were checked for traffic records, as they were currently licensed in and residents of King County. A comparison was made to 687,228 currently licensed drivers of the same age and sex.

The results indicated that:

1. All groups of illegal drug users had higher accident and violation rates than the corresponding general population group (29 percent higher overall).
2. Few illegal drug users had clear records, i.e., no accident or violation.
3. Illegal drug users had higher rates of certain violations, i.e., reckless driving, negligent driving, hit-and-run, and defective equipment but lower rates of speeding, failure to stop, and failure to yield.
4. The narcotics group (but not the others) had a slightly higher percentage of injury accidents than expected.

The conclusions that arrests for illegal drug use would be valuable in predicting driving performance seems only partly justified as it is not clear that all illegal drug users had been arrested, nor that a comparison was made between those arrested and those not arrested. Also, no data were obtained on driving exposure (e.g., miles driven)--drug users could have higher citation rates because of greater exposure.

Finkle (3) studied 10,436 routine drinking-driver arrests in Santa Clara County, California. The basic data were from the chemical testing of blood and urine samples. Detailed interviews were apparently not conducted.

The results indicated that about 25 percent had a drug involvement, as determined by the arresting officer or a chemical analysis. In total, 273 different drugs were encountered on 2,688 occasions. The most common were tranquilizers (n = 518), analgesics (n = 315), and stimulants (n = 309). In 1,406 cases or 13 percent of the total, there were "dangerous" drugs, i.e., those requiring a prescription. About 60 percent of drug cases involved drivers with 0 to 0.05 percent blood alcohol content (BAC), 10 percent with 0.05 to 0.10 percent BAC, 23 percent with 0.10 to 0.15 percent BAC, and 7 percent with more than 0.15 percent BAC.

A total of 700 drug analyses were done on drivers with blood alcohol levels in excess of .15 percent. Of these, 22 percent were positive. Only 6 percent of cases positive for drugs were negative for alcohol. About 75 percent of those involved with drugs were males in their twenties and forties. Female drug positives tended to be in their forties. The results were useful in the administration of justice in that the district attorney issued complaints in 77 percent of cases with drugs detected by analysis, chiefly for driving under the influence of alcohol and drugs.

Apparently this study did not involve a search for illicit drugs such as narcotics, hallucinogens, or cannabis, and the prevalence figures relate to prescription and over-the-counter drugs. The study is a good one, considering its aims, methods, and conclusions.

Kielholz (4) made a study of 1,030 hospitalized persons injured in traffic accidents in seven areas in Switzerland. Apparently, not all were drivers, and the ages were also uncertain. In all, 35.2 percent had some alcohol in their blood, and 21.1 percent had .08 percent or more. The highest percentage under the influence were bicyclists (43.1 percent) and motorcyclists (43.8 percent), followed by motorists (39.7 percent) and pedestrians or codrivers (25.8 percent). Reference is made to an earlier study made by the same author in which the ratio of alcohol to medication was 8:1. Apparently drug analyses were not done for the 1,030 hospitalized persons.

Brief reference is made to a study with 320 Basle policemen showing that at a BAC of .08 percent and over, a 130 percent increase in numbers of severe driving faults could be observed.

It is concluded that the main danger of psychotropics is that they intensify the effects of alcohol rather than exerting a direct influence on the driving capacity of a person. No data are presented to support these conclusions.

By way of critique, it should be noted that the study would not include persons killed in accidents or given injuries too minor to require a hospital stay. It is uncertain how these deletions would affect the results.

A preliminary study of traffic deaths in Puerto Rico was reported by Kay (5). Some 262, or 48.5 percent of the total of 540, were studied for blood alcohol levels primarily because they occurred within 25 miles of San Juan. The data show an increase in fatalities from 1960 (n = 346) to 1968 (n = 545) and a slight decline (n = 540) in 1969. The proportion of males to females also declined in 1969. The ratio of pedestrians to drivers was 2:1.

Blood alcohol content was determined in 179 cases for which death occurred soon after the accident. Of the analyzed cases, 48.6 percent were positive for alcohol; of these, 48.3 percent had a blood alcohol level of 0.15 percent or more. Among pedestrians, 45.3 percent of samples analyzed were positive, with most at 0.15 percent or more; 46.0 percent of passenger deaths were positive (only 20 percent with 0.15 percent or more). However, 66.7 percent of driver samples were positive.

Drug analyses were done in a few cases, but the number is uncertain. In 1969, there were three cases of carbon monoxide poisoning among drivers (5 percent or more) and 12 cases positive for drugs (6 morphine, 2 barbiturates, 3 tranquilizers, and 1 salicylates).

It was concluded that both alcohol and morphine are a serious problem. However, it should be noted that this study involved only fatalities around Puerto Rico and that the number of drug analyses is not certain. Details are not given on how many drug samples were analyzed, what methods were used, what body fluids

were studied, or what drugs could be detected. The conclusion about morphine appears weak.

Woodhouse (6) studied laboratory analyses of body fluids for fatally injured drivers. Cooperation was requested from alcohol safety action programs, coroners, and medical examiners in 57 areas in the United States. A total of 1,731 kits were sent out and 710 specimen collection kits supposedly containing fluids from fatally injured drivers were obtained from December 1971 to September 1973. Kits were expected to obtain samples of urine, blood, bile, and alcohol washings from the face and hands. However, 11 were not from drivers. Of the kits received, 79.3 percent furnished alcohol washes; 56.5 percent urine, blood, and bile; 74 percent urine; 97.6 percent blood; and 75.3 percent bile.

The analyses used were thin-layer chromatography followed by gas chromatographic confirmation of the positives. If any doubt existed, mass spectrometric analysis was also done. A large number of sedatives and hypnotics (including alcohol), tranquilizers, analgesics, stimulants, antidepressants, antihistamines, narcotics, and hallucinogens (e.g., cannabis, MDA) were screened. Information on the type of accident and fault for the driver was also obtained.

The results were that:

1. Only alcohol among all drugs was significantly involved in the at-fault category of accidents;
2. Forty-seven percent of drivers were legally drunk, 15.2 percent gave evidence of drug use, and 38 percent gave evidence of marihuana use.
3. Alcohol is the only drug for which time of day is a significant influence.
4. Regional variations were unimportant.
5. The groups of tranquilizers, antihistamines, and stimulants were not large enough for meaningful analysis.

Several limitations of a very serious nature make the interpretations of the results impossible. The results for cannabis suggested that the analytic tests were unreliable. Drugs may be in the system for days after their impairing effects have worn off. The sampling methods used resulted in an accidental sample of an uncertain nature in relation to all fatally injured drivers.

The aim in the study by Moser et al. (7) was to determine whether drug use is related to rates of traffic accidents and convictions. The data were driving history and demographic factors for 1,889 arrestees in six large cities in the United States. Those excluded were Federal prisoners, military prisoners, and persons arrested for drunkenness, for driving while intoxicated, for gambling, for traffic violations, and for certain minor administrative crimes (contempt of court, bail forfeiture, etc.). Narcotics violators were included in three cities and excluded in three. Driving records were obtained for 46 percent from State authorities, and interviews concerning drug use were held (for about

50 percent). The major comparisons made were between drug users and nonusers, and among various types of users in terms of driving histories. Some (about 50 percent) arrestees also provided urine samples for drug analyses. The driving history and drug interview data relate to 865 drivers.

The major results were:

1. Rates of accidents and violations were higher among heavy and moderate psychedelic drug users and among occasional tranquilizer and cocaine users than among nonusers.
2. Users of psychedelics were the only group to have more accidents and convictions than nonusers of drugs.
3. When all drug users and nonusers are compared, the nonusers consistently have more accidents and violations than the users.
4. The above results are supported by the urinalyses in that those having no drugs in their systems had higher conviction and accident rates than those who had positive urinalyses.

Several limitations are pointed out for this study, the main one being that the sample population is "arrestees" rather than a random sample of drug users. Also the lack of significant differences could be in part due to the lack of exposure information, e.g., miles driven, drug use while driving, etc.

Kapur (8) reported laboratory analyses of drugs found in patients suspected of drug use and seen at several university hospitals in Toronto and other hospitals in Ontario. The data were the results of thin-layer chromatography, gas-liquid chromatography, and colorimetric analyses for the following drugs: amphetamines, barbiturates, codeine, most alcohols, the common tranquilizers, PCP, quinine, and salicylates. Over the 9-month period of October 1972 to June 1973, 1,560 cases were studied. The drugs found analytically were compared to those expected by clinic physicians.

The major results were:

1. Nine hundred and thirty-eight cases or 60.1 percent were positive for one or more drugs.
2. The most common drugs were alcohol (44.6 percent) and barbiturates (39.5 percent), alone or in combination with other drugs.
3. Physician suspicions for barbiturates were correct 61 percent of the time, for alcohol 71.8 percent, meprobamate 80 percent, methyprylon 94.1 percent. Suspicions for most other drugs tended to be mostly unfounded.
4. Positive tests for drugs such as sedative hypnotics were often found to be missed by physicians.

The author tentatively concludes that the patterns of drugs seen in emergency rooms are very similar to those seen in drinking-driver cases. No comparative data are given to support this conclusion.

The paper by Waller (9) contains a review of material on drugs and highway crashes and some newly presented results from one of the author's earlier papers (*New Engl. J. Med.*, 1965).

The general argument in the review is that psychoactive drugs other than alcohol are so widely used as to be expected to cause driving problems. A large amount of anecdotal and epidemiological work suggests that some accidents are due to drug impairment. However, except for amphetamines, these effects are not marked. Several types of drug users do present problems, but not necessarily because of their drug use. One would be psychopathic persons who repeatedly have problems with authority, concerning driving laws as in other situations. The second category would be problem drinkers whose elevated risk is mostly due to their drinking. A third would be prescription drug and cannabis users who do not have an increased risk of accidents.

In the author's previous study, he indicated that drug users had higher rates of convictions for driving offenses. However, it was not pointed out that their contacts with the police and community service agencies began when they were very young. Most were known to the motor vehicle authorities before they began using drugs. They had patterns of "wide ranging antisocial acts" with high citation rates but low accident rates. It is suggested therefore that drug use was incidental to the high citation rates and that the citations are more a matter of lifestyle and personality than a result of drug effects.

In critique, it might be pointed out that this is a valuable insight which would have been more valuable if more data had been given. A table showing the proportions of drug users, by type of drug (known and not known to driving authorities), would have made the conclusion stronger.

The aim of the study by Wangel (10) was to determine whether drivers who consume ordinary therapeutic doses of drugs get more intoxicated by alcohol than other drivers not on drugs but with the same blood alcohol level (BAL). The data were drawn from interviews and alcohol analyses performed by a forensic laboratory in Denmark. The study is one of comparative records and interviews. The data came from "more than 6,000 cases" where there was complete medico-legal examination of persons involved in accidents (where concussion, drug addiction, or stupor was not present). The cases were divided into two groups:

1. An alcohol-free group having a BAL of less than 0.15 promille, consisting of 1,191 males and 35 females; 119 males and 5 women had consumed drugs in the past 24 hours.
2. The alcohol group with BAL > 0.15 promille, consisting of 4,805 males and 436 females; 770 males and 13 females had consumed drugs in the past 24 hours.

The drug-user group was divided further into users of analgesics, hypnotics, "pharmacological" drugs (meprobamate), all drugs in common, and those who do not remember their drug.

The results were:

1. Consumers of drugs and nonconsumers of drugs had the same blood alcohol level.
2. The most common tranquilizer used was meprobamate, but it did not potentiate the consumption of alcohol.
3. Consumption of drugs was higher in the group having alcohol in the blood.

A number of methodological questions arise with this study. It is uncertain whether only drivers or all accident victims were included. There is not much information on the interview which was given nor on whether the reports of drug use (except for alcohol) were supplemented with laboratory analyses.

Another report by Waller (11) discusses 2,672 consecutive persons with known medical problems whose driving licenses were under review in California. Review was usually because of a medical report or court record. It is emphasized that the results pertain only to persons with medical problems that are known to licensing authorities and not to all medical conditions. A comparison sample of 922 California drivers was also chosen. The data used were demographic data and driving records for the previous 3 years. The drivers with medical conditions were divided into seven groups: epilepsy, cardiovascular disease, diabetes, alcoholism, drug usage, mental illness, and "miscellaneous." Those not in the alcoholism or drug use groups most closely represented the comparison population--the former were more often in lower class occupations. Data on driving exposure in terms of miles driven were also obtained.

The results were:

1. All categories of drivers with medical problems had higher than expected accident rates except for drug users.
2. All categories of drivers with medical problems had higher than expected violation rates except for the cardiovascular group.
3. On license review, the largest proportions of revocations were for drivers in the drug use, epilepsy, and alcoholism groups (all over 50 percent).
4. Initial reports to license authorities were usually made by law enforcement officials for those in the alcoholism and drug use categories and by self or medical agencies in the others.

The tentative conclusion respecting drug use is that the high violation rates are a "reflection of social rebellion" rather than a direct drug effect. It would have been useful had this study differentiated "drug users" as to type, e.g., narcotic users, prescription drug users, etc.

Waller and Goo (12) made a further study of some of the data in an earlier paper (*New England J. Med.*, 1965) by the first author. Driving and health records were searched for 2,160 persons known to the California Department of Motor Vehicles and with organic and psychosocial disorders. The study is a comparative records study. The conditions were diabetes, epilepsy, cardiovascular disease, alcoholism, mental illness, illegal drug use, and a miscellaneous category. A comparison group of 922 California drivers not known to have medical conditions was also obtained. The data used were demographic characteristics, driving records for the previous 3 years, and exposure in terms of miles driven. This study examines the number and types of crashes and citations for each medical group.

The major results were:

1. Twenty-eight percent of drivers with organic conditions, 27 percent of the psychosocial group, and 19 percent of the comparison group had crashes; the comparable figures for violations are 51, 63, and 38 percent.
2. All medical groups had higher than expected proportions of crashes involving weaving, running off the road, and being on the wrong side when not passing.
3. Drivers with medical conditions, especially alcoholism, more often committed driving errors prior to accidents than expected.
4. Drivers in the alcoholism and drug use groups more often had crashes attributable to high speed and passing (alcoholism only significant) than expected.
5. Drivers in the alcoholism and drug use group had more citations for driving while license was suspended, improper equipment, and other nonmoving violations.

Conclusions are acceptable, except that it is not clear that they apply only to medical conditions serious enough to attract attention sufficient to have their licenses reviewed. Drivers with similar medical conditions but not attracting attention may have lower crash and citation rates.

Rees (13) reports a survey taken to determine the proportion of motorists taking psychotropic drugs in a rural area of Wales. The number of people driving was determined by asking police officers. Of the 4,088 people over 17 years of age who lived in the area, 59.8 percent of men and 16.4 percent of women "drove a motor car." Of those, 3.4 percent had been taking sedative, tranquilizing, or antidepressant drugs for at least 3 months in the past 5 years. Most were taking them for psychiatric rather than somatic reasons. These data were gathered from the records of physicians. About 3 percent of the male drivers and 5 percent of the female drivers were taking psychotropic drugs while driving. About 2.3 percent were currently taking psychotropic drugs.

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Braunstein et al. (14) studied the role of alcohol and drugs in traffic fatalities in Suffolk County, New York. Conclusions are also made about the laws governing alcoholic drivers.

Apparently, analyses to screen drugs were performed on 188 consecutive driver fatalities during 1965 and 1966. (It is uncertain whether or not the 188 includes 34 persons who died long after their accidents.) In addition to the screening tests, interviews were held with "several" patrolmen concerning their views about drinking-driving laws. Analyses were made for "acidic, basic, and neutral drugs, which include the total spectrum of drugs which could impair normal driving." The study was nonexperimental and examined autopsy data. Thin-layer and gas chromatographic analyses were used.

The major results were that all drugs other than alcohol were rarely found in fatally injured drivers. Only three of the autopsied drivers had sedatives in their blood (barbiturates and Dilantin) and a few had salicylates and chloroquine derivatives. However, 83 had "significant" blood and brain alcohol levels (i.e., 0.04 percent or above). Blood alcohol levels were highest in those aged 20 to 50.

The main conclusions were that:

1. Drugs other than alcohol have played a minor role in fatal accident causation.
2. Alcohol is a major causual factor in driver fatalities.
3. Patrolmen felt that the drinking-driving laws were cumbersome, resulted in time-consuming paperwork, and were not helpful in preventing accidents.
4. Mandatory loss of license should be imposed on anyone found driving while intoxicated.

By way of critique, it is possible to question the empirical basis for all of the conclusions. It is unclear exactly what drugs were screened for, and some drugs could not be accurately screened at that time (e.g., cannabis, amphetamines). It was concluded that alcohol is a major *causal* factor in fatalities but no data on the causal role of alcohol are presented--only data on alcohol tests in fatally injured drivers. The study of patrolmen is small and briefly reported. The evidence that mandatory license suspension would work is not given.

Miller (15) developed and used several batteries of tests for assessing drug effects at the University of Michigan, Ann Arbor. The tests included the American Automobile Associations' Auto Trainer, a Whipple steadiness test (hand steadiness), and the Ortho-rater for testing visual acuity and depth perception, as well as self-ratings and ratings of others.

The author conducted experimental studies of various drugs on normal subjects and a variety of psychiatric, arthritic, and

neurological patients. The conditions for the first study were: (1) twice the normal dose of meprobamate, (2) dexedrine, (3) meprobamate plus alcohol, (4) alcohol alone, and (5) placebo. No behavioral effects were found except for some unsteadiness with alcohol. A more extensive battery of tests (51 behavioral measures) also found no reliable effects with normal subjects. Four groups of six patients each showed some improved thinking under benactyzine, especially in obsessive-compulsives.

Chronic administration of meprobamate and "Tranquil" (a triple-bromide) were studied with 24 anxiety neurotics and 12 normal subjects. Behavioral measures, self-ratings, and other ratings were used. Meprobamate in doses of 1,600 mg daily and double the usual clinical dose slowed reaction times but improved time estimations. Emylacamate in 800-mg doses (twice as high as usual) slowed reaction time and increased feelings of calmness.

Twenty-eight psychiatric, arthritic, and neurological patients received the battery on the 12th and 14th day after starting daily (three times) administration of carisoprodal (Soma). There were no significant differences between drug and placebo periods.

Twenty-four normal males received 20 mg of chlordiazepoxide (Librium) or matching placebos. Under the drug, (1) judgment scores indicating an increase in speed and decrease in accuracy deteriorated, (2) visual acuity decreased, and (3) lateral phoria scores for near and far vision decreased.

Brief reference was made to other studies but details were not sufficient. It was concluded that:

1. Tests of behavioral toxicity should be used to evaluate new compounds.
2. There is no evidence to show how much behavioral toxicity on laboratory tests would be significant for driving.
3. Most of the tranquilizers tested "appear not to have serious behavioral toxicity" for normals.
4. Patients on drugs should be restricted from driving.

Conclusion 3. seems not justified by the data presented for Librium, as significant behavioral toxicity was found for normal subjects.

COMMENT

The impression gained from reviewing the 15 articles selected is that few firm conclusions can be made about the contribution of drug use to driving risk. Although a number of epidemiological studies have been done, the methods used are still fairly primitive. There is a considerable amount of dependence on self-report estimates of drug use after driving and accidents. The technology to utilize body fluids in assessing even the contribution of drugs to fatalities is still uncertain. Controversy still exists about whether various types of drug users have or do not have elevated accident and

violation rates. Many studies do not contain sufficient detail on the populations studied or the laboratory tests done.

Too many papers depend upon blood or body fluid analyses of drivers in accidents, without being able to state how the drug-fluid level relates to the actual accident. Several papers (e.g., Kaye, Kielholz, and Finkle) indicate that drugs occur among drivers who were involved in accidents or fatally injured. However, it is not clear that the use of these drugs contributed to the accident. Many of the drugs could have been taken many hours or days prior to the accident, long after the clinical effects have worn off. We are not sure that a fatally injured driver had his accident or fatality because of, or despite, his drug use.

Little information seems to exist on the frequency of drug use in various driving populations, i.e., those not in accidents. We have indications from Rees' paper and others that many drivers drive after drug use and after alcohol and drug use. However, we are not sure what the actual risk is. There appears to be no study of the level of drugs in the body fluids of drivers in general. This makes it very difficult to be sure that the levels found in accident and fatality populations are any different than levels occurring in the nonaccident population. This is a considerable weakness in the epidemiological research performed so far, and one which should soon be remedied.

Another weakness in much of the research is that few studies seem to be directly concerned with drug use and driving. Many (e.g., Kielholz, Braunstein et al., Wangel, Milner) seem most oriented toward drinking and driving. The question of drugs and driving is of minor interest and does not receive equal attention to that afforded alcohol. Although probably justified in terms of *known* extent of the problem, this situation is likely to contain a self-fulfilling prophecy.

A major difficulty surrounds the problem of whether drug users of different types have more accidents and charges. Some interesting studies (Moser et al., Crancer and Quiring) do not include any exposure information. That is, we have no information on car ownership, miles driven, etc., which would allow a real comparison of drug users and nonusers. Only Waller's study seems to include this, suggesting that users do not have higher than expected accident rates, but do have high violation rates. This is supported by the Crancer and Quiring study but not by Moser et al. However, the difficulties in comparing the samples used are considerable. It is difficult to find any clear replication studies where two investigators have used similar populations and similar methodologies. Naturally, then, it is difficult to find more than unexplainable inconsistency.

By way of strengths, the studies by Waller and by Finkle should be mentioned. Of all of those reviewed, they are the most convincing.

They involve large samples, clearly defined and up-to-date methodologies, and careful conclusions. It would be worthwhile repeating Finkle's studies with more modern analytic methods and Waller's with a different (large) sample of drug users. Both approaches and methodologies could be copied in other studies.

Other strengths in the papers are somewhat difficult to find, except those of a general nature. It is clear that a beginning has been made studying some problems of drugs and driving. We have information on the frequency of prescription drug use (in some populations); prescription drug use and driving; and drug use, drinking, and driving. This is probably sufficient to indicate the need for warnings to patients and physicians, as Milner suggests. However, it is not sufficient to generate the need or support for detailed, sophisticated countermeasure programs. It is also clear from several papers that the major "drugs and driving" problem may be only an aspect of the "drinking-driving" problem. That is, that drivers who have been drinking are most likely to have been using drugs as well.

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OTHER DRUGS

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SUMMARY

This review will summarize a limited number of experimental studies concerning effects of tranquilizers, muscle relaxants, and antihistamine drugs, as well as combinations of these drugs with ethanol, on human performance related to driving. The first group of studies utilized batteries of psychological and/or psychomotor tests to assess drug effects, while the second group used driving simulators. Procedures and results of each study will be summarized, and this will be followed by a general critique of methodologies which have been used along with suggestions for improved methodologies.

Drug Effects on Human Psychomotor Performance

Idestrom and Cadenius (1) studied effects of acute oral doses of amobarbital (150, 300, and 450 mg), chlordiazapoxide (20 and 40 mg), a piperazine phenothiazine, dipiperon (20 and 40 mg), and placebo on a battery of tests which included choice reaction time (visual), tapping speed, critical flicker fusion, hand coordination, standing steadiness, and auditory discrimination. Twenty-one male students about 20 years old participated in the testing. Each subject received all drug treatments in a random order under double-blind conditions. Tests were conducted at an unspecified time following drug administration (less than 1-1/2 hours), and performance compared with scores on a predrug test. There was no pretraining on the tasks and no indication is given as to whether performance changed over time.

In the original group of subjects, only the critical flicker fusion test was significantly affected by drugs (amobarbital, 150 mg; chlordiazepoxide, 40 mg; and dipiperon, 20 and 40 mg). Tapping speed was also reduced by 150 mg of amobarbital, but the 300-mg dose had no effects. In a subgroup of 15 students who received 450 mg amobarbital, significant effects of the 150-mg dose were no longer apparent. However, the high dose produced significant impairment on most (7 out of 10) tests.

This study has several good methodological features. Multiple drug doses were employed and orderly dose-effect relations were observed on most tests even though drug-produced changes did not generally reach statistical significance. Subjects were used as their own

controls, and the use of a range of doses of amobarbital showed that the tests employed were at least sensitive to a high dose of sedative drug. The critical flicker-fusion test stood out as being sensitive to small doses of drug, and indicated that both dipiperon and chlordiazepoxide may affect visual processes. The pretreatment time, however, may have been too short to see peak effects of benzodiazepines or phenothiazines.

Heimann, Reed, and Witt (2) studied effects of acute oral doses of perphenazine (10 mg), imipramine (75 mg), opipramol (75 mg), and placebo on heart rate, blood pressure, facial movements, eye movements and eye fixation (via videotape analysis), and a battery of psychological tests including pattern recognition, cancellation, word fluency, digit span, arm-hand steadiness, complex visual-auditory discrimination, and eye-hand coordination (copying a geometric pattern). Twenty medical and graduate students 20 to 25 years old were tested. Each subject was exposed to all treatment conditions in randomized order under double-blind conditions. Tests were conducted 1, 3, and 5 hours after drug ingestion.

Neither perphenazine nor opipramol has any significant objective effects on performance at the doses given. Imipramine significantly increased mean arterial blood pressure and produced subjective reports of discomfort, but altered only one performance measure. Inclusion of an independent physiological measure provided independent evidence that an effective dosage of imipramine was used, and strengthens the conclusion that the drug produced no behavioral impairment at this dose on the tests employed. Higher doses, however, might have revealed behavioral effects. In view of the lack of drug effects reported, no conclusion can be drawn about the sensitivity of the behavioral tests employed.

Hughes and Forney (3) at the Indiana University School of Medicine studied the effects of chronic doses of several antihistamine compounds--diphenhydramine (50 mg), clemizole (40 mg), tripelennamine (50 mg), and placebo--as well as ethanol (45 mg/150 lb) and combinations of each antihistamine with ethanol. These investigators employed a battery of reading and numerical calculation problems, all performed under delayed auditory feedback (a technique which is supposed to produce "stress" and enhance sensitivity of the tests). They also use a pursuit-tracking task in which the subject must superimpose a black spot upon a wave pattern generated on an oscilliscope screen.

In the chronic dosing regimen, four drug doses were ingested prior to testing, two the previous day (noon and bedtime) and two on the day of testing (at breakfast and 1 hour prior to testing). Sixteen medical and graduate students 21 to 29 years old participated. Each subject was exposed to all eight treatment conditions in random order under double-blind procedure. No pretraining was given to the subjects and there is no indication of whether performance was stable. Eight out of 13 variables measured showed a significant main effect of drug treatment. This was due to the

ethanol treatment (at a dose which produced blood alcohol levels of about 50 mg percent).

Ethanol alone or combined with an antihistamine generally produced some impairment on the behavioral tests, although these effects were not significantly different from placebo effects, as judged by the criterion of the Tukey 'W' post-test. Antihistamines alone had no discernable effects on performance, although subjects generally identified antihistamine treatment as a depressant drug. There were no noticeable additive effects of antihistamines plus ethanol. Subjective reports provide independent evidence that effective doses of antihistamines were employed, although higher doses of these drugs may have revealed behavioral effects.

In another study using identical procedures, Hughes, Forney, and Richards (4) studied effects of chronic doses of chlordiazepoxide (15 mg/day) and diazepam (6 mg/day) alone and in combination with acute doses of ethanol (45 mg/150 lb). Sixteen medical and graduate students participated as subjects. Drugs were administered in three divided doses for 2 days prior to testing and tests were conducted 1 hour after the last dose (5 mg chlordiazepoxide and 2 mg diazepam). Drugs alone had no discernable effects on performance; the greatest impairment was seen in treatments that included ethanol. No additive effects of tranquilizers with ethanol were notable, although diazepam plus alcohol did have a somewhat greater effect on performance than ethanol alone on 3 out of 13 tests. In this study, significant F tests were seen on only 5 out of 13 variables, and impairment by ethanol was more marginal than in the previous study. Doses of tranquilizers used were very low; the students could not identify subjective effects of the tranquilizers. Higher doses may have revealed behavioral effects.

Linnoila and his coworkers in the University of Helsinki in Finland have completed a series of studies concerning effects of drugs and drug combinations on motor skills related to driving. These studies used a group design in which each subject was exposed to only one drug treatment. There was high fall validity in the relationship between the behavioral tests employed and the skills used in driving performance. In a complex visual and auditory choice reaction test, subjects pushed an appropriate combination of foot pedals in response to three stimuli and also pressed a button in response to presentation of a masked target tone. The researchers recorded cumulative reaction time to a fixed number of stimuli as well as the number of errors. In the coordination test, subjects tried to keep a black dot superimposed on a moving track by turning a steering wheel. A 30-second test was run under fixed speed and an additional test under subject-controlled speed. In the self-controlled test, both the percent of time off the track and average speed were measured.

In one study (5), Linnoila looked at acute effects of oral doses of two antihistamine compounds--meclastine (1.5 and 3 mg) and diphenhydramine (25 and 50 mg)--and of a muscle relaxant, chlormezanone (200 and 400 mg), and placebo. Each drug was studied alone and in

the choice reaction time and coordination tests, in combination with ethanol (0.5 g/kg). Three hundred medical and technical students and cadets with an average age of 22 years were tested; there were 15 groups of 20 subjects each. Each subject was exposed to a single drug combination and one group received no drug treatment. Tests were conducted at 30, 90, and 150 minutes following drug ingestion. No pretraining was given on the tasks, and marked practice effects were apparent for most measures. When taken alone, none of the drugs had any effect on performance. However, ethanol combined with both doses of diphenhydramine and with the high dose of meclastine slowed driving speed at 30 minutes after drug ingestion in the subject-controlled coordination test, and ethanol plus diphenhydramine (50 mg) impaired performance in the fixed-speed coordination test. These results are suggestive of an interaction between ethanol and diphenhydramine, but results are difficult to interpret because of inappropriate statistical procedures (multiple t-tests were used and drug groups were compared with the no-drug group rather than with the group receiving placebo) and also because of the unstable baseline, which was showing practice effects over time.

Saario, Linnoila, and Maki (6) studied effects on psychomotor skills related to driving of (1) chronic doses of a sedative compound, PLP (6-(4-methyl-1-piperazinyl) morphanthridine) (10 mg), nitrazepam (10 mg), and placebo of (2) acute doses of ethanol (0.5 g/kg), and of (3) the combinations of each drug with ethanol. They used the previously described coordination and reaction time tests plus a complex visual signal detection attention test. Subjects were 17 male and 3 female students 20 to 25 years old. Under the chronic dosing regimen, a single dose of drug was taken each night between 10 and 11 p.m. for 14 days. Testing was carried out on days 7 and 14, one test with ethanol and the other with a placebo drink. Three testing trials were then conducted at 30, 90, and 150 minutes after administration of the drink. Each subject was exposed to all treatment conditions in a random order under double-blind conditions. In this study, subjects were trained prior to testing and reached a stable level of performance on the coordination tests (but not on the attention test).

Subjects felt that alcohol impaired their performance and that impairment was enhanced by the sedative drugs. Although there are not statistical analyses presented to indicate significance of individual treatment effects, nitrazepam plus alcohol produced the most noticeable average impairment on all four tests, especially at 30 minutes after the drink. Also, nitrazepam alone increased driving time in the subject-controlled coordination test. Serum levels of nitrazepam and PLP, which were analyzed on days 1, 7, and 14 of treatment, indicated that nitrazepam but not PLP was present in the blood at the time of testing. This objective confirmation of the presence of drug plus the orderliness of the time course data lends credence to the observation of a drug interaction between nitrazepam and ethanol.

Franks et al. (7) studied the effects of ethanol (0.75 g/kg), caffeine (300 mg/70 kg), and placebo, as well as the combined effects of ethanol and caffeine, on a variety of psychological and psychomotor tests including standing steadiness, manual dexterity, numerical reasoning, perceptual speed, verbal fluency, and reaction time (visual, auditory, and complex). They tested 68 male and female university students 20 to 28 years old. Each subject was exposed only to one drug treatment and was given a single predrug run on the test battery. Tests were conducted 40, 100, and 160 minutes after the start of drug intake (it took 20 minutes to consume the ethanol drink). Ethanol (at plasma levels of .72 to .92 mg/100 ml) produced marked impairment on virtually all the performance tests, while caffeine alone had only nonsignificant effects on a few tests (e.g., impaired standing steadiness, and improved performance on perceptual speed and complex reaction time tests). Caffeine antagonized ethanol-induced performance deficits on the complex reaction time test (significant at 40 and 160 minutes) and on the visual and auditory reaction time tests at 160 minutes after ingestion. Caffeine did not antagonize ethanol effects on any other measures.

Effects of Drug on Driving Simulator Performance

Loomis and West (8) studied acute effects of two divided oral doses of secobarbital (100 mg), chlorpromazine (50 mg), meprobamate (400 mg), and phenglycodol (300 mg). Doses were administered about 4 to 4-1/2 hours apart. Four-minute tests on the driving simulator were conducted at 1 and 2 hours following each drug ingestion. Eight male subjects 23 to 40 years old and weighing 150 to 185 pounds participated. Reaction time measures were obtained from eight presentations of an amber light (time to release of a gas pedal) and a red light (time to switch closure under a brake pedal). Red and yellow lights were scheduled to appear regularly every 12 seconds during the 4-minute test. An additional measure was the cumulative time when the auto was not centered over the roadbed. Speed on the road was always controlled by the subjects. Participants were pretrained to a criterion performance on the driving test. Each received all treatments in the same sequence under double-blind conditions.

Secobarbital produced a clear decrement in performance on all three measures in all individual subjects. Effects were most marked at 1 hour after the first dose and 1 and 2 hours after the second dose. Chlorpromazine produced performance decrements only after the second dose (possibly a cumulative effect). Meprobamate had small equivocal effects on two out of five test runs, while phenglycolol had no effect on performance. An important feature of this study is the demonstration of clear behavioral effects of acute doses of secobarbital on stable baselines of performance in all individual subjects. This indicates that the driving simulator used is sensitive to drug effects and provides a comparison for the relative extent of impairment produced by other drugs.

Miller and his associates at the University of Michigan conducted a series of studies concerning drug effects on both driving simulator performance and on a battery of tests which included measurements of visual acuity and phoria (8 tests, 30 variables measured). In the driving simulator test, subjects were required to keep a simulator car centered on a roadbed and to apply the brake following six irregularly spaced presentations of a red light. Three trials were run, one at a fixed low speed of the roadbed, one at a fixed high speed, and the third with speed controlled by the subjects. Accuracy (time in contact with the center of the roadbed) and reaction time scores were obtained for each trial.

Uhr, Pollard, and Miller (9) studied effects of chronic doses of meprobamate (1,600 mg); five Tranquil tablets (active ingredients: sodium bromide, 0.485 mg; potassium bromide, 0.97 g; and ammonium bromide, 0.164 g); and placebo on the driving simulator performance and the test battery. The subjects were 32 volunteers, from 21 to 41 years old. Fifteen were men, 17 women; 23 had been diagnosed as anxiety neurotics and 9 were normal. Drugs were ingested for 21 consecutive days and testing was conducted at the end of that period. Each subject was exposed to all treatment conditions in mixed order under double-blind conditions. Subjects were given one practice session on the test battery, which was conducted under the influence of a 15-mg dose of phenobarbital, but no information is given as to whether performance was stable.

Out of the entire test battery, including driving performance, only two measures showed significant drug effects. Reaction time scores in the high-speed driving test were shorter for both drugs than for placebo treatment, and estimates of 20-sec time intervals were more accurate (longer) under meprobamate than under placebo. Those tested were not able to report any subjective effects of the drug treatments. There were no procedures used to verify that subjects had ingested the drugs in the proper quantities and at the specified times. This could be important in view of the relative lack of either objective or subjective drug effects.

In another experiment, Uhr and Miller (10) administered acute oral doses of the muscle relaxants emylcamate (400 and 800 mg) and meprobamate (800 mg), and of placebo4to 49 prisoner subjects 1 hour prior to the test battery. The highest doses of both drugs produced a significant slowing of reaction times, and meprobamate reduced driving accuracy (significant only for the fast-speed test). More studies using drugs or drug doses with clear behavioral activity would be needed to establish the sensitivity of this driving simulator test battery.

Linnoila and Hakkinen (11) studied effects of acute oral doses of diazepam (10 mg), codeine (25 mg), ethanol (0.5 g/kg), and placebo, as well as combinations of drugs and ethanol, on simulated driving performance. Seventy professional drivers from the Finnish army, 19 to 22 years old, participated as subjects. They were divided into groups of 10; each group received a single drug-drink combination, and one group received no drug treatment. Subjects were

trained on the driving simulator until they felt comfortable. Tests were 40 minutes long and were conducted 30 minutes after drug ingestion. The simulated driving program was very complicated and involved following instructions for turns and stops as well as reacting to "emergency" situations, such as cars pulling out onto the road. Driving speed was controlled by the subjects. Frequency measures were obtained for driving off the road, steering wheel reversals, for the number of collisions and neglected instructions, and for the use of brakes, the clutch, the gearshift, and turn signals.

Some of these measures seemed to be sensitive to drug effects. There were more neglected instructions and more collisions under all drugs than under placebo. In addition, 6 out of 10 subjects drove off the road at least once under diazepam plus alcohol, while only one did so under alcohol alone and none under diazepam alone or placebo. (Three drove off the road under codeine and three under codeine plus alcohol.) The diazepam plus alcohol group also has the slowest average driving speed.

Statistical significance of the results cannot be evaluated since the drug groups were compared with the no drug treatment group rather than with the placebo group, and the placebo group did have some performance changes that were in the same direction as the drug groups. In addition, groups were relatively small and variability was large. Results do indicate that some measures on this driving simulator test may be sensitive to drug effects and that an ethanol-diazepam combination may produce more impairment than either drug alone, although the pretreatment time was probably too short to see peak effects of benzodiazepines.

It is important to determine the effects of drugs on driving performance in real driving situations for at least two reasons: first, to see whether results from laboratory experiments are predictive of drug effects in real driving situations, and second, to suggest priorities about what drugs to study more extensively in the laboratory. Since experimental studies of drug effects on driving performance in wholly naturalistic situations are generally not feasible, information must be obtained from correlational analyses of drug ingestion and automobile accident rates.

Smart, Schmidt, and Bateman (12) at the Addiction Research Foundation in Toronto interviewed 30 psychoactive drug users who were involved in psychiatric treatment, had been diagnosed as drug-dependent, and who had held a driver's license for some time during the previous 6 years. Interviews covered driving history (miles driven, numbers and types of accidents) as well as drug use over 6 years preceding the interview. Those accident reports which were verified against state records indicated some underreporting of accidents. Obtained accident frequencies for each individual subject were compared with expected frequencies for that subject. Expected frequencies were corrected for age, sex, and exposure (miles driven).

Thirteen out of 30 subjects reported one or more accidents and this overall accident rate was higher than the overall expected rate for the group. Accident rates which were higher than expected rates were associated with dependence on certain drugs and drug combinations and not with others. Subjects reporting mixed addiction to alcohol and barbiturates (N=7), tranquilizers alone (N=2), and amphetamines mixed with alcohol, barbiturates, and tranquilizers (N=3) had accident rates only slightly higher than expected. Subjects reporting addiction involving amphetamines alone or amphetamines mixed with barbiturates and tranquilizers (N=5) as well as subjects reporting addiction to alcohol plus tranquilizers (N=3) had accident rates much higher than expected, while subjects reporting dependence on barbiturates alone (N=6), barbiturates and tranquilizers (N=2) or alcohol, barbiturates, and tranquilizers (N=2) had accident rates lower than expected. Most subjects who reported using drugs within 12 hours prior to their accidents were in the group whose addictions involved amphetamines (6 out of 8 reported such use).

In normal humans who are not drug dependent, barbiturates generally impair psychomotor performance, while amphetamines do not impair and may enhance performance. Thus, we might predict that barbiturates but not amphetamines would be related to higher than expected accident rates. This study found the opposite relationship. This suggests that drug effects on driving performance could be different in drug-tolerant than in nontolerant individuals. Alternatively, drugs could influence driving performance by some means other than direct effects on psychomotor skills related to driving. Amphetamines, for example, are known to alter judgment about performance capabilities. Another interesting possibility is that drugs affect accident rates by altering the probability that people will engage in driving in the first place. Amphetamines, which energize activity, and were related to higher than expected accident rates, might increase the likelihood that people will drive, while barbiturates, which are primarily sedating, and were related to lower than expected accident rates, might actually reduce the probability that people will drive after using drugs. This study at least suggests that more driving research needs to be focused on effects of stimulants and on drug effects in drug-dependent or drug-tolerant individuals.

CONCLUSIONS AND COMMENTS

Three of the studies reviewed found that acute doses of barbiturates (1,8) and alcohol (7) dramatically impaired human psychomotor performance. No other drugs or drug combinations in any of the studies reviewed here had effects of comparable magnitude. Some alteration of performance was reported for acute doses of chlordiazepoxide (40 mg) and dipiperon (20 and 40 mg) on a critical flicker-fusion test (1), and for 50 mg of chlorpromazine (8), 800 mg of emalcymate, and 800 mg of meprobamate (10) on simulated driving performance. Additive interactions of drugs with moderate

were suggested for acute doses of 50 mg of diphenhydramine (5), and of 10 mg of diazepam (11), and for chronic doses of 10 mg of nitrazepam (6).

Drug treatments which had no significant effects on psychomotor performance or driving simulator tests included acute doses of 300 mg of amobarbital and 20 mg of chlordiazepoxide (1); 10 mg of perphenazine, 75 mg of imipramine, and 75 mg of opipramol (2); 400 mg of meprobamate and 300 mg of phenglycolol (8); 10 mg of diazepam and 25 mg of codeine (11); 200 and 400 mg of chlormezanone (5); and caffeine (7). Other treatments producing no effect were chronic doses of 1,600 mg of meprobamate and Tranquil (9); 10 mg of PLP and nitrazepam (6); 15 mg/day of chlordiazepoxide and 6 mg/day of diazepam (4); as well as acute and chronic doses of several antihistamines including 50 mg of diphenhydramine, 1.5 and 3 mg of meclastine, and 50 mg of tripelenamine (3,5).

Drug treatments showing no additive interaction with ethanol included chronic doses of 50 mg of diphenhydramine, 40 mg of clemizole, 50 mg of tripelenamine (3); 15 mg/day of chlordiazepoxide and 6 mg/day of diazepam (4); and acute doses of 15 mg of meclastine, of 200 and 400 mg chlormezanone (5), and of 25 mg of codeine (11); and chronic doses of 10 mg of PLP (6).

The finding that a particular drug has no effect on performance in a particular situation does not mean that the drug is behaviorally inert. Drug doses could be inadequate (i.e., at the low end of the dose-effect curve); drug absorption time could be too short; investigators could have failed to verify that chronic dosing procedures were followed by subjects; or behavioral tests could be insensitive to drug effects. These possibilities must be eliminated before a meaningful conclusion can be drawn about the lack of a drug effect. These methodological problems are discussed in the summaries of individual articles when they apply. Below is a more general discussion of the important methodological considerations which must be made for a meaningful analysis of drug effects on human performance.

Testing a Range of Drug Doses

Only a few studies in the present review utilized more than one dose of drug (1,5,10). Studying a range of drug doses (establishing dose-effect relationships) is very important for several reasons. First, drugs may affect performance differently at different doses--enhancing performance at one dose range, and depressing or impairing performance at another range. Second, people can differ dramatically in their sensitivity to a drug, whether because of drug history (tolerance), differences in drug absorption and metabolism rates, or other unknown factors. Testing a range of dosages would reveal functional relationships between drug dose and performance measures and would lead to a dose-profile of behavioral toxicity. Finally, people ingest drugs over a wide range of dosages depending on the context and intent of drug intake,

from low dosages taken for therapeutic intent to extremely high dosages taken for recreational intent.

If only a single drug dose is studied, it is important to include some independent physiological (2), biochemical (6), subjective (3), or behavioral measure which indicates that an active drug dose was employed. This is especially important if the drug turns out to have no effect on the behavior variables under investigation.

Determining the Time-Course of Drug Effect

It is a good idea, if possible, to conduct behavioral tests for several hours after ingestion of acute drug doses (2,7,8,11). Time course data can provide valuable information about the onset and dissipation of drug effects. It is also important to consider the time course of drug effects in chronic dosing studies, where some investigators have controlled the time between testing and the last drug ingestion (3,4,11), while others have not (9). Finally, time course must be considered in drug interaction studies, where absorption time for the two drugs may be quite different (11). If the intent is to conduct behavioral tests at the time of peak effect of each drug, then pretreatment times must be adjusted accordingly.

Establishing Sensitivity of Behavioral Tests

In order to obtain meaningful information about drug effects on performance measures, it is crucial to demonstrate that behavioral tests used are sensitive to drug effects. This can be done by studying a range of drug dosages, including high doses with clear behavioral activity or, when this is not feasible, by including a standard drug such as a barbiturate at doses that produce some behavioral effects (1,8). The finding that a particular drug at a particular dosage has no effect on a particular set of performance measures does not mean that the drug is behaviorally inert, since the finding could as well mean that behavioral tests employed are insensitive to drug effects. Increasing the number of tests in a battery or increasing the number of variables measured does not necessarily increase the sensitivity of behavioral tests, since performance of individual subjects on a number of sequentially administered tests will probably not be independent.

Studying Drug Effects on Stable Baselines of Performance

Several studies reviewed gave no pretraining to subjects on behavioral tests or gave insufficient training such that marked practice effects could be seen in the data (5). Studying drug effects on a stable baseline of performance has at least two advantages. First, it decreases variability of performance measures and makes it much more likely that drug effects will be detected. Second, since driving is a highly practiced skill, it makes the laboratory test situation more naturalistic.

Advantages of Using a Within-Subject Design

Individuals may differ in their sensitivity to drugs as well as in their baseline levels of stable control performance. Group designs will reveal the proportion of subjects in a population who have substantial behavioral effects at a given drug dose, but may mask more subtle, though equally important, effects of drugs in individual subjects. Within-subject experimental designs eliminate intersubject variability by repeatedly observing drug effects on stable behavioral baselines in single individuals. This technique will reveal functional relationships between drug dose and performance changes; the consistency of these relationships can then be evaluated across individuals. A within-subject design maximizes the sensitivity of experimental procedures and makes it likely that subtle behavioral effects of drugs will be detected. It might be advisable to conduct more studies which make a detailed analysis of single drugs or single drug combinations over a range of doses in individual subjects rather than attempting to screen single doses of many drugs from different pharmacological classes within a single study, as has so often been the case.

Establishing the Validity of Behavioral Tests

The validity of behavioral tests as predictors of drug effects on driving performance can only be established empirically be correlating drug effects on performance tests with drug effects in natural driving situations. It should be stressed that behavioral test situations need not have "face validity" to be sensitive and valid indicators of drug effects on driving performance. Conversely, behavioral tests such as driving simulators, which do have face validity, may not be empirically valid indicators of drug effects on driving performance. Much more information is needed about the relationship between psychoactive drug ingestion and accident rates (12) to establish the validity of laboratory tests.

It is clearly important to specify effects of drugs on driving performance since both automobile driving and drug ingestion are ubiquitous practices among large portions of the populations of industrialized societies. This is a formidable task since it involves as a preliminary step the specification and development of human performance tests which are sensitive to drug effects and which are valid predictors of drug effects in real driving situations. Specification of sensitive and valid performance tests must then be followed by studies involving multiple dosage testing, preferably using within-subject experimental design of a wide variety of commonly used drugs and drug combinations.

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