G. Nicholas

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Final Report

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16. Abstract

This final report presents the results of a study of the relationship between drugs (other than alcohol alone) and highway safety. The state of the art of current research is examined. Conclusions and recommendations for future action and research are made. Topics examined include epidemiological studies, experimental studies, analytical methods for measurement of drug presence, measurement of drug effects on behavior, and legal constraints on drug/driving research and countermeasure development.

Other reports produced under the contract include: *Drugs and Driving: A Selected Bibliography* and *A Report of an International Symposium on Drugs and Driving.*

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METRIC CONVERSION FACTORS

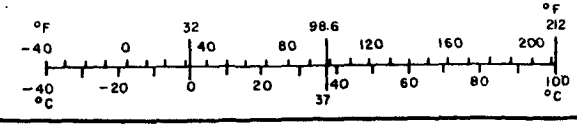
Approximate Conversions to Metric Measures

Symbol	When You Know	Multiply by	To Find	Symbol
		LENGTH		
in	inches	*2.5	centimeters	cm
ft	feet	30	centimeters	cm
yd	yards	0.9	meters	m
mi	miles	1.6	kilometers	km
		AREA		
in^2	square inches	6.5	square centimeters	cm^2
ft^2	square feet	0.09	square meters	m^2
yd^2	square yards	0.8	square meters	m^2
mi^2	square miles	2.6	square kilometers	km^2
	acres	0.4	hectares	ha
		MASS (weight)		
oz	ounces	28	grams	g
lb	pounds	0.45	kilograms	kg
	short tons (2000 lb)	0.9	tonnes	t
		VOLUME		
tsp	teaspoons	5	milliliters	ml
Tbsp	tablespoons	15	milliliters	ml
fl oz	fluid ounces	30	milliliters	ml
c	cups	0.24	liters	l
pt	pints	0.47	liters	l
qt	quarts	0.95	liters	l
gal	gallons	3.8	liters	l
ft^3	cubic feet	0.03	cubic meters	m^3
yd^3	cubic yards	0.76	cubic meters	m^3
		TEMPERATURE (exact)		
°F	Fahrenheit temperature	5/9 (after subtracting 32)	Celsius temperature	°C

*1 in = 2.54 (exactly). For other exact conversions and more detailed tables, see NBS Misc. Publ. 286, Units of Weights and Measures, Price $2.25, SD Catalog No. C13.10:286.

Approximate Conversions from Metric Measures

Symbol	When You Know	Multiply by	To Find	Symbol
		LENGTH		
mm	millimeters	0.04	inches	in
cm	centimeters	0.4	inches	in
m	meters	3.3	feet	ft
m	meters	1.1	yards	yd
km	kilometers	0.6	miles	mi
		AREA		
cm^2	square centimeters	0.16	square inches	in^2
m^2	square meters	1.2	square yards	yd^2
km^2	square kilometers	0.4	square miles	mi^2
ha	hectares (10,000 m^2)	2.5	acres	
		MASS (weight)		
g	grams	0.035	ounces	oz
kg	kilograms	2.2	pounds	lb
t	tonnes (1000 kg)	1.1	short tons	
		VOLUME		
ml	milliliters	0.03	fluid ounces	fl oz
l	liters	2.1	pints	pt
l	liters	1.06	quarts	qt
l	liters	0.26	gallons	gal
m^3	cubic meters	35	cubic feet	ft^3
m^3	cubic meters	1.3	cubic yards	yd^3
		TEMPERATURE (exact)		
°C	Celsius temperature	9/5 (then add 32)	Fahrenheit temperature	°F



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Kent B. Joscelyn, J.D.
Principal Investigator

Roger P. Maickel, Ph.D.
Principal Investigator

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SYNOPSIS

This study reviewed existing research literature on drug use (other than alcohol) and highway safety. The objective of the study was to ascertain the "state of the art" of research and to define areas of the drug/driving problem that require further research. The study also sought to identify, insofar as present knowledge permits, countermeasures that could be implemented in the immediate future.

The research approach involved several methods of acquiring information on the research literature. A literature search using traditional and computer-assisted search techniques identified over 10,000 potential sources published prior to 1975. Of these, over 2,500 were reviewed in detail by the project staff. From these a file of approximately 600 documents was created and delivered to the National Highway Traffic Safety Administration (NHTSA). A bibliography was prepared that contains abstracts of these documents indexed by author and title. This report, *Drugs and Driving: A Selected Bibliography,* is one of the workproducts of the study.

An International Symposium was convened as another method of information identification. Researchers and practitioners met for three days in April, 1975, to discuss the state of the art of research and future research needs. The proceedings of the symposium are presented in a volume entitled *A Report of an International Symposium on Drugs and Driving.*

The collected literature, the information gained through the symposium, and subsequent communications with the participants were synthesized by the research staff to produce this technical report on the drugs and driving problem.

This study is one of a family of projects that make up the NHTSA drugs and driving research program. The major focus of this project was the examination of the existing research literature. Thus, the conclusions and recommendations reflect the limitations of existing research. Other NHTSA-funded projects are concerned with continued examination of the problem through the collection of data on the involvement of drugs in traffic crashes as well as the design of future studies to bridge the gaps noted in the existing literature.

The research literature suffers from a variety of methodological problems that makes the development of precise descriptions of the drug and driving problem difficult if not impossible. A full understanding of the limitations of existing research requires a familiarity with some of the obstacles that face researchers. The following sections briefly describe some of the problems that underlie research in this area, discuss experimental and epidemiological research findings, and present the major conclusions and recommendations of the study.

BACKGROUND

The study of the relationship between drug use and highway safety is complicated by a series of underlying problems that tend to be barriers to research.

The first problem is that there is not a common definition of the term "drug," nor an adequate knowledge of the nature and extent of drug use. There are widely varying estimates of the actual number of drugs. Even restriction of the term to therapeutic agents does not eliminate the variance. Estimates of the number of therapeutic agents range from 5,000 to more than 40,000. A list of therapeutic agents would not include

industrial toxicants, environmental pollutants, or something as common in the driving environment as carbon monoxide. Though the exclusion of such agents is recognized as a limitation, this study focused on drugs as substances used, either licitly or illicitly, by individuals to alter or treat a physiological condition or psychological state.

Social attitudes toward drug use have changed over the past two decades. Drug-taking has become everyday behavior for wide segments of the U.S. population. In particular, the use of psychoactive drugs has greatly increased. The most frequently prescribed drug in 1974 was diazepam (Valium®), a psychoactive agent with the potential to impair driving behavior.

The research literature on drug use and abuse is voluminous. The major import for our considerations is that almost all studies conclude that sizeable segments of the driving population use a wide range of drugs that have the potential to impair driving behavior.

The literature has several limitations. Most studies have not focused on the driving population. Data on drug use by drivers are usually not directly available and must be inferred. Information on miles driven while "under the influence of a drug" is almost non-existent. Information on patterns of drug use and driving exposure is needed to develop adequate estimates of risk.

The second problem area relates to the general understanding of drug effects. The effect that a drug produces is a function of the level of the drug (or the active metabolite) at the site of the action. Some minimum concentration must occur before effects are observed. For many drugs the concentration within the blood or urine correlates well with the concentration at the site of action in the body, such as the central nervous system. For other drugs this is not true.

Drug concentrations result from the administration of a particular dosage of a drug. Thus, relationships between dosage and response or effect can be developed. The nature of the effect caused by a given dosage of a drug can vary within the same individual from time to time. Long-term or chronic use of the drug may produce tolerance, or the user may simply become accustomed to the drug effects and compensate for them. The effects of psychoactive drugs vary greatly with the psychological and physiological state of the individual. Thus, when drugs are used at normal therapeutic levels the effects may vary significantly within a single individual. Variance will also occur across a population, as the same dosage will not affect all individuals in the same manner.

Drugs are not retained in the body indefinitely but are excreted following metabolism. This results in a drop in the drug level or concentration as time passes. At some point in time the drug level will drop below the minimum concentration necessary for observable effects. Some drugs are processed quite simply by the body and quickly excreted. Other more complex drugs are retained by the body after their action has occurred. Thus, mere presence of a drug can not be equated with an effect in all cases.

This fact highlights the third problem. The highway safety community has had the most experience with a single drug—alcohol. Alcohol is a unique drug in the way it is processed within the body. The alcohol concentration can be measured quite simply and accurately in breath, blood, or urine and the concentration correlated with effect. Thus, it is possible to relate alcohol presence to impairment of driving behavior.

This familiarity with the simple relationships between alcohol presence and effect has

led to misunderstanding and misinterpretation of study results involving other drugs. The findings of drug presence in a subject have been interpreted by some to mean that the subject was necessarily affected by the drug. In those cases where only screening tests have been performed (i.e., tests that detect presence but do not determine drug concentrations), it is usually not possible to determine drug effects.

This, in turn, leads to the fourth problem—methods for the accurate detection and quantification of drugs in body fluids are still in a state of infancy. Methods for some drugs are highly developed and readily available, but for other drugs, often those of greatest interest, methods are not well developed nor are they widely available. Such methods often require highly sophisticated instrumentation and specially trained personnel. These capabilities may exist but are not in general use. Thus, body fluids of crash victims are not routinely screened for all potential impairment agents, as they frequently are for alcohol. The cost of routine screening for the broad spectrum of drugs having the potential to impair driving behavior is likely to be prohibitive. Further, it is doubtful that sufficient personnel and equipment are available to implement such a program in the immediate future.

The fifth problem also relates to measurement methods and is even more complex than the measurement of drug presence. It is the measurement of drug effects.

It would be highly desirable to be able to develop a clear relationship between a given dosage of a drug and driver impairment. A number of issues prevent this being done with a high degree of confidence at this time.

It is possible to determine a dosage level for many drugs that produces behavioral impairment sufficient to support the conclusion that driving behavior would be impaired. Unfortunately, it may be that only gross impairment can consistently be measured. For example, the dosage may be sufficient to cause the subject to lose consciousness.

At lower dosages the test results may be less conclusive simply because of the artificiality of the testing situation. The subjects are aware that a test is underway, and they may compensate for drug effects. Researchers anecdotally relate cases where a test dose is administered and the subjects fall asleep during the short wait prior to the test. When roused to perform the test, they perform in a manner that is not distinguishable from a subject who has not taken the drug. This illustrates the artificiality of the testing situation and highlights a major problem with laboratory evaluation of the influence of drugs on driving behavior.

The testing problem is further complicated because the driving task has not been adequately defined. Thus, testing systems that accurately replicate the driving task do not exist. Driving simulators have been rather convincingly shown to provide less than an adequately realistic test environment. Actual driving, either on a driving range or the highway, in dual-control vehicles may be a more realistic approach, but is still an artifical situation. The on-road approach poses serious legal and ethical issues. In summary, no well-developed and validated testing systems capable of detecting and measuring drug effects on driving behavior now exist.

The sixth major problem facing researchers is the plethora of legal and ethical constraints applicable to this area. The majority of these constraints flow from the body of law dealing with the use of human subjects in research. This body of law has its roots deep in the ethics of our society, and most of its applications are reasonable and proper. Although appropriate, the operation of law does limit the conduct of inquiry.

For example, for most drugs a therapeutic dosage level is established. Studies which wish to examine dosage levels significantly higher than the recommended therapeutic level are usually prohibited as constituting undue risk to the subjects. Thus, it may not be possible to study human behavior experimentally at the abusive dosage levels that may be encountered in the accident population. Drug research is subject to increasing inquiry and concern by many groups examining the use of human subjects in research. Protocols that were approved in the past may not receive approval in the future. This suggests that increasing dependence may have to be placed on animal studies and on epidemiological studies to estimate the risk particular drugs present.

Another legal barrier to research is quite real but less realistic. No general researcher-subject privilege exists in the United States. Thus, researchers seeking to obtain information must warn the driver, who is a research subject, that the researcher may be compelled to disclose the driver's responses. Given the potential civil and criminal liability a driver may face, it is unlikely that reliable information can be obtained in the face of such a warning.

Researchers examining the problems of drugs and driving need a researcher-subject privilege, as do researchers examining the problem of accident causation more generally. Congress has provided a limited privilege for drug researchers that can be granted by either the Attorney General or the Secretary of Health, Education and Welfare. Either privilege under this statute should be obtained for drug and driving researchers, or a separate privilege statute should be sought by the Department of Transportation.

These problem areas constitute the environment that researchers have faced as they have undertaken examination of the drug and driving problem. Another problem, which is an equally real constraint on research and is reflected in the quality of the literature, is that funds for drug/driving research have been extremely limited. This has led many researchers to take shortcuts or adopt procedures that were less costly, with a resultant degradation of the quality of the research. In many cases this has resulted in inconclusive or incomplete results that can not be methodologically defended.

The following sections describe the two major bodies of research literature.

Experimental Studies

Research studies that have examined the effects of a single drug or multiple drugs on human behavior in a laboratory setting have been classified as experimental studies. These studies usually involve the administration of a known dose of a drug(s) to a subject and the measurement of the subject's behavior by single or multiple testing techniques.

Most of the studies reported in the literature are *acute dosage* studies. Subjects are usually given a single administration of a drug. Acute dosage studies are simple and less costly than *chronic dosage* studies, which involve administration of a number of dosages over a period of time. The chronic dosage studies are thought to provide more information about dose-response relationships because they more nearly replicate the usual pattern of drug use.

Many of the experiments reported in the literature have design problems that weaken the findings. Experimenters commonly fail to use adequate controls to minimize problems of subject variance, participant bias, observer bias, and intervening variables.

Blind and double-blind experiments using placebos and crossover designs have been

reported but are more limited in number. These more complex and lengthy studies are costly to conduct.

Many of the studies utilize subjects who are atypical of the driving population. Often young college students are used. This usually represents a sample of convenience. Few researchers report the use of adequate control measures for the potential effects of sleep deprivation, emotional strain, use of other drugs, and other factors unique to a subject that may influence findings.

Some relatively unique problems emerge, as in the case where the substance used as a placebo contained an active agent; thus it was not a bona fide placebo.

The literature also illustrates common errors in statistical analyses. Statistical methods are often applied incorrectly. Reported conclusions are not supported by the data presented. Such problems are evident in study reports complete enough to permit adequate reviews of the statistical methods employed. Many study reports, however, are so incomplete that no judgment can be made concerning the adequacy of the design, conformance to it, and thus the validity of the results.

While the literature is replete with examples of questionable studies, it also contains some noteworthy reports of experimental studies on or relating to the effects of drugs on driving performance. As noted previously, excessive dosages of many drugs can cause impairment. Such dosage levels are usually associated with chronic abuse or overdose cases and are not what one would expect to frequently encounter.

Many experimental studies report effects of dosage levels that one could reasonably expect to encounter in the general user population. These studies identify agents within the following classes as having the potential to impair behavior believed to be associated with the driving task.

- analgesics and antipyretics
- anesthetics
- anorexics
- antidepressants
- antihistamines
- antinauseants
- antivertigo agents
- antianxiety agents
- cardiovascular blocking agents
- parasympathomimetic agents
- psychostimulants
- psychotropic agents
- sedative/hypnotic agents

The body of experimental literature, taken as a whole, demonstrates that drugs affect human behavior and performance, but most of the findings are merely suggestive of relationships between laboratory test performance, driving performance, and traffic crash causation.

The literature, however, is very valuable as an indicator. If one knows that a drug has the potential to impair behavior and performance skills closely related to the driving task, and that the drug is in common use by the driving population, one should look to see if the drug is present in accident-involved drivers.

Epidemiological Studies

The basic objective of epidemiological studies, in this area, has been to identify the role that drugs play in traffic crash causation. Few such studies—less than 30—have been conducted in the last decade. Most have been very limited in scope, so that their findings cannot be generalized as representative of the general driving population or accident populations. Some also exhibit significant methodological weaknesses that make their findings of limited value.

A very few studies have actually clinically examined traffic crashes to ascertain the behaviors that led to the crash and document the role drugs played. Those studies have examined only a very limited set of crashes.

More commonly, researchers have attempted to ascertain if drugs were present in accident-involved drivers. Usually, this is done by testing body fluids for drug presence. In additon to the problems of limited testing methods, the interpretation of the results is in many cases highly problematical. Mere presence does not equate to impairment. Further, if the impairment did exist and was slight, it might not have played a causative role in the crash. Thus, positive findings of drug presence in crash victims require very cautious interpretation.

Other study approaches have attempted to collect data on drug use by drivers through questionnaires and/or secondary sources. These studies are replete with problems of data reliability and representativeness of the subjects. As in the experimental studies, the study population was often a sample of convenience.

A review of the epidemiological literature discloses other problems shared with the experimental literature: incomplete reporting of methods, data, and analytic techniques, as well as, in some cases, misinterpretations of reported data by the researchers.

Studies which attempted to use a sampling approach were often thwarted by non-cooperation of the driving population or other participants whose cooperation was necessary to ensure an adequate data base. Missing data problems are so severe in several studies as to render the results inconclusive.

An examination of the research approaches used in several of the studies that tested body fluids for drug presence leads one to conclude that the drugs tested for were chosen on the basis of equipment available for testing and the interest and/or qualifications of the researchers, rather than on the basis of the drugs one would expect to find in the accident population. The result is that many of the large studies have failed to test for drugs that have the potential for impairment and are in common use. For example, no large-scale study in the United States tested for the presence of the active metabolite of diazepam, one of the most frequently prescribed psychoactive agents.

The epidemiological studies do convincingly report the use of drugs by the driving population and do report the presence of drugs in accident-involved drivers. Since the test methods have not examined for many commonly used drugs, a fair assumption is that the frequency of drug presence is probably higher than that reported.

Unfortunately, the lack of representativeness of the study populations and the extent of missing data make it impossible to generalize the results of any one study to the U.S. driving or accident populations.

As in the case of the experimental studies, more detailed descriptions of the findings of the epidemiological studies are presented in the body of the technical report. It is sufficient to say here that the epidemiological studies report finding drugs in the acci-

dent population from almost every class identified as having the potential for impairment in the experimental studies. Note again that the mere finding of drug presence does not necessarily mean impairment or that the drug played a causative role in the traffic crash.

The epidemiological studies also note frequent involvement of alcohol and drugs in traffic crash victims and drivers. The consistency with which this is reported across studies is highly supportive of the conclusion that drug-alcohol interactions present a highway safety problem.

The epidemiological literature, taken as a whole, strongly supports the premise that drugs do play a significant role in traffic crash causation. The limitations of existing research do not allow a precise statement of the nature or extent of that involvement.

The methodological problems noted in the existing literature strongly suggest that future studies must be rigorously designed and carefully implemented. Data must be collected from a representative sample of the population. Drugs chosen for study must be representative of those that have the potential for impairment and are used by the driving population. Analytical methods must be used that have the capability of detecting with a high degree of reliability the presence of *all* pharmacologically active forms of the drugs chosen for study.

CONCLUSIONS AND RECOMMENDATIONS

The review of the research literature, the dialogue with colleagues during and after the research symposium, and an examination of the problems underlying existing research led to the following conclusions and recommendations.

Existing research establishes that:

1. The adult population of the United States commonly uses many drugs that have the potential to adversely affect driving behavior.
2. Drivers involved in traffic crashes have been found to have drug concentrations sufficient to affect behavior.
3. Drivers involved in crashes or arrested for impaired driving have been found to have both alcohol and drugs present in concentrations sufficient to affect behavior.

Existing research is not sufficient to establish:

1. The role that drug usage plays in traffic crash causation in the United States.
2. The nature and extent of drug usage by drivers involved in traffic crashes in the United States.
3. The nature and extent of drug usage by drivers at risk who are not involved in traffic crashes in the United States.

Past research efforts have been constrained by:

1. Lack of funds available for the support of large-scale research efforts such as those required for definitive examination of the relationship between drug usage, driver behavior, and traffic crash causation.
2. The "state of the art" of knowledge and technology for the detection and measurement of drug presence.
3. Lack of information relating the pharmacological aspects of drugs and driver impairment.
4. Legal restraints that impede the collection of information.

Research findings with regard to countermeasure programs suggest that:

1. Large-scale countermeasure programs focused on the drug/driving program do not appear warranted at this time. The nature and extent of the problem must be better defined before a large-scale response can be developed or supported.
2. In the light of the present lack of proven methods for effectively dealing with other drug-related problems, any countermeasure approach should be carefully developed and intensively evaluated before large-scale implementation is attempted.
3. Information on the pharmacological characteristics of drugs with the potential to affect driving should be widely disseminated. Information on the potential for impairment from polydrug use—in particular, alcohol and drugs—should also be disseminated.
4. Existing laws prohibiting driving under the influence of drugs should be enforced. Videotape records of driver behavior appears to be a highly persuasive evidentiary approach.

Future research efforts within the mission area of the National Highway Traffic Safety Administration should include:

1. Studies which examine drug usage patterns of the driving population. These efforts should focus on establishing exposure data for all agents, including prescription drugs, over-the-counter medications, recreational chemicals, and other chemical agents. Survey approaches using interviews and questionnaires supported by separate verification systems appear the most feasible. Exposure information is needed to define the problem and form the basis for further epidemiological studies.
2. Studies which examine accident populations and the driving population for concentrations of specific drugs believed to be involved in crash causation or which are widely used and have significant potential for behavioral impairment. Such studies, to be effective, must be large-scale multidisciplinary efforts. Major emphasis must be placed on experimental design. Such projects should be planned to span several years. Provisions should be made for outside advisors to assist in the planning of such efforts, and outside reviewers to monitor technical performance of contractors. The review group should include individuals with expertise in chemistry, pharmacology, medicine, research methodology, survey design, and the collection of data in the highway safety environment.
3. Studies which examine the nature and extent of existing countermeasure efforts focused on drugs and driving. The literature is almost non-existent in this area. Field studies to document existing practices at the state and local level are required.
4. Studies which focus on the development and evaluation of countermeasure programs. Such efforts should be carefully integrated with the programs suggested in the paragraphs above.

The National Highway Traffic Safety Administration should facilitate and improve research on the problem of drugs and driving by:

1. Obtaining legal privilege for researchers and countermeasure program personnel as is provided for personnel operating under programs of the Department of Health, Education and Welfare (DHEW) and the Department of Justice (DOJ). Either separate legislation establishing a privilege should be sought or provision should be made to utilize the existing privilege provided DHEW and DOJ.

2. Establishing more extensive communications with other government agencies sponsoring drug research. Active exchange of information, technology, facilities, and expertise would enhance the effectiveness of NHTSA-sponsored research and action programs and increase fiscal effectiveness.
3. Establishing a Scientific Advisory Board to advise NHTSA on the design and implementation of research and countermeasure programs dealing with drugs and driving.
4. Supporting periodic scientific meetings of researchers and practitioners active in the drugs and driving area to facilitate communication. Rigorous planning should be required to ensure that the meetings have a "redeeming scientific value" of direct benefit to the highway safety community.

COMMENT

The foregoing conclusions and recommendations were arrived at by the principal investigators and the research staff in as objective a manner as possible. They are believed to reflect conservative conclusions supported by the weight of scientific evidence. It is expected that our colleagues, after examination of the same literature, would concur in these judgments as being supported by fact.

The review process, coupled with the prior research experience of the principal investigators, leads them to hold personal opinions that go beyond the conclusions and recommendations stated previously. These views are stated here as commentary or insights.

The principal investigators believe that drugs do play a significant role in traffic crash causation. We cannot state, on the basis of existing research, that X percent of the crashes are caused by drugs. We do not believe any responsible researcher could make such a statement. Yet, taken as a whole, the experimental and epidemiological literature clearly indicates to us that drugs are involved in traffic crash causation.

Thus, we believe a first priority should be to determine the nature and extent of the role of drugs in crash causation. This will require large-scale research efforts conducted over an extended period of time. Adequate funding and time must be provided. Poorly designed and hastily executed research will be as inconclusive as similar efforts have been in the past. It will be more costly in the long run to fund such limited efforts than to fund adequate long-term projects.

The drug and driving problem is a part of the larger problem of drug use and abuse in our society. This must be understood as attempts are made to define the drug/driving problem and to develop countermeasures. At this time the implementation of large-scale countermeasure efforts does not seem advisable.

We do believe that available information about the drug and driving problem should be deliberately disseminated to health professionals responsible for the prescription and dispensing of drugs.

The problem posed by drug-alcohol interaction is particularly troublesome for us. Driver impairment may result from use of a licit drug in the prescribed manner plus the ingestion of a limited amount of alcohol. This impairment may be insidious and unrecognized until too late. There is a clear need for a heightened awareness by prescribers, dispensers, and users of medication of the potential for drug-alcohol interactions.

1.0 INTRODUCTION

This is a final technical report reviewing the research literature that discusses relationships between drugs (other than alcohol alone) and highway safety.

The report is the product of a study conducted under the sponsorship of the U.S. Department of Transportation, National Highway Traffic Safety Administration, under contract DOT-HS-4-00994. The period of performance for the contract was from June 1974 to December 1975.

1.1 Background

Indiana University received a contract in June of 1974 from the National Highway Traffic Safety Administration to review current problems associated with the use and abuse of drugs (other than alcohol alone) and driving.

The central objectives of the study may be summarized as follows:

1. Ascertain and document on the basis of existing research literature the relationship between drug use (other than alcohol alone) and highway safety.
2. Ascertain the "state of the art" of research in the area of drugs and highway safety.
3. Define areas of the drug/driving problem that require further research and suggest, insofar as present knowledge permits, possible drug/driving countermeasures that can be implemented in the immediate future.

To achieve these objectives a basic research plan was developed. The major steps in this research effort were to:

1. Conduct an initial literature search to identify published studies dealing with the drug/driving problem.
2. Circulate an initial bibliography among known researchers to develop additional published and non-published sources.
3. Conduct an international symposium of leading researchers to identify the state of the art of current knowledge and to develop directions for future action.
4. Collate and synthesize the information obtained in the literature search and the symposium and through an analytical process develop a series of reports to include:
   - A Symposium Report
   - A Selected Bibliography
   - A Research Review

The *Symposium Report* and the *Selected Bibliography* have been produced and published as separate volumes. This volume contains the Research Review and is the final technical report of the project. A Synopsis that summarizes the project and the major findings is included in this volume.

The following sections briefly describe the technical approach used in developing the bibliography and conducting the Symposium. The contents of the *Selected Bibliography* and the *Symposium Report* are described.

1.2 Literature Search

The basic objective of the literature search was to draw together materials that discuss and describe the drug/driving problem. A scientific examination of the problem

might have limited the literature search to the archival literature, ignoring non-refereed articles or technical reports, as well as summary articles that appear in the non-technical literature. This narrow perspective was discarded in favor of a more eclectic approach, developed with an understanding that the sponsor must respond to requests for information and comment on a wide range of literature sources. Accordingly, the literature search included the examination of source documents that would not be normally considered in a purely scientific review.

The materials included in the bibliographic report were selected on the basis of their apparent relevance and perceived usefulness to the U.S. highway safety community. The principal investigators do not vouch for the scientific validity of all the materials included. Thus, caution must be exercised in using the cited references. The *user* must decide the validity of the source after consulting the original source.

1.2.1 Search Methods

Several standard search methods were used to develop the reference list. Manual searches were made of journal indices, abstract services, bibliographies, author indices, and reference lists of known works in the field.

Computer-assisted searching with the following systems was also used:

- SciSearch (Institute for Scientific Information)
- BIOSIS (Biosciences Information Service of Biological Abstracts)
- CBAC (Chemical Abstracts Service)
- SUNY-MEDLARS (State University of New York-National Library of Medicine)

In addition to these services which were directly available to the research staff, separate searches were completed using other computer-based systems for the project.

NHTSA personnel accessed several computer-based information systems that contain abstracts of the highway safety literature. Included was the TRIS (Transportation Research Board Information Service). Other search systems accessed the international literature.

Personnel of the Indiana University Aerospace Research Applications Center (ARAC) conducted a search of information systems developed under NASA sponsorship. This search covered some 10,000 technical journals and the unclassified research reports of the federal government listed by the Defense Documentation Center and the National Technical Information Service.

Significant contributions to the search efforts were made by individuals and organizations that searched private collections. Such supportive searches were performed by the following individuals and organizations:

- James Nichols, Ph.D., NHTSA, Washington, D.C.
- Gerald Milner, M.D., Melbourne, Australia
- NHTSA Reference Library, Washington, D.C.
- Addiction Research Foundation, Toronto, Canada
- National Safety Council, Chicago, Illinois
- Highway Safety Research Institute, University of Michigan, Ann Arbor, Michigan

The use of the computer-based systems and the manual searches produced a large quantity of material (in excess of 10,000 citations). Index references were examined and documents selected for review. After review of the documents, a core list was devel-

oped and abstracts prepared. This set formed the basis for the development of the literature report and the research review.

Certain limitations in the search method must be noted and considered when assessing the validity of this study. The use of the index systems, either manually or with computer assistance, requires the exercise of discretion in the selections of search topics, keywords, and other selection keys. While every effort was made to be as inclusive as possible, it is clear that some works must have been overlooked.

Further, the identified works were screened, because all identified material could not be feasibly included in the review. The decision to exclude material as well as to include documents represents an exercise of discretion. While every attempt was made to be consistent, it cannot be expected that this expectation was met in every case.

Finally, the search was greatly dependent upon the publication and indexing of a relevant article in one of the source systems utilized. The publication process is a lengthy one. It is common to find work reported several years after it has been completed. The indexing and dissemination of abstracts on published works often follows the original publication by several months or years. Entry into a computer-based information system takes even longer. Thus, it is likely that material published in the last two years (since 1973) is not completely reported.

Problems were also encountered with translations of titles and abstracts. Significant variances were found between abstracts and articles that were examined in detail. Accordingly, it is reasoned that some articles that were not examined because of an apparent lack of relevance of the abstract may have contained relevant information.

The mass of material encountered dictated that only that which appeared most relevant be included. More than 10,000 titles were reviewed, over 2,500 articles or documents examined, and over 600 selected for inclusion in the bibliographic file.

The reader should be very careful to recognize that this collection does not represent an inclusive list of all selections in the field. It is believed, however, that the citations form a useful information base.

1.2.2 Bibliographic Presentation

The literature search resulted in the production of two types of information sources for use by the highway safety community.

First, a research report file was developed for use by NHTSA. This consists of a hardcopy file of over 600 documents. File indices include an author index, a title index, an abstract index, and a numerical locator index. Included with the file is a *USERS MANUAL* that provides instructions on the use of the file. The *USERS MANUAL* contains a topical index and an expanded author index that lists every author regardless of order of appearance.

Second, a separate report entitled *Drugs and Driving: A Selected Bibliography* has been prepared for general dissemination. This bibliographic reference work includes abstracts of all materials included within the research report file. Also included are the topical index, title index, and the expanded author index, all cross-referenced to the abstracts. This report has been designed as a quick reference guide to the major works encountered in the review of the literature.

The topical index includes a list of drugs and agents discussed in the literature with cross-references to the abstracts and source documents.

It must be emphasized that documents have been included on the basis of apparent relevance. The *user* must examine the source material to determine the essential validity of the reported findings.

1.3 Symposium

In furtherance of the objectives of the study, an International Symposium on Drugs and Driving was held at Indiana University in April, 1975. Over thirty leading researchers and practitioners were invited to participate in working discussions. A limited number of formal presentations were made, followed by working group discussion of key issues.

A formal report of the Symposium has been developed as one of the workproducts of this contract. The report includes the presentations of the speakers and summaries of the working group discussions. Major topics include:

- An Overview of the Drug/Driving Problem
- Risk Identification—Drugs and Highway Safety
- Measurement of Drug Effects on Behavior
- Measurement of Drugs in Biological Samples
- Legal and Practical Constraints on Drug/Driving Research
- Countermeasure Development for Drug/Driving Problems
- An Overview of Current Research and Future Needs

The discussions and speakers' papers present detailed examinations of major issues encountered in the literature and focus on the current state of knowledge. Readers interested in a full treatment of the problems of drugs and driving should read the *Symposium Report in conjunction with this technical report.*

1.4 Technical Report—Scope and Approach

This technical report has been developed as an overview document reporting the major findings of the study. The report format has been developed to facilitate examination by an interested reader who does not necessarily have an extensive background in this specialized area. The report is divided into three major parts.

The first part (Chapters 2 and 3) presents background material on drugs and drug use in the United States. A basic explanation of the pharmacological action of drugs is provided to establish a frame of reference for examination of the technical sections that follow. Information on trends of drug use is presented to illustrate the scope and magnitude of the problems associated with such use in our society.

The second part of the report (Chapters 4, 5, and 6) discusses some of the practical limitations on the state of knowledge. What is known about drugs and highway safety is limited by the tools of inquiry available to those studying the problem. Chapter 4 discusses the limitations associated with the identification and measurement of drugs in biological samples. Chapter 5 focuses on the constraints on research that arise when one seeks to measure the effects of drugs and correlate such effects with driving behavior and traffic crash causation. Chapter 6 discusses a very real and practical constraint on research and countermeasure programs—the existing law. A sound grasp of these limitations, set forth in the three chapters, is necessary to understand the current state of knowledge, the limits of existing research, and the problems associated with the development of future inquiry.

The third part of the report (Chapters 7 and 8) examines existing research studies in detail. Chaper 7 reviews experimental studies that have focused on the measurement of drug effects believed related to driving. Chapter 8 examines past epidemiological studies that have sought to better define the risk posed by drug use within the highway setting. The final chapters present the conclusions and recommendations of the study.

Because this report is an overview, its discussions are by necessity summaries of diverse and complex topics. The same subjects are treated in greater detail in the *Symposium Report* referenced in Section 1.3. The *Selected Bibliography* referenced in Section 1.2 contains a wealth of sources allowing more detailed examination of the problem. Readers with a continuing interest in the topic are urged to examine the companion volumes for a more complete treatment of the subject matter.

2.0 UNDERSTANDING DRUG EFFECTS

To understand the relationships between drugs and highway safety it is necessary to have some understanding of the basic actions of drugs. The definitions and terminology commonly used in the literature describing drug actions must be familiar to the reader to adequately deal with the subtleties that abound in this complex problem area. The objective of this section is to present minimal information on drugs and their effects, defining basic terminology and thereby creating a common conceptual framework to facilitate understanding of the technical sections of this report.

2.1 Definition of a "Drug"

There is no common agreement on the definition of a drug, nor on how many drugs are used by our society. The World Health Organization defines a "drug" as "any substance that, when taken into a living organism, may modify one or more of its functions." This definition includes substances prescribed as medications or available as "over the counter" nonprescription medications. Also included are chemical agents such as carbon monoxide, oxygen, and a wealth of industrial chemicals. In its broadest sense the definition would also include food and food additives. Such an interpretation, while logically consistent, is inconsistent with the general public understanding of the term "drug." More common definitions restrict the term to substances used for the treatment of illness, or to substances which adversely affect human or animal biological systems. Dorland's *Illustrated Medical Dictionary* defines a drug as:

> "any chemical compound or any infectious biological substance not used for its mechanical properties, which may be administered to or used on or for patients, either human or animal, as an aid in the diagnosis, treatment or prevention of disease, or other abnormal conditions, for the relief of pain or suffering, or to control or improve any physiological or pathological condition."

The various definitions of the term "drug" have led to different estimates of the total number of drugs. The *American Drug Index* lists more than 20,000; the *Merck Index* lists more than 40,000; and the more conservative *British Pharmacopeia* lists slightly over 5,000 substances. The effects that these substances have on human behavior vary widely and are determined by the pharmacological action of the drug.

2.2 Pharmacological Action of Drugs

The effects attributable to the direct or indirect chemical action of a drug are referred to as the pharmacological actions of that drug. A drug exerts action on existing biological processes only. A drug can increase or decrease blood pressure, alter heart rate, stimulate or depress respiration, cause drowsiness, alter muscular tension, etc., but no drug has only a single effect. A drug cannot cause an organism to do something that requires development of a new biological system, such as the growth of a new extremity. The effect that a drug produces is a function of the dosage and the physiological and psychological state of the recipient.

The vast majority of drugs must be chemically altered in order for the body to dispose of them via excretory pathways such as the urine. For most agents, the chemical changes are carried out by unique catalytic systems called liver drug metabolizing

enzymes. A notable exception to this biological process is ethyl alcohol, which is altered by a unique and highly specific enzyme system.

These changes are referred to collectively as "drug metabolism." The new compounds that result from the metabolism are referred to as metabolites. In many cases, the conversion from drug to metabolite is a conversion from a pharmacologically active agent to an inactive substance that will be excreted from the body. In a significant number of instances, the chemical change within the body leads to the production of an "active metabolite" that is pharmacologically potent and produces its own effects on biological systems. In other cases, the drug as ingested produces some effects, and the metabolite produces other effects on the body. While the pharmacological action of many drugs has been established, for other drugs it is not known precisely which metabolite or component of the drug produce the observed effects. Some examples of drug metabolism are presented in Table 2-1.

TABLE 2-1

Examples of Drug Metabolism in Humans

Parent Drug	*Metabolite*	*Pharmacological Activity*
Ethyl alcohol	Acetaldehyde	Sedative/hypnotic General cellular toxicity
Diazepam	Desmethyldiazepam	Anxiolytic Anxiolytic, more potent and longer acting than parent
Amphetamine	p-Hydroxyamphetamine	Stimulant Sympathomimeticamine, *not* stimulant
Phenobarbital	p-Hydroxyphenobarbital	Anticonvulsant Inactive
Sulfamidochrysoidine	Sulfanilamide	Inactive Antibacterial agent
Imipramine	Desmethylimipramine	Antidepressant Antidepressant, more potent and longer acting than parent
Primidone	Phenobarbital	Anticonvulsant Anticonvulsant

The rate at which the drug metabolism occurs is highly variable from individual to individual and reflects the heterogeneous nature of our species. This phenomenon, known as "individual variation," must be considered when examining information on the pharmacological action of various drugs. Data tend to represent average estimates, and variance can be expected within a population.

The effect that a drug produces is a function of the level of the drug (or the active metabolite) at the site of action. Some minimum concentration must occur before effects are observed. This minimum concentration, which varies for each drug, is referred to as the threshold level or minimum effective level. As drug concentrations increase above the minimum effective level, the effects increase until a maximum is reached. Increasing the concentration of the drug after the maximum effect is achieved does not increase the effect. Figure 2-1 illustrates the relationship between drug level concentration and effects for a typical drug.

Drug levels are usually described in terms of the ratios of the drug present in body tissue or fluids to the weight or volume of the body matter. In animals, where tissue samples can be readily obtained, the concentrations may be expressed in micrograms of drug per gram of brain. In man, where samples of blood or other body fluids are more common than tissue, concentrations are often expressed in micrograms of drug per milliliter of body fluid. Other units of measure may be used, depending upon the quantity of the drug required to produce an effect. Many psychoactive agents require very small concentrations to reach the minimum effective level.

For many drugs the concentration within blood, urine, or other body fluid correlates well with the drug concentration at the site of action in the body, such as the central nervous system. For other drugs, this is not true; the drug presence in blood does not correlate precisely with the drug presence at the site of action and may not correlate with the drug effects.

Drug levels result from the administration of a particular dosage of a drug. Thus, relationships between dosage and response (effect) can also be developed. A typical dose response curve is presented in Figure 2-2. Caution must be used in interpreting dose-response curves, because there is significant variance in the response of individuals to the same dose of a particular drug. Such curves usually represent the average response of a group of subjects.

It is critical to understand that some minimum dose and concentration exists below which the effects of a drug's action are not detectable. This may indicate that at or below such dosage levels the drug is devoid of pharmacological activity. Thus, mere presence of a drug in an individual does not ensure an effect.

Drugs are not retained in the body indefinitely but are excreted following metabolism. The biological processes which remove drugs from the body result in a drop in the drug level or concentration as time increases. The modern science of pharmacokinetics focuses on the examination of such "decays," usually examining the temporal change in concentrations in blood plasma. The plasma decay may be simple, with a basic linear relationship, or it may be complex and multiphasic. Drugs which display the more complex decay patterns often have different effects associated with the different phases. Figure 2-3 presents a typical plasma decay curve for a single-phase drug, such as ethyl alcohol. A biphasic curve for a more complex drug, such as secobarbital, is presented in Figure 2-4.

The natural metabolic processes of the body may be expected to reduce the drug concentration below the minimum effective level over time. Again, this means that drug presence may be detected when no response would be expected.

The relationship between time and response (or effect) for a dosage sufficient to produce a concentration above the minimum effective level is illustrated for a typical

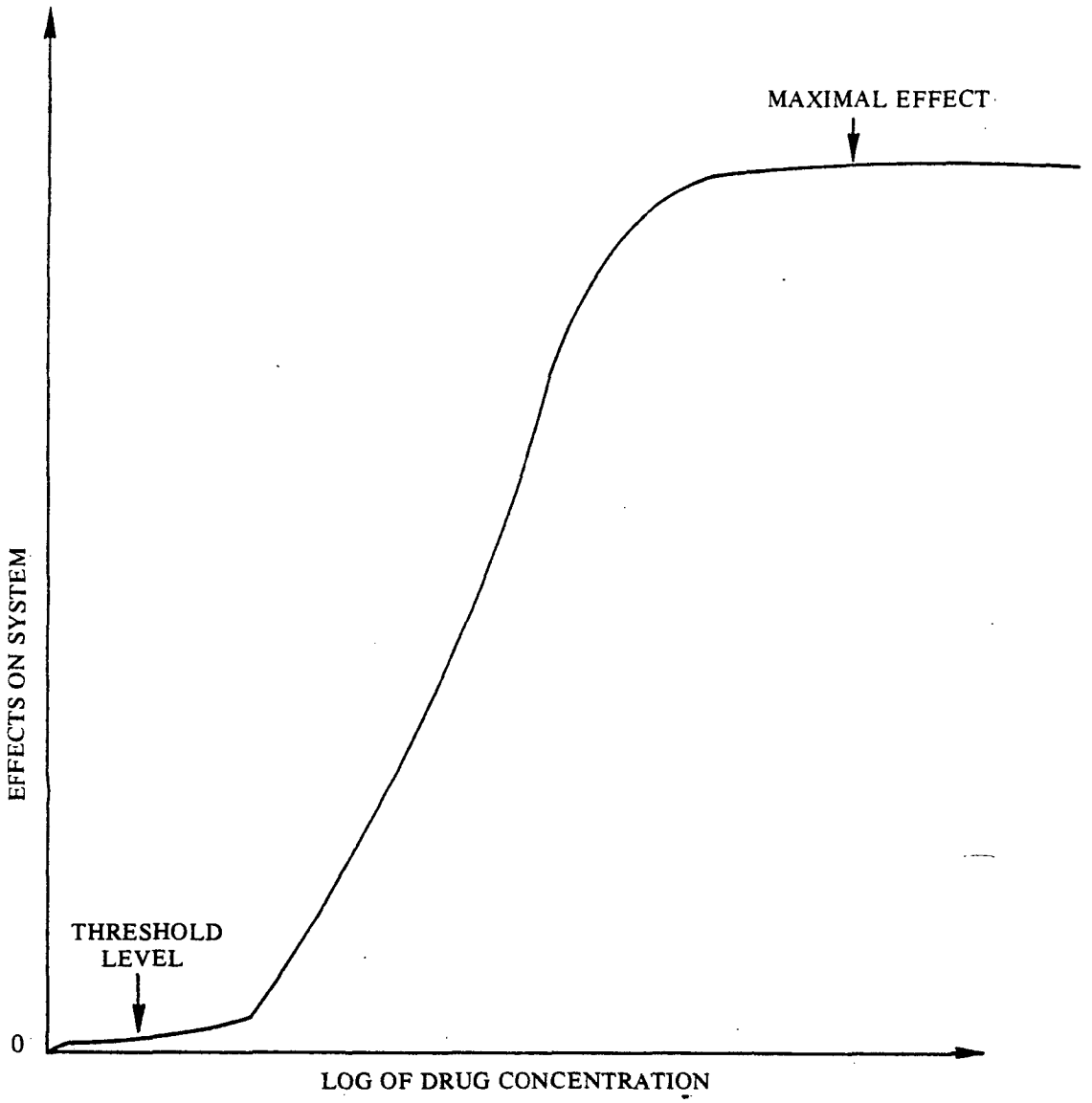

FIGURE 2-1: IDEALIZED CONCENTRATION-EFFECT CURVE

For any isolated receptor system, no effects can be measured until the threshold level of drug is reached. From this point, increasing levels of response will be seen with increased dosage (in a first-order relationship) until the maximal effect is obtained.

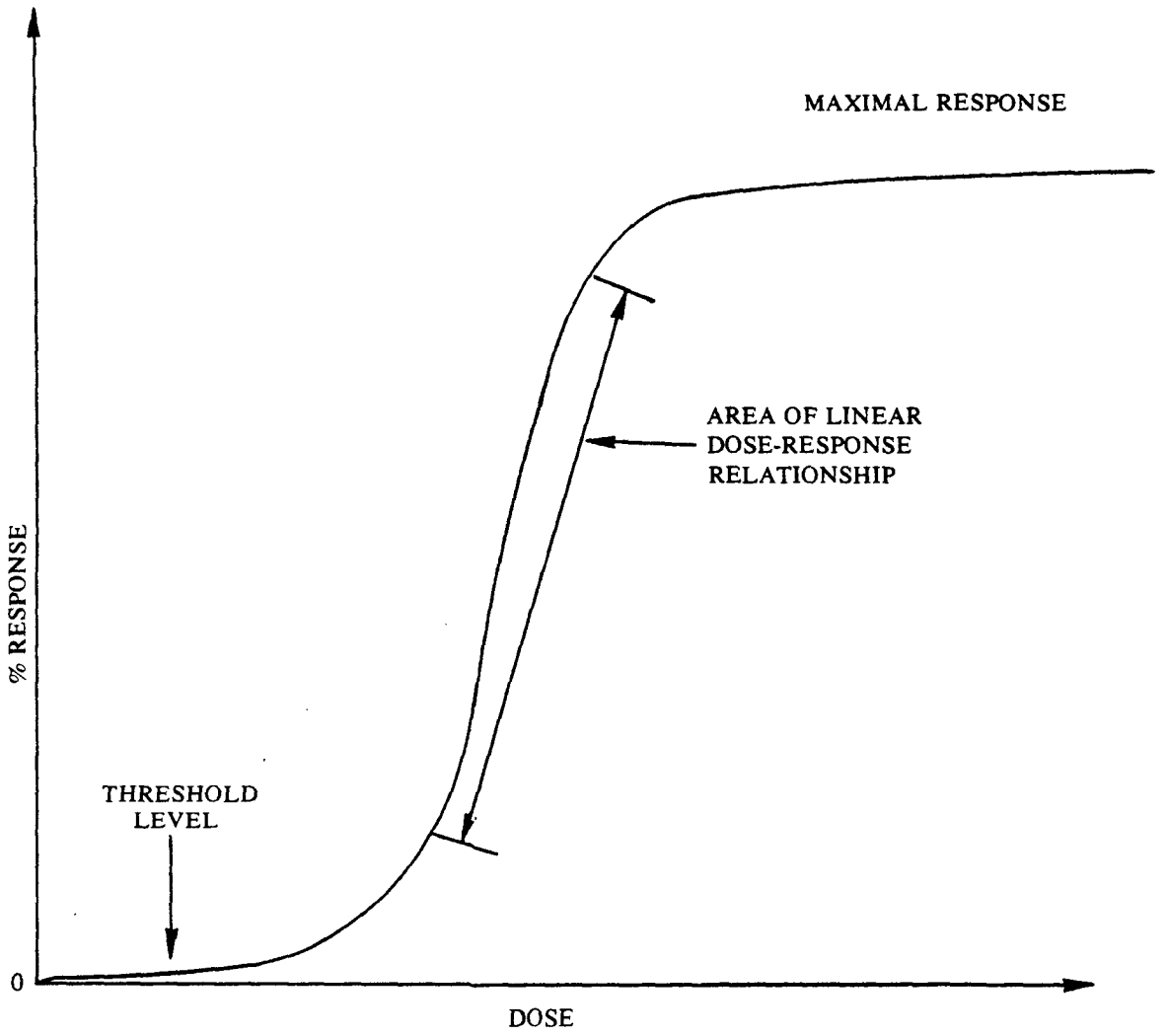

FIGURE 2-2: IDEALIZED DOSE-RESPONSE CURVE

This curve is analogous to the concentration-effect curve presented in Figure 1, except that the response is generally measured as a percent of the group responding. A 50% response is known as the ED_{50} (effective dose 50%).

drug in Figure 2-5. As shown in the figure, some initial time lag occurs after a dose is administered before the minimum effective level is reached. The effect will increase with the passage of time until a maximum is reached, and then the effect will decrease as the drug is excreted from the body or rendered inert by biological processes.

To adequately understand the dynamics of a drug's effects it is necessary to examine its pharmacological characterization, including its effects vs. concentration, dose response, plasma decay, and time-response. Mere detection of drug presence is not evidence of drug action unless it can be demonstrated that the amount present exceeds the minimum effective concentration.

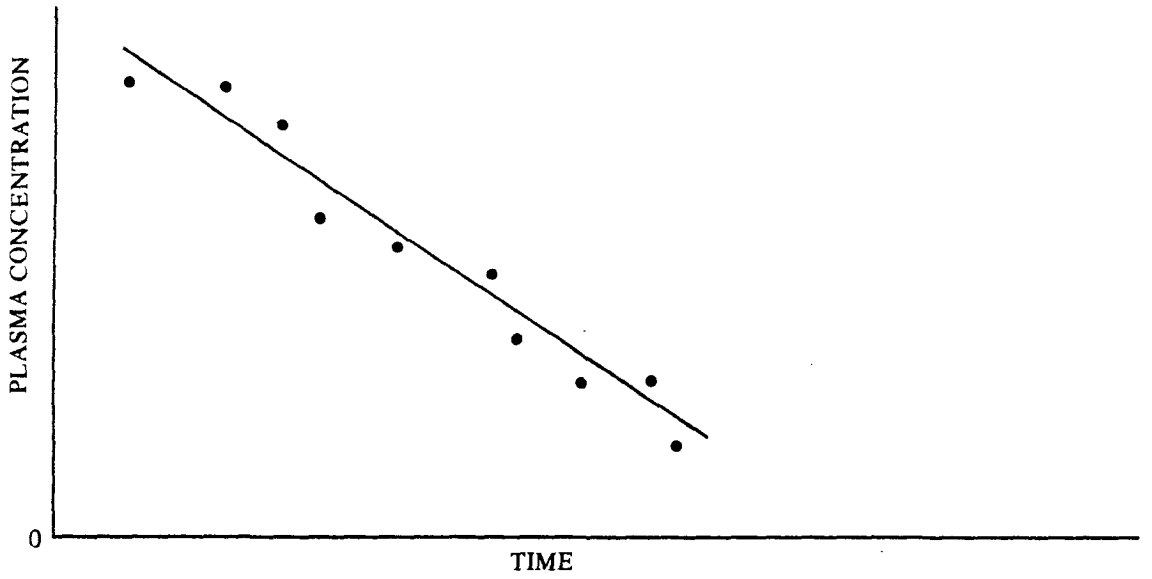

FIGURE 2-3: LINEAR PLASMA DECAY CURVE

This decay is that of a linear responding drug such as ethyl alcohol. The kinetics are zero order.

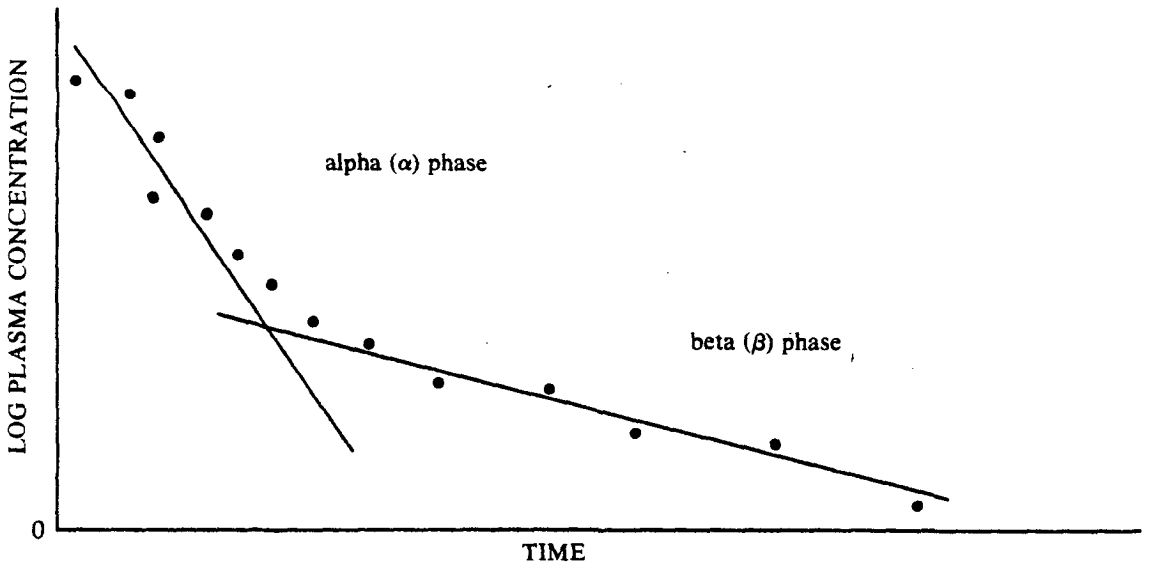

FIGURE 2-4: LOGARITHMIC PLASMA DECAY CURVE

This decay is that of a biphasic logarithmic responding drug such as secobarbital. The kinetics are first order.

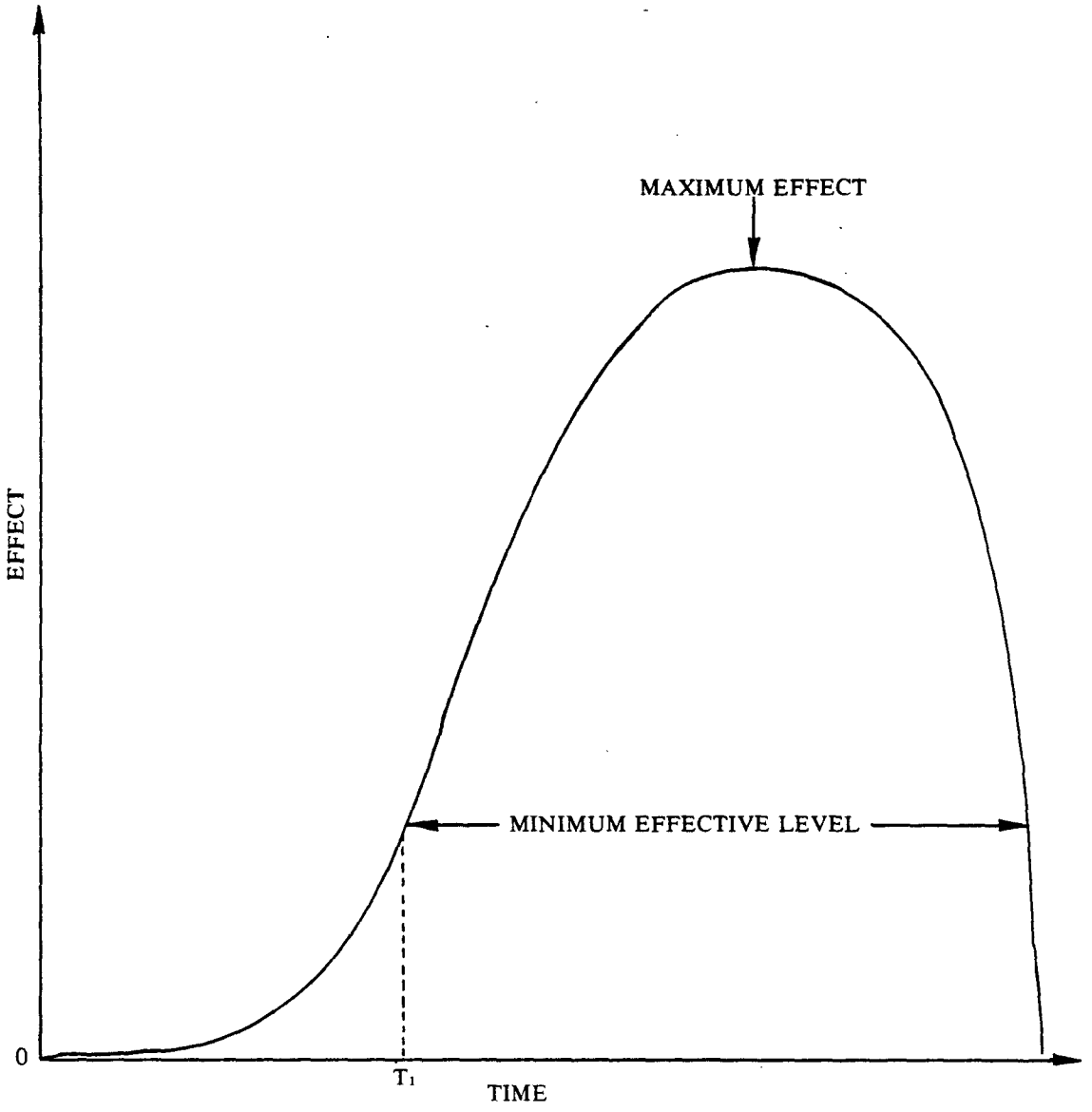

FIGURE 2-5: IDEALIZED TIME-RESPONSE CURVE

Delay time (T_1) for onset of action is the time required after administration of a drug to reach the minimum effective level at site of action. In the real world the shape of the curve is rarely symmetrical; skewing is common.

2.3 Drug Interactions

The preceding discussion dealt with the pharmacological action of a single drug administered to a subject assumed to be free of physiological or psychological complications.

In our society it is quite common to find individuals using more than one drug at the same time. This may occur as a result of deliberate therapy under a physician's direction, as a result of self-medication, or through the combination of a therapeutic agent with alcohol. The frequent polydrug use in the United States makes it necessary to understand the basic pharmacological actions that flow from combined drug use.

A variety of possible effects exist. The effect of two or more drugs taken simultaneously may be simply additive, so that the total effect represents the sum of the individual effects. Table 2-2 presents an example of this case.

TABLE 2-2

Additive Effects of Drugs as Exemplified by Barbiturates

Drug(s) Administered	*Narcosis Time*
Secobarbital (100 mg.)	4.2 Hours
Pentobarbital (100 mg.)	5.3 Hours
Secobarbital (100 mg.) + Pentobarbital (100 mg.)	9.4 Hours

In contrast, the effects of one drug may reduce the effects of another. Such a situation is called "antagonism" and is illustrated in Table 2-3.

TABLE 2-3

Antagonistic Effects of Drugs as Exemplified by Stimulant-Depressant Combination

Drug(s) Administered	*Narcosis Time*
Amphetamine (10 mg.)	0 Hours
Secobarbital (100 mg.)	4.2 Hours
Amphetamine (10 mg.) + Secobarbital (100 mg.)	2.3 Hours

A more complex case occurs when the effect of the combination of drugs is greater than the sum of their individual effects. This is called "potentiation" or "synergism." Table 2-4 sets forth an example.

TABLE 2-4

Synergistic Effects of Drugs as Exemplified by Sedatives

Drug(s) Administered	*Narcosis Time*
Ethanol (50 g.)	0 Hours
Secobarbital (100 mg.)	4.2 Hours
Ethanol (50 g.) + Secobarbital (100 mg.)	7.6 Hours

Interactions may occur between drugs that are in the same pharmacological class or in different classes. Drugs are categorized within a class on the basis of having similar effects on an organism. Each class is defined in terms of its predominant therapeutic use and predominant action.

It must be recognized that many drugs are actually compounds containing a number of active ingredients[13] The method of compounding may alter the effects of the drug. Thus, it is critical when examining reports of drug effects to ensure that the same drug compounds are compared, not different compounds of the same type of drug.

2.4 Side Effects

Side effects of drugs are those actions that occur in addition to the desired therapeutic effect. Such actions may range from minor unpleasantness that can be ignored in light of the prime therapeutic action to life-threatening toxicity with fatal reaction. The nature of side effects can be general or highly individual. Side effects are sometimes particularly good illustrations of the existence of individual variation in response to particular drugs and dosage levels. Table 2-5 lists some commonly encountered side effects that might present potential problems for a driver.

TABLE 2-5

Side Effects of Drugs

Pharmacological Class	*Therapeutic Usage(s)*	*Side Effect(s)*
Antibiotics	Combatting infections	Visual, auditory disturbances, dizziness
Antidiabetic Agents	Treatment of diabetes	Fainting
Antihypertensives	Treatment of high blood pressure	Fainting, dizziness, orthostatic hypotension
Antimotion Sickness Agents	Prevention of Motion Sickness	Drowsiness
Antispasmodics	Treatment of ulcers, "nervous stomach"	Visual disturbances
Antitussives	Relief of cough	Drowsiness
Cardiac Glycosides	Treatment of congestive heart failure	Visual disturbances, muscular weakness
Diuretics	Treatment of edema, hypertension	Fainting, muscular weakness
Ophthalmic Diagnostic Agents	Refraction, visual testing	Visual disturbances

This is not meant to be a complete listing but only an indication of the variety and types of problems to be expected. Of particular relevance are the uniqueness of species differences and individual variations.

2.5 Residual Effects

In addition to the direct and side effects of drugs, one must also be aware of residual effects. These effects generally arise because the direct effects of the drug have ceased. The most obvious effect is when the underlying condition for which a drug was used therapeutically returns following cessation of drug use. Cessation of the use of insulin by a diabetic would be an example of this type of effect.

More common residual effects are thought of in terms of "hangover," "withdrawal," or "letdown." These terms appear in the literature but are not always used with precision. The post-use impact of a drug such as the "morning after" symptoms of excessive alcohol use are often referred to as a hangover. Similar effects are noted with other drugs even when used at therapeutic levels. The popular literature is replete with references to opiate "withdrawal," although it is far less frequently observed clinically. The physiological and psychological demands of the body for a drug and the dysfunctional responses associated with cessation of use are referred to as "withdrawal" symptoms. Reference is also found in the literature to "letdown," although it is less precisely defined. A common example cited is the effect produced in an individual, who has been using stimulants such as amphetamines to compensate for sleep deprivation, when the drug effect ceases. In such cases, sudden extreme fatigue is reported to accompany the cessation or tapering off of the stimulant effect.

Thus, the cessation of drug use or merely the reduction of the drug concentration

below the minimum effective level within a subject may produce deleterious effects that dysfunctionally alter behavior.

2.6 Individual States

The significance of individual variation has been noted in the general discussion of drug metabolism and again in the comments on side effects. The effects that a particular dosage of a drug(s) will produce is highly dependent upon the state of the individual at the time of administration.

Physiological conditions such as the presence of disease or other chronic conditions can significantly vary metabolic rates. Sleep deprivation and other physiological stresses can directly alter the response to a particular drug. Even under normal conditions variance exists from individual to individual and within the same individual as a function of time.

The variability within an individual can be a function of an individual's psychological state as well as physiological condition.

For example, an individual who is in a mental state and setting that promotes a social response may experience significant effects from a concentration of a drug. An example would be a "pleasurable high" experienced from a low dosage of a recreational chemical, such as alcohol, in a social setting where such behavior was expected and acceptable. In contrast, drug effects can be masked if the motivation is strong until significant concentration levels are reached.

Individuals who use a drug regularly may develop a physical tolerance, so that larger doses are required to obtain the effect obtained by lower doses at the start of usage. In other cases no physical tolerance may exist but the experience with the drug may allow an individual to compensate so that the effects appear minimal. The compensation capability of individuals makes behavioral measurement of drug effects extremely complex.

2.7 Alcohol as a Unique Drug

Ethyl alcohol has been demonstrated to play a causative role in traffic crashes. This drug has been the focus of major safety programs designed to reduce crash losses. The effects of alcohol on human behavior have been widely described. It is, perhaps, the most familiar drug within the highway safety community, and discussions of the problems that may exist because of other drugs tend to start with an alcohol analogy.

Unfortunately, alcohol is not a typical drug in either its pharmacological action or its usage, so that an adequate base for reasoning by analogy does not exist.

The pharmacological action of alcohol is direct and relatively simple; dose-response relationships are quite well established (in comparison to other drugs); the plasma decay is simple and linear; and reasonable correlations between drug concentrations and effects can be made. While individual variation exists, the range of variance is smaller than that of many other drugs. The concentrations of alcohol required to produce effects are relatively high, and analytical procedures for the detection and quantification of alcohol are relatively simple.

Behavioral effects can readily be demonstrated and are quite widely known within the population because of the wide use of alcohol as a recreational chemical.

All these factors have made the task of identifying the risk posed by alcohol in traffic crashes simpler than that for most other drugs that present the potential for impairment.

In the same sense these factors have facilitated the development of countermeasures, particularly those relying on the legal system. The presence of alcohol within the human body can be directly correlated with effects if it is present in a sufficient concentration. This is in direct contrast with other agents that may be present yet are not pharmacologically active.

The primary usage patterns for alcohol involve licit usage as a recreational chemical. This is in direct contrast with other agents whose primary usage is therapeutic, or other recreational chemicals whose usage is illicit.

The unique nature of alcohol precludes any automatic assumption that the research methods and countermeasures developed to deal with alcohol in the highway safety setting can be simply transferred to deal with other drugs.

2.8 Summary

For the purpose of the discussions presented in the following chapters it is important to remember the following key points about drugs and drug effects:

- No drug has only a single effect. The effect is a function of the concentration level of the drug and the state of the individual.
- The response to a given dosage of a drug varies from individual to individual.
- The state of an individual and the setting in which a drug is taken can influence the effect.
- Mere presence of a drug within the body is not always evidence of a drug effect.
- Side effects of drugs as well as primary effects can present the potential for driver impairment.
- Alcohol is an atypical drug and cannot be automatically used as a model for drug/driving research and countermeasure programs.

3.0 DRUG USAGE IN THE UNITED STATES

This chapter presents background material on the usage of drugs in the United States. The vast range of chemical agents that can affect behavior has been noted in the previous chapter.

In assessing the potential risk posed by drug usage in the highway setting, one must review the general availability and use patterns for the agents that have the potential to impair driving behavior.

The objective of this chapter is to present a general summary of the existing literature on drug usage and relate this information, to the extent the data permit, to usage by individuals at risk in the highway setting.

3.1 Background

The use of chemical agents by society is not new to mankind nor unique to the United States. Alcoholic beverages have been used for more than 8,000 years, coffee drinking has been recorded for more than 3,000 years, opiates have been used as euphoria producers and as medications for more than 5,000, and recreational chemicals, such as the hallucinogens, have been used for similar periods of time.

Our modern perspective of drugs, as chemical agents developed to treat mankind, has its foundation in four sets of events that may be characterized as stages in the "pharmacological revolution." These stages have not only expanded the range of chemical agents available for use but have set the conceptual framework for their use.

The first stage dates back less than two centuries to the Koch-Pasteur era of development of vaccines to control communicable diseases. The continuation of this stage may be seen today in the emergence of new preventive vaccines and the search for the cure to the "common cold."

The second stage was characterized by the development of antibiotics (sulfa drugs, penicillins, etc.) to combat disease. This stage, which began about 40 years ago, continues in the search for chemical cures for diseases such as cancer.

The third stage, perhaps most relevant to our concerns, began in the early 1950's with the development of tranquilizers and other agents to treat abnormal mental functioning. This stage continues to expand with the development of a range of drugs that alter behavior in the continuing search for chemical "cures" for mental illness.

The fourth stage, barely a decade old, centers around the development of the oral contraceptive, a chemical agent that may be used to selectively alter normal processes.

Thus, although "drugs" have been known to mankind for more than 80 centuries, it is only within the last two centuries that the pharmacological revolution has taken place. Furthermore, for the first 180 years of that revolution, the emphasis was placed on the development of agents that combatted physiological impairment arising from mankind's enemies—the world of microorganisms. In the last two decades, the emphasis in drug development has been placed on agents that alter human behavior. The consequences of this shift in direction, for better or for worse, include changes in the attitude of society toward drugs and drug usage. It is essential to remember that drug usage is a behavioral phenomenon reinforced by satisfying, rewarding effects, such as decreased discomfort or increased pleasure, and subject to societal influences, such as peer pressure.

In considering drug use in the United States today, it is essential to realize that

drug-taking is an active type of behavior. As such, it is just as much a part of everyday behavior as is motor vehicle operation. It is subject to the vagaries, pressures, and interactions that accompany other societal phenomena. Drug usage must be viewed as an integral part of society behavior, not a unique phenomenon capable of being examined in an isolation chamber.

3.2 Literature Limitations

A great deal has been written about drug use in the United States. The literature ranges from incredible polemics to carefully designed and reported research studies. A number of research efforts have attempted to broadly review drug use patterns (1). The studies have dealt with a limited set of drugs, so that the full range of agents that have the potential to affect driving behavior is not fully treated in any existing study. Moreover, the studies generally report usage by broad population groups that include both drivers and non-drivers. Data are seldom presented in a form that allows realistic extrapolation to the driving population. Also, most of the major studies were published several years ago and report data that is at least four years old and often eight to ten years old.

Problems also exist with the interpretation of the data presented. The wide variance in individual usage of a drug makes the application of "average use" or per capita usage figures difficult. Consider the implications of an estimate that X percent of the total population is using an oral contraceptive. It must be assumed that the actual use rate is much higher than X percent for females between the ages of 16 and 45 and much less for males.

Data which reflect total sales or total manufactured units are subject to similar problems of interpretation, because one cannot simply assume a uniform distribution in usage among all individuals.

Data which report prescriptions written are subject to even more difficulty. Some prescriptions are intended for one-time use while others may be for a chronic condition and therefore provide for many refills. While a reasonable expectation of usage may exist at the time of issuance, some patients have shown unusual resourcefulness in acquiring excessive amounts of prescribed medications. Maronde and Silverman (2) report some startling examples of excessive drug acquisition. One patient received 4,260 units of chlordizepoxide ordered in 9 prescriptions by 6 physicians. Another obtained 3,142 units of diazepam in 42 prescriptions by 12 physicians. All of this occurred in one year's time. Thus, a mere count of prescriptions issued is not an adequate measure of drug usage.

Data that represent gross sales, prescriptions, or dosages dispensed do provide a general indication of the relative exposure of the agents involved. Such data must be viewed in a relative rather than absolute context.

It is clearly desirable to have more definitive information on drug usage by the driving population. In particular, it would be desirable to have combined information on drug usage and miles driven while the agent was being used.

The combined information is necessary to adequately develop risk estimates. Many factors enter into the development of such estimates. For example, individuals who use a drug under acute or subacute dosage conditions, in essence a single dosage or at most several days usage, may experience more significant side effects or deleterious behav-

ioral effects than an individual using a drug in a chronic dosage (longer term) mode. The likelihood of greater effects increasing risk may be ameliorated by the probability that the condition that may have required the acute dosage may have also precluded driving. In contrast, the individual who uses a drug in a chronic mode is likely to have a higher probability of driving and may also be exposed to other risk-increasing factors such as polydrug use, including alcohol/drug interactions.

The limitations of existing literature require that caution be exercised in interpreting data on drug usage. In the following sections, basic information on drug usage is summarized. The reader is cautioned to consider the comments above and to place the information in context. Data are presented as they appear in the literature.

For purposes of presentation, four general categories have been used, based on the usual ways the substances are encountered or obtained for use. The four categories are as follows:

- Prescription Drugs—Substances obtainable legally only after authorization by a medical practitioner.
- Over-the-Counter Drugs—Substances available without prescription, but generally used in a manner similar to prescription drugs.
- Illicit Drugs—Substances obtained and used in contravention of legal restrictions.
- "Non-Drug" Drugs—Substances having significant pharmacological activity but not generally considered as drugs by the public.

It is possible, of course, that some specific agents may fit into more than one of these categories; in such a situation, the agent in question will be assigned to one or more categories, depending upon usage. For example, antihistamines may be prescription drugs or over-the-counter drugs, depending on the agent or the dosage amount. Amphetamines and barbiturates are primarily prescription drugs, but must also be considered as part of the illicit drugs category. Alcohol should be considered as an over-the-counter drug, but, because of public thinking, is more commonly thought of as a "non-drug" drug.

3.3 Prescription Drugs

This category includes all agents that are legally obtainable only on the basis of a medical practitioner's authorization. Such compounds, or mixtures of compounds, are generally restricted in terms of availability either because of pharmacological potency, dependence potential, or other serious probable hazards for the user. A summary table of the ten most prescribed therapeutic items in the United States in 1974 is presented in Table 3-2. This tabulation is a summary of data collected from the National Prescription Audit and published in "Pharmacy Times" in 1975. While it does not give the actual number of individuals taking a drug at any given time, it does show that four of the most commonly prescribed medications contain compounds that can adversely influence driver behavior. The active ingredients that may cause problems include:

- caffeine (in the 3rd and 8th ranked)
- chlordiazepoxide (ranked 4th)
- codeine (in the 8th ranked)
- diazepam (ranked 1st)
- d-propoxyphene (in the 3rd ranked)

In addition, these substances may interact with ethyl alcohol to produce additional detrimental actions on behavior.

TABLE 3-2

Most Frequently Prescribed Drugs

Rank	*Trade Name*	*General Name*	*Active Ingredient(s)*	*Therapeutic Applications(s)*
1	Valium®	diazepam	diazepam	anxiolytic agent, muscle relaxant, minor tranquilizer
2	various	ampicillin	ampicillin	antibiotic
3	Darvon compound® 65	—	d-propoxyphene, aspirin, phenacetin, caffeine	analgesic
4	Librium®	chlordiazepoxide	chlordiazepoxide	anxiolytic agent, minor tranquilizer
5	Premarin®	—	conjugated estrogens	estrogen replacement therapy, menopause
6	various	tetracycline	tetracycline	antibiotic
7	Lasix®	furosemide	furosemide	diuretic
8	Empirin Compound with Codeine®	—	aspirin, phenacetin, caffeine, codeine	analgesic
9	Ovral®	—	norgestrel, ethinyl estradiol	oral contraceptive
10	V-cillin K®	—	potassium phenoxymethyl penicillin	antibiotic

3.4 Over-the-Counter (OTC) Drugs

This class of drugs consists of individual chemicals and combinations of chemicals that are considered to be safe for use (by the general public) when taken according to the directions on the package. Even the Food and Drug Administration has stated, in a recent brochure: "People are capable of treating some of their illnesses . . . Mature persons are familiar with the signs and symptoms of the common, minor, everyday ailments which can be self-treated successfully" (3). Some estimates of the magnitude of the OTC drug dosage may be seen in a few figures. More than 4,000 OTC products are on the market, with a net annual gross sales exceeding $3.5 billion. It has been estimated that of every 1,000 people in the United States, 750 will have some symptoms of an illness each month; of these, 250 will go to a physician while the remaining 500 will seek help from OTC remedies (4).

In the period from 1959 to 1970, more than 300 new cough and cold remedies were introduced to the market; the annual sales of cough and cold remedies is now close to a billion dollars. The 1971 market for vitamins was over $350 million; in comparison, that for internal analgesics such as aspirin and acetyl-p-aminophenol was in excess of $750 million. Among OTC remedies, the chemical constituents most likely to create problems for the driver-user are listed in Table 3-3. It would be impossible to list all of the trade names involved for the thousands of items involved; rather, an attempt has been made to list therapeutic areas in order of usage volume (5). Even with this limited appraisal, it should be obvious that OTC drugs cannot be ignored either as possibilities in themselves, or in combination with prescription drugs, other OTC agents, or alcohol.

3.5 Illicit Drugs

This category includes not only those agents that have no licit medical usage at the present time (such as cocaine, heroin, LSD, marijuana, etc.), but also prescription

TABLE 3-3

Frequently Purchased Non-Prescription Drugs

Sales Rank	*Therapeutic Use(s)*	*Active Ingredients Affecting Performance*
2*	Cold and allergy remedies	Antihistamines, sympathomimetic amines, alcohol, caffeine
4	Patent medicines and tonics	Alcohol
5	Cough remedies	Codeine, terpin hydrate, alcohol, antihistamines
8	Appetite depressants	Phenylpropanolamine
9	Sleep facilitators	Antihistamines, scopolamine derivatives
10	Antifatigue agents	Caffeine

*Other Ranking OTC Drugs
1—Analgesics, antipyretics
3—Vitamins
6—Antacids
7—Laxatives

drugs that find their way into the street drug trade (such as amphetamines, barbiturates, sedative/hypnotics, narcotics, etc.). A listing of the major items involved in illicit drug use is presented in Table 3-4. It is obvious that marijuana is far and away the most commonly reported agent. Indeed, its usage rate today is probably about the equivalent of the sum of all the other illicit agents combined (6). The potential for marijuana or marijuana-alcohol combinations to have an adverse effect on motor vehicle operation seems real; because of the frequency of usage of marijuana, the probability of its involvement with driver behavior must be considered as significant. The remainder of the illicit drugs would appear to be less of a problem, primarily because of a lesser frequency of usage, both by any given individual or by numbers of individuals.

TABLE 3-4

Illicit Drug Usage

Rank	*Class*	*Active Ingredient(s)*
1	Marijuana	Δ^9—tetrahydrocannabinol
2	"Downers"	barbiturates, methaqualone
3	"Uppers"	amphetamines
4	Cocaine	cocaine
5	Hallucinogens	LST, DMT, phencyclidine, STP, MDA, mescaline
6	Opiates	heroin, morphine, meperidine
7	Miscellaneous	volatile solvents

3.6 "Non-Drug" Drugs

A final category to be considered are the many substances that are pharmacologically active but not generally considered to be drugs. Some idea of the types of substances that must be included in this category may be seen in the listing presented in Table 3-5. Obviously, alcohol must be considered as the major candidate in this category (in terms of usage frequency); in addition, it certainly has a significant ability to cause behavioral and performance perturbations. Nicotine (as present in tobacco smoke) has been shown to have some behavioral effects, although this is an area requiring further study. Caffeine (as present in coffee, tea, and cola beverages) is, like alcohol, a patent pharmacological agent with known ability to influence behavior/performance. Environmental toxicants include a variety of substances such as carbon monoxide, volatile solvents, and other agents present in the highway or the workplace environment.

TABLE 3-5

Frequently Used "Non-Drugs"

Class	*Active Ingredient(s)*
alcoholic beverages	Ethyl alcohol, aldehydes, ketones
coffee, tea, colas	Caffeine
environmental pollutants	Volatile solvents, carbon monoxide
tobacco products	Nicotine

These "non-drug" drugs can interact with other agents listed in Sections 3.3, 3.4, and 3.5, resulting in an altered effect of either or both agents. Since such interactions may occur accidentally as well as deliberately, it must be assumed that the likelihood of an interaction, with its resultant effect(s), is considerable.

Current estimates are that about 20 gallons of beer, one gallon of wine, and two gallons of distilled spirits are consumed each year per capita. Coffee consumption alone, as a caffeine source, has been estimated to exceed over 180 billion doses per year. The number of cigarettes smoked in the United States is about 540 billion per year (7).

3.7 An Overview Study

While one can obtain a sense of drug usage from the type of information presented in the previous sections, it is difficult to place the usage in perspective. The fact that the data presented have been drawn from a variety of sources that used different populations and different methods of data presentation combines to make comprehension difficult. One study conducted in New York State by Chambers (8) presented a summary that provides a broad perspective of drug usage patterns among a population likely to include drivers. The study is subject to a number of methodological limitations that its author duly acknowledges. Thus, it should be considered as only an estimate or indication of usage rates.

The highlights of the report as presented by the author of the study are set forth below.

> The data secured through the study indicate that of the estimated 13,690,000 people in New York State age 14 and older:
>
> 1. some 377,000 people use barbiturates, e.g., Seconal, Tuinal, etc., on a regular basis (at least six times per month) and 205,000 of these people are employed . . . among these employed users, sales workers have the highest rate of regular use (1,230 per 10,000) and some 11.3% report using the drugs while on the job;
> 2. some 173,000 people regularly use the non-barbiturate sedative/hypnotics, e.g., Doriden, Noludar, etc., and 72,000 of these people are employed . . . among these employed users, the unskilled workers have the highest rates of regular use (180 per 10,000) but none of these workers report using the drugs while on the job;
> 3. some 525,000 people regularly use the minor tranquilizers, e.g., Librium, Miltown, Valium, etc., and 157,000 of these people are employed . . . among these employed users, the clerical and other white collar workers have the highest rate of regular use (570 per 10,000) and some 3.7% of these workers report using these drugs while on the job;

4. some 85,000 people regularly use major tranquilizers, e.g., Thorazine, Mellaril, Stelazine, etc., and 55,000 of these people are employed . . . among these employed users, sales workers have the highest rate of regular use (210 per 10,000) but none of these workers report using the drugs while on the job;
5. some 37,000 people regularly use antidepressants, e.g., Tofranil, Elavil, etc., and 13,000 of these people are employed . . . among these employed people, the rate of regular use is the same for clerical, skilled, semi-skilled and unskilled workers (30 per 10,000) but none of these workers report using the drugs while on the job;
6. some 110,000 people regularly use prescription pep pills, e.g., Dexedrine, Benzedrine, etc., and 51,000 of these people are employed . . . among these employed people, sales workers have the highest rate of regular use (140 per 10,000) and all of these workers report using the drugs while on the job;
7. some 225,000 people regularly use prescription diet pills usually containing amphetamines, e.g., Dexamyl, etc., and 117,000 of these people are employed . . . among these employed people, sales workers have the highest rate of regular use (360 per 10,000) and some 28.6% of these workers report using the drugs while on the job;
8. some 21,000 people regularly use controlled narcotics other than heroin, e.g., Demerol, Morphine, Dilaudid, etc., and 19,000 of these people are employed . . . among these employed people, sales workers have the highest rate of regular use (90 per 10,000) but none of these workers report using the drugs while on the job;
9. some 485,000 people regularly use marijuana and 293,000 of these people are employed . . . among these employed people, sales workers have the highest rate of regular use (680 per 10,000) and some 44.0% of these workers report using marijuana while on the job;
10. some 50,000 people regularly use LSD and 25,000 of these people are employed . . . among these employed people, sales workers have the highest rate of regular use (260 per 10,000) and some 26.7% of these workers reported using LSD while on the job;
11. some 34,000 people regularly use methedrine and 10,000 of these people are employed . . . among these employed users, sales workers have the highest rate of regular use (70 per 10,000) and all of them report using the drug while on the job;
12. some 41,000 people regularly use heroin and 34,000 of these people are employed . . . among these employed users, sales workers have the highest rate of regular use (210 per 10,000) and all of them report using the drug while on the job.

These highlighted figures are a numerical projection of the more "stable" of the drug users and consequently constitute minimums. Persons who had become personally and socially dysfunctional as the result of drug use, e.g., "heroin street addicts," "speed freaks," "acid heads," etc., generally were not available for interview. Thus, only those drug users with a place of residence or routine "at home" hours were located. In some cases these minimal figures should be multiplied by three or four in order to project maximum involvement. Since these dysfunctional drug users are not part of the employed labor force, the projections of use within the various occupational groupings are reliable as they are reported.

3.8 Summary

The literature on drug usage in the United States, taken as a whole, indicates that a wide range of chemical agents with the potential to adversely affect driving behavior are used by wide segments of the population. The extent of usage of any agent (or all agents) by the driving population cannot be reliably determined from the existing literature.

DRUG USAGE IN THE UNITED STATES

The patterns of drug usage by the general population strongly suggest that drugs with the potential to adversely affect driving behavior are regularly used by a significant segment of the driving population.

In a like sense, reliable estimates of drug usage for other individuals at risk in the highway setting, such as pedestrians, cannot be developed. The trends that demonstrate increasing drug usage with age suggest that older pedestrians may be more likely to be affected by drugs.

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4.0 DETECTION AND MEASUREMENT OF DRUGS

The ability to identify and quantitatively measure drugs in humans is a necessary element of the drug/driving problem and the development of countermeasures.

The ability to determine with certainty that a particular drug played a causative role in a traffic crash rests upon such analytical measurements, as well as on a knowledge of the relationship between the drug and its effect on driving behavior.

Measurement techniques for drug detection and quantitation exist and (for some drugs) can be performed relatively simply and inexpensively. For other drugs, although analytical methods exist, they are complex, demanding technology that exists only in a few laboratories.

In many cases the analytical procedures have been developed to deal with samples obtained in research or clinical settings, with results that are satisfactory for research or treatment needs. The same procedures may be inadequate to deal with samples collected from real-world settings, such as accident scenes, where contamination can be expected. The analytical results may be adequate for research or treatment decisions but unacceptable for use in legal proceedings because of lack of compliance with full forensic standards.

Limitations of drug detection and measurement techniques place constraints on the interpretation of the results of existing research. These same limitations constitute practical constraints for the development of countermeasure programs.

The following sections discuss the "state of the art" of drug detection and measurement to provide a basis for evaluation of research studies examined in this report. This discussion also presents general requirements for analytic methods to aid in the formulation of future efforts dealing with drugs and driving.

4.1 Current "State of the Art"

Although analytical chemistry, as a science, has progressed rapidly in the past two decades, this progress has come predominantly in the development of new varieties of technology; the application of these technologies to specific problem areas such as the determination of drugs in biological samples has remained largely an unfinished task. Thus, even though the classical techniques of volumetric and gravimetric analysis have given way to modern techniques such as spectrophotofluorometry, gas-liquid chromatography (GLC), mass spectrometry (MS), and radioimmunoassay (RIA), the development of specific analytical methods and their application to problems such as drugs and driving remains a difficulty. Why is this so? The problems in working with biological samples are formidable, the difficulties in determining substances in the parts per billion range or lower are significant, and the complication of chemically similar metabolites or endogenous compounds is always present. In addition to these methodological problems, any applications to the area of drugs and driving are faced with the practical and legal constraints imposed by the situation itself.

In discussing the assay of drugs in biological materials, we must consider the typical range of concentrations of the desired substance in the sample. A typical dosage of drug to a human or an experimental animal may range from 1μg to 100 mg/kg of body weight —a range of 100,000. In fact, most drug dosages in human clinical medicine are in the range of 5 to 500 mg; based on the average 70 kg human, this represents a range of 0.071

to 7.1 μg/g of body weight. Thus, if the drug were absorbed instantaneously, distributed uniformly throughout the body, and, if there were no metabolic transformations and excretion, a sample of 1.0 ml of blood would contain 0.071 to 7.1 μg of drug. However, drug absorption varies in speed, drug distribution throughout the body is not uniform, and drugs are metabolized and excreted. As a result, the concentrations cited above are achieved—if at all—only for an instant in time. In dealing with the assay of drugs in biological samples, we are generally working in the range of 1 to 10,000 ng/g.

Perhaps one of the best ways to describe present analytical problems is to consider a few classes of drugs as typical examples.

4.1.1 Barbiturates

The barbiturates typify a class of structurally similar drugs for which a large number of analytical methods exist. Some methods are well established and documented; others are newer and relatively untested. Despite the existence of such a large body of analytical information, current needs still demand further evaluation, validation, and characterization of known methods.

All of the more reliable, established methods are dualistic in nature; that is, one analysis is directed towards a positive chemical identification of the drug, and the other serves to accurately measure the amount of drug. In some instances, one method can provide both types of information; this generally causes a decrease in certainty.

The identification, or qualitative, phase of barbiturate analyses can be accomplished by gas chromatographic retention (GC), derivitized gas chromatographic retention (GC-D), thin-layer chromatographic mobility (TLC), high-pressure liquid chromatographic mobility (HPLC) infrared spectroscopy (IR), mass spectroscopy (MS), or radioimmunoassay (RIA). All of these have the full potential for specific positive identification of barbiturates; the degree of difficulty varies greatly. Only two of these, IR and MS, provide specific structural information. While such information virtually eliminates all problems of false identification, it is not always a panacea. Requirements of time, personnel, facilities, and cost are widely variant from TLC (lowest) to MS (highest).

The measurement of drug levels presents different problems from those of identification. The reliability of the quantitative phase of an analysis can be highly dependent on the reliability of the qualitative phase. In any quantitative analysis, the measurement of some chemical parameter requires choosing the appropriate parameter to measure.

There are at least seven methods applicable to quantitative barbiturate measurement: ultraviolet/visible absorption spectrometry (UV/VIS), fluorometry (FLUOR), thermal conductivity (TC), flame ionization detection (FID), electron capture (EC), mass spectrometry (MS), and liquid scintillation counting (LS), as in radioimmunoassay. In each of these methods, the accuracy and precision may be determined by the reliability of the separative or qualitative phase of analysis and not by any intrinsic property of the quantitative method itself. Problems of unreliability or technical difficulties may contraindicate potential pairs.

Despite this wide availability of methodological information, barbiturate analysis is not considered "routine" by most laboratories dealing with the drug-driving problem. The duration of time required for an assay procedure is lengthy and the overall problems are several orders of magnitude more complex than those for alcohol.

4.1.2. Cannabinoids

The cannabinoids are representative of a number of drugs for which much analytical knowledge has been and is being accumulated; no one method has been amply tested and evaluated. The area is neither unexplored nor fully explored. Where existing reports are available, there is a need for greater investigation of strengths and weaknesses; where methods have not been examined, research and development should be initiated. Many methods are hampered by a lack of basic science data on the pharmacology of marijuana in humans. Four methods have thus far exhibited the greatest promise: GCMS, MS, HPLC, and RIA. Nevertheless, considering the usage popularity of marijuana and the extent of marijuana research activity, it is frustrating to realize that positive evidence of recent marijuana usage to a sufficient extent to impair performance is available only with extensive analytical efforts available only in a handful of laboratories.

4.1.3. Antihistamines

The category of drugs exemplified by the various antihistamines may well be the largest. For this and many other classes of drugs, the number of satisfactory analytical procedures ranges from very few to none. The reasons for such a dearth of information are many, and they apply not only to antihistamines but to many licit and illicit behavior-modifying drugs. The most significant and prevalent of these reasons are:

- The class of drugs encompasses a wide range of chemically diverse substances.
- Dosage levels vary over a broad range, but are predominantly all very low.
- There is insufficient data on the pharmacokinetics and metabolism of the compounds.
- There is a great discrepancy between *blood* levels, which best reveal the physiological state of the individual, but are very low and difficult to accurately determine, and *urine* levels, which are much easier to assay but correspondingly less meaningful.

All of these reasons point to a need for research to develop usable methods. The analytical problems associated with the host of drugs in this category belong strictly in the realm of research. Application to a service role cannot come until the necessary foundations have been laid.

4.2 The Overall Assay Procedure

In any consideration of assay procedures, a sequential series of steps must be considered as a basis for rational and effective sample handling and the production of satisfactory results. These may be depicted as follows:

SAMPLE COLLECTION
QUALITATIVE IDENTIFICATION
QUANTITATIVE MEASUREMENT
INTERPRETATION

4.2.1 Sample Collection

The first step is obviously the actual collection of a physical sample. In the case of a motor vehicle operator who has been apprehended for "driving under the influence,"

the sample may be breath, blood, or urine—or, possibly, saliva. In the case of an autopsy, the sample may be blood, urine, body tissue, stomach contents, or bile. Regardless of the nature of the sample, several restrictions must be placed upon it and its handling if accurate and useful drug level data are to be obtained.

4.2.1.1 Quantitation

Quantitation must be assured and maintained. For example, at some point prior to quantitative measurement of the drug, a similar quantitative estimate of the sample must be made. It would be useless to know that a given sample of blood contained 100 μg of secobarbital if one didn't know if the sample of blood were 1, 10, or 100 ml. In the case of liquid or gaseous samples, handling must ensure that leakage or evaporative losses do not occur, since such losses may selectively influence the validity of analytical results.

4.2.1.2 Stability

Stability of the compounds in the sample must be ensured. For example, samples of blood, urine, or breath should not be subjected to elevated temperatures while being transported from the site of sample collection to the site of analytical processing. The ideal situation would be to have on-site analyses; failing this, the next best situation would be the precaution of low-temperature ($< 10°C$) storage of all samples from collection to measurement. Even under these conditions, some drugs may still be biologically unstable (because of enzymatic activity, extremes of acidity or alkalinity, the presence of oxygen or metallic ions, or the presence of chemically reactive compounds in the biological samples). Thus, analytical laboratories must take cognizance of these problems and utilize appropriate precautions and/or correction processes.

4.2.2 Qualitative Identification

At some point in the analytical processing of a sample it is necessary to confirm that the drug being assayed is, in fact, what it is. While this may sound facetious, it is a most real problem and one that merits discussion at this time. For example, it may be possible to quantitatively determine that a sample contains an amount of substance "X" at the level of 1 mg/g; unless the nature of "X" is known, such quantitative information is useless.

Qualitative identification may well be an inherent part of an overall quantitative analytical method (as will be discussed later in this paper) or it may be an additional test or tests performed on the biological sample itself or on some extract therefrom. The critical factor is that it clearly and specifically identify the drug as such; only with absolute confidence in identification can one proceed to the next step, that of quantitative measurement.

4.2.3 Quantitative Measurement

Obviously, the determination of how much of a drug is present in a sample requires the application of some technique to permit accurate and precise quantitative measurement. In recent years, virtually all such techniques have required the use of some electronic system known as an instrument. The important restrictions to the overall process of quantitative measurement are simple: the process must be precise, accurate,

and have a sensitivity suited to the need of the particular problem. As will be shown later in this paper, these restrictions, while relatively simple, occasionally present a severe problem for the worker in the field.

4.2.4 Interpretation

The final step in the overall process is the point at which someone assembles all of the information available into a reasonable and meaningful package. This step requires that all aspects of the determination be known. Was the sample obtained, handled, and processed properly? Was qualitative identification of the drug performed in such a manner as to permit confidence in the conclusions? Was the quantitative measurement sufficiently accurate and precise? Only if all of these questions can be answered affirmatively can the conclusion be drawn that drug "X" was indeed present in that sample at a concentration of y units per unit weight (or volume) of sample.

4.3 Characteristics Demanded of Assay Procedures

What are the parameters of useful assay procedure? What should be considered in developing a new assay procedure or in modifying an extant procedure for use under different conditions? These are some of the questions which have been posed for many years. Basically, they can all be summed up in the single question "What are the characteristics of a good assay procedure?"

4.3.1 Specificity

A most serious limitation of any method is the degree of specificity. If one wishes to determine the concentration of compound X in a biological sample, the analytical procedure must be able to differentiate X from A, B, C, D, or any other compound present. For many drugs, the situation is complicated by the fact that compound X may differ only slightly in chemical structure from A, B, C, or D. Specificity in a method must exist in a manner which is constant regardless of variations in the composition of the biological sample. The method should be capable of determining the desired substance accurately, even in the presence of impurities of 100 or 1,000 times higher concentration. There are several common ways to assure the specificity of a method. The final measurement step may be very specific, as, for example, a fluorescent assay with specific wavelength of activation and emission. A chemical reaction may be peformed prior to the final assay step, the specificity of such a reaction being the determining factor. Specificity is commonly achieved by some form of physical separation, e.g., chromatography or partition, that may take place with the initial treatment of the sample or may be delayed until some chemical reaction has been carried out to produce a derivative.

In most methods, specificity is actually achieved by some combination of these techniques. The most important fact is that the final measurement must determine only the compound of interest or must be able to correct for the presence of interfering substances.

4.3.2 Sensitivity

There is no absolute definition of how sensitive a method should be. A good working definition is that the absolute limit of sensitivity (the smallest amount of substance

which can be measured with precision) should be approximately one order of magnitude less than the usual levels of compound being measured. This allows for variations in day-to-day phenomena and makes results less dependent upon such variations. Because most drugs of interest are present in biological samples at concentrations in the range of 10^{-9} to 10^{-3} moles per liter, it is obvious that the ultimate sensitivity of most methods will be in the lower portion of this range. However, the sensitivity of any given method should be adjustable to fit the circumstances of the specific research situation.

4.3.3 Speed

In all analytical methodology, the truism "Time is money" is quite applicable. However, this is particularly the case for analytical methods used in the forensic laboratory. The ideal method would be one that could obtain a sample, process it, and deliver intelligible results in a few minutes. While some modern versions of breath alcohol measuring devices are, indeed, capable of such rapidity, the current state of technology for drugs in general is not as far advanced. A more reasonable expectation for most drugs is somewhere in the order of magnitude of several hours. In this regard, it must be emphasized that the time required to process a single sample may not be significantly less than that required to process a series of samples.

4.3.4 Simplicity

In developing analytical methods over the past 20 years, scientists have attempted to devise procedures that were relatively foolproof and, if possible, even idiotproof. A less complicated method will obviously have fewer opportunities for error than a more complicated procedure; steps which are not absolutely necessary should be avoided. The ideal method is one which can be successfully performed by an individual with minimal training. In addition, the degree of simplicity of a given analytical procedure often determines the amount of time necessary to perform the procedure, and thus the number of samples which can be assayed per unit of time. Because each workday contains only a limited amount of time, a faster procedure (usually a simpler procedure) will permit more samples to be processed each day. It is more important to remember, however, that specificity or reliability should not be sacrificed merely to increase the output of results.

4.3.5 Reliability

This term covers two aspects of analytical methods; reproducibility from day to day and from laboratory to laboratory, and production of replicate analyses of the same sample which vary less than $\pm 5\%$. This degree of reproducibility is necessary to provide experimental confidence in working with samples of such small size that duplicate runs may not be possible. The method must also have a sufficient degree of accuracy in that recovery of a standard amount of substance run through the procedure should be relatively constant (within a $\pm 5\%$ range).

4.3.6 Economy

While the cost of an individual assay may seem small, the actual cost of a program dependent upon multiple assays may be great. For example, at a cost of $1.00 per

assay, a daily run of 20 samples would have a total cost of $5,200 per year. Thus, a reduction in the cost of consumables of 20¢ per assay would be a savings of $1,040. Similarly, reduction of the time used in an assay procedure from 150 min. to 120 min. may net a labor savings of $2,000 to $3,000 per year.

4.3.7 Safety

This aspect of analytical methodology is the one which is most often ignored. No procedure should be developed and used without at least a consideration of possible hazards involved. For example, when perchloric acid is used in a method, any subsequent step which involves heating should be performed with care unless most of the perchlorate has been removed.

4.4 The Need for Coordinated Information Storage and Retrieval

One problem noted in all state-of-the-art considerations is a lack of organization and centralization of the existing literature on analytical methodology. There is a great and ever-growing need for a better system of reviewing the existing data and reporting on emerging data. A comprehensive literature search for the preparation of an annotated review of existing drug measurement methodology could be extremely useful, but it would require a careful delineation of goals and objectives to achieve maximum utility. These goals are summed up in a single central theme. A review is needed to collate and tabulate *objective* data from all existing literature with respect to two principal characteristics: scientific reliability and service practicality. Specific aspects include ancillary material related to pharmacokinetic knowledge. For example, many of the limitations for drug measurement methods are due to insufficient knowledge of the metabolism and pharmacokinetics of many behavior-modifying drugs. As previously mentioned, analytical methods for determining the use or effects of marijuana are severely limited by inadequate data concerning the fate of the drug, both chemically and kinetically. For a number of drugs, such as glutethimide or many of the narcotics, very little is known about the relative proportions, distribution, or activities of the unchanged drug vs. its many metabolites. Analytical methods are invariably based on choosing some set of parameters which are to be correctly, accurately, and precisely measured. If these parameters are insufficiently understood so as to be unmeaningful, the analysis itself cannot be any more meaningful.

A literature search and retrieval system should collect and collate existing data on drug levels; for each report, there should be as much of the following information as possible.

- Pharmacological activity - therapeutic, toxic, lethal?
- Physiological status of subject
- Amount of drug administered
- Route of administration
- Time of sampling
- Source of sample
- Specificity of analytical methods
- Number of subjects, range of values

In addition, there should be further research on drug levels to eliminate existing gaps in the data, to eliminate existing ambiguities, and to validate existing data.

4.5 The Need for Chemical Information and Substances

In many cases, the unavailability of reference drugs and their metabolites poses a serious limitation to work in many critically needed areas. This is true not only for investigations of pharmacokinetics and drug metabolism, but also the advancement of analytical methods in more highly characterized classes of drugs. Obtaining materials for these kinds of research can frequently be very difficult and frustrating. Any or all of the following materials are critical:

- Drugs and metabolites of known purity
- Drugs and metabolites, stablelabelled (^{2}H, ^{13}C)
- Drugs and metabolites, radiolabelled (^{3}H, ^{14}C)
- Standard reference materials (calibration substances) as supplied in other areas to maintain high levels of accuracy and precision for quality control of methods

4.6 Summary

While it is obvious that the process of detection and measurement of drugs in biological samples is critical to effective solution of the drug/driving problem, it should be equally obvious that the current "state-of-the-art" with regard to analytical methodology is far from satisfactory. Within the constraints and limitations imposed by demands for chemical accuracy, legal requirements, and pharmacological significance, present day technology is—at best—inconsistently satisfactory. For some drugs, such as ethanol, a variety of simple, inexpensive, and highly reliable analytical procedures are available, utilizing samples of breath or blood. Indeed, hand-held instruments for quantitative analysis of breath ethanol make such measurements hardly more difficult than statistical analyses with a pocket computer.

For virtually all other drugs, however, analytical procedures are limited to samples of blood; technological development has only reached the stage of instrumentation requiring 25-50 square feet and having initial costs exceeding $25,000 per unit; and, in most instances, a considerable amount of unit chemistry is involved, demanding expenditure of time and availability of facilities.

Finally, it must be recognized that the complexity of pharmacological agents and their actions is such that after ingestion of only a single drug, as many as 35 metabolic products—some active, some inactive—may be found in the body. In the case of a polydrug user, the total number of drugs and metabolites present in the body at any given time may well exceed 100! Such a situation is far beyond the reach of current methodology; even if it were within that reach, the interpretation of the analytical results in terms of overall pharmacological actions (and the extrapolation to driver performance) would be a veritable miasma.

There is no doubt that appropriate advances in technology for the detection and measurement of drugs is a necessary part of any future research and development in the drug/driving area. However, perhaps the most significant aspect of this future effort will be to follow the axiom, "Make haste, slowly." A great expansion of knowledge in other areas will be required to make new developments in analytical methodology useful to the highway safety community.

5.0 MEASUREMENT OF DRUG EFFECTS

The prior chapter focused on the problems associated with the detection and measurement of drugs in humans. Of equal concern are the problems associated with the detection and measurement of the effects of drugs on human behavior, and more specifically, on driver behavior.

A full understanding of the drug/driving problem will require the ability to detect and measure drugs in crash-involved drivers and pedestrians and relate a drug level to behavioral effects. This requires information on the behavioral effects of drugs. Such information can only be developed through a carefully designed program of testing and measurement of drug effects.

The actual testing must examine behaviors related to the driving task. In addition, diverse test procedures are required to produce the information necessary to evaluate the meaning of drug presence in crashes.

First, the behavioral tasks involved in driving must be adequately defined. Second, testing methods must be developed to reliably examine human performance in the driving situation (either directly or indirectly). Third, tests must be conducted to demonstrate the effects that particular concentrations of drugs have on driving performance.

The following sections examine the issues associated with the first two research areas set forth above. A discussion of the results of experimental testing for drug effects is presented in Chapter 7.

5.1 Driving Task Analysis

Analysis of the tasks involved in the operation of a motor vehicle has been a research interest at least since the first national conference on that topic called by President Hoover in 1924. The goal of researchers in this area is to develop empirical models that define the parameters of human behavior involved in the driving task and relate those parameters to the probability of accident occurrence.

Studies of driver behavior and the driving task have been fraught with methodological difficulty reflecting the complexity of the problem. A study by Miller and Dimling (1) comments on the nature of existing research.

> Individual studies of the relationship between various driver characteristics and measures of driver performance have hitherto been plagued with every methodological flaw imaginable. In particular, the following has generally been the case: (a) The driver characteristic in question, i.e., the independent variable, has often been inadequately defined or measured. This is especially true not only when dealing with admittedly complex biographical and psychological variables, but even when dealing with supposedly simpler human parameters such as reaction time, visual acuity, fatigue, tolerance, etc. (b) The index of performance, i.e., the dependent or criterion variable, is also usually inadequately measured or defined. The typical index used here has almost always been a record of accidents or violations; the shortcomings of such a gross measure of performance have been discussed earlier. Some of the difficulties encountered in the measurement of dependent variables have not been the fault of the experimenter; rather, they are due to our limited understanding of complex factors such as exposure rates, random fluctuations in accident rates, etc. (c) The approach taken to the study of the relationship has almost always been univariate and linear. It appears to us more likely that this is a multivariate nonlinear world. (d) The sample size of drivers has often been

> too small, sometimes absurdly small. The list of methodological inadequacies can be made much longer. What has been said thus far, however, should be sufficient to suggest that considerable effort has been expended over the years in carrying out empirical investigations of factors correlating with driving performance which have yielded results in which we can have no confidence. Most studies are so full of methodological flaws that it is actually impossible to assess the degree of validity, reliability, or generality of their conclusions. Empirical studies are needed and worthwhile, but methodologically they must be vastly superior to the average level of the past.

Thus, the first major problem associated with the assessment of the effects of drugs on driving behavior is that the driving task is not well defined.

5.2 Development of Test Methods

The development of tests that measure human behavior have been the subject of intense effort by experimental psychologists for many years. Specialized applications have also been of interest to human factors researchers, and measurement of drug effects has been a special focus of psychopharmacologists in recent years.

Tests have been developed to examine human behavior and provide greater insight into basic mental processes. Researchers have tended to develop tests that relate directly to the particular subject matter of their research. One finds tests developed to assess specific aspects of human performance in a laboratory setting without reference to real-world activity. For example, cognitive ability may be tested without reference to any particular application. The psychological literature tends to contain material on the development of tests rather than on the real-world relevance of the tests.

A somewhat similar bias exists in the pharmacological literature. Pharmacologists have focused on the examination of drug effects and have tended to develop tests that allow detection of the effects. The tests may be quite adequate for detection of drug effects; unfortunately, the test results may not be directly correlatable with the driving task.

The foregoing has been a very simplistic summary of the state of test development. The field is actually very complex and involves people from many disciplines in interdisciplinary research. A wide variety of testing procedures in use examine many facets of human behavior. Yet, the literature does not demonstrate direct correlations between test results and the driving task.

A limited effort has been made to develop tests that are more directly related to the driving task or are believed to simulate subtasks involved in driving. These efforts are encouraging but the results are not conclusive. Some of the approaches in common use are briefly described in the following sections.

5.2.1 Observation of Vehicle Operation

A number of research studies have examined the driving task through observation of a subject operating a motor vehicle. In some cases the vehicle is operated on the highways while in others the operation is restricted to a driving range or quasi-laboratory situation. If the nature of the experiment involves the degradation or potential degradation of the subject's driving ability, the use of dual control vehicles as a safety measure is common. Use of dual control vehicles to study subjects who have been given drugs has been reported by several researchers. Most studies have been confined

to driving ranges. One recent study by Klonoff (2) involved operation on a driving range and on the streets of a major city by subjects who had received a drug believed to impair driver behavior.

The observation or "in-vehicle" approach provides some relief from the artificiality of the pure laboratory situation. The driving task more nearly replicates the complexity of actual driving than, perhaps, do simulators or single-parameter tests. Operation on a driving range is still artificial, as it is virtually impossible to create test situations that replicate the range of road and traffic conditions encountered in driving. Moreover, these studies are generally performed on a clear day using a typical subject. Environmental variables such as snow, rain, fog, and darkness may not be encountered. Such closed-course systems do not correlate well with the totality of the driving task and are relatively expensive if quantitative measurement of performance is a part of the experimental design.

Actual highway operation, even with dual control vehicles, appears to present significant risks. This is particularly true if prior evidence indicates that the drug is likely to adversely affect the subjects' driving behavior. The risks may be legally unacceptable. Such studies should not be undertaken without a rigorous examination of ethical and legal issues.

5.2.2 Driving Simulators

Driving simulators are attractive measurement devices because they present the opportunity for exposing the subject to controlled conditions and facilitate the measurement of responses. An ideal simulator is one that would produce all the possible conditions that would be encountered in the real-world driving situation. Unfortunately, no such simulator exists. A descriptive discussion of existing simulators is presented by Hulbert and Wojcik (3). While an unknown number of less sophisticated simulators exist, only a limited number of well developed devices are in use. Hulbert and Wojcik report that a 1970 study by *Kuratorium fur Verkenhrssicherheit* listed 17 devices in use in 11 locations in the United States and 11 in nine locations overseas.

Simulators are generally viewed as having severe limitations as a valid measurement instrument. Perhaps the single most severe criticism of driving simulators is the inability to create in the artificial atmosphere of the laboratory the real-life stresses of on-the-road driving. No effective way to introduce the stress of an eventual crash has been developed. The questionable validity of simulators has been critically examined by Edwards, Hahn, and Fleishman (4). They found almost no correlation between simulator performance and actual driving.

5.2.3 Performance Tests

A multitude of procedures have been devised over the years to measure and evaluate human performance. These tests or modified versions of them have been used to evaluate human behavior because of a belief that a relationship exists between the tasks of the test and driving tasks.

Some tests focus on the measurement of decision-making ability by using mathematical problems, card sorting, or similar tasks requiring reasoning and decision-making. Other tests examine vigilance and attention. Many of these tests also involve psychomotor components, as buttons must be pushed, or levers pulled. Tests that focus di-

rectly on psychomotor skill measurement are also used and include tapping, tracking, and other tasks that require physical and mental coordination.

The basic problem with the utilization of these tests and the interpretation of the results is the lack of evidence that the tests, the test results, or the behavioral impairments observed are actually related to driver impairment or accident causation. Gross impairment, as in the case where the subject is totally unable to function, is likely to be relevant. Such a drug effect is likely to be detected by simple observation and without the need for recourse to more sophisticated testing.

Another problem inherent in behavioral testing is the artificiality of the situation. This results in two areas of concern. First, the actual driving situation is not replicated, so that the results are not necessarily valid. Second, the subject is aware that a test is in process and is likely to react differently than in a non-test situation. The ability of individuals to compensate for drug effects if motivated has been previously discussed in 5.2. Thus, it is likely that testing does not detect effects that might be observed in the real world.

It has been argued by a number of researchers that, if one accepts the artificiality of the testing situation and the ability of individuals to compensate, any demonstrated deleterious effect is most significant. This line of reasoning concludes with the view that it is likely that drugs produce more significant effects in real-world situations than those observed on tests. While the argument is not illogical, it is not supported by clear empirical evidence.

5.3 Summary

At present well-developed and validated testing systems capable of detection and measurement of drug effects on driving behavior do not exist.

The development of adequate testing systems is dependent upon definition of the driving task, which has not yet been done in clear empirical terms.

Present test systems are limited because it has not been shown that the test results can be related to the real-world driving task or to accident causation. Tests are available that measure specific aspects of human behavior and are capable of detecting and quantifying alterations in behavior due to drugs. Given the artificial nature of the test environment and the lack of empirical evidence relating the tests to the driving tasks, test results can be best viewed as indicators rather than conclusive proof. Obviously, the more gross the behavioral effect the stronger the inference that may be drawn from the test results.

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6.0 LEGAL AND ETHICAL CONSTRAINTS

The two prior chapters have examined constraints on research and countermeasure programs that arise because of the limitations of current technology or the lack of data. This chapter focuses on constraints that arise from the operation of law in our society.

Social research and social programs are subject to legal and ethical constraints that are designed to protect the individual and society. Presently, the law imposes significant constraints on the examination of the drugs and driving problem and on social responses to identified problem areas.

The purpose of this chapter is to examine major legal constraints on research and countermeasure programs. Legal limitations, whether reasonable or unreasonable, must be considered in the design of research and the development of countermeasure programs. Legal restraints that are unnecessary or unreasonable should be examined with a view to modification.

6.1 Basic Legal Issues

The constraints flow from two basic and intertwined bodies of law. The first deals with the use of human subjects in research and the second with the right of privacy of the individual.

The body of law that deals with the protection of human subjects is neither neat nor well defined. The principles are set forth in numerous ethical codes such as the Nuremberg Code (1) that was formulated in response to the painful and brutal experiments conducted in Nazi concentration camps. The principles and concepts are formally stated in the regulations published by the Department of Health, Education, and Welfare (DHEW) governing the use of human subjects in research (2).

These codes provide that anyone who participates in research must be a true volunteer. Further, the decision to volunteer may be made only after the subject has been fully informed of all risks that might be incurred. This is known as the principle of *informed consent*.

A subject must be fully advised of all risks of physical, psychological, or social injury that may result from participation in a research endeavor. The DHEW regulations require that participating institutions engaging in research must establish review panels to examine the research procedures used by all individual researchers to ensure that they fully meet the standards set forth in the guidelines.

The definitions of physical and psychological injury are relatively well established, although this is an expanding area of the law. The definition of social injury is not as well established. One area of social injury that has become more well defined is that of "invasion of privacy." The right has been expressly recognized by Congress in the Privacy Act of 1974 (3) which states in part that: "The right to privacy is a personal and fundamental right protected by the Constitution of the United States."

This act further provides for specific procedures to be followed by federal agencies or their agents, which includes researchers under grant or contract, in the collection, storage, and dissemination of information. The basic provisions of the act are being implemented by administrative regulations issued by the various agencies of the federal government. It appears, as of the time of this report, that these regulations will incorporate specific provisions requiring anyone collecting information on behalf of the government

to fully disclose to the individual from whom the information is sought: the purpose of the collection, the way the data will be used, and to whom it may be disclosed.

Such an explanation is consistent with the concepts of informed consent already incorporated within the other areas of law previously mentioned.

The impact of these requirements can be fully appreciated when other aspects of the law are considered. First, there is no general privilege which allows a researcher to treat data as confidential (4). Thus, research data may often be obtained for use in civil or criminal litigation. Second, legislation exists (Freedom of Information Act) *requiring* public disclosure of information that is in the custody of federal agencies (5). Some agencies, such as the National Highway Traffic Safety Administration, even have additional requirements in their enabling legislation requiring the disclosure of information collected in the course of research or countermeasure programs (6). Thus, in most cases, researchers and program managers must advise subjects that information supplied for research or treatment purposes cannot be kept confidential.

The obvious difficulties posed by this situation have been recognized by some states that have enacted statutes to protect information collected in traffic crash investigations (7). A broader protection was provided by Congress for DHEW and the Department of Justice (DOJ) for information obtained in the course of drug research or the operation of drug treatment programs (8). This statute has withstood a strong challenge and appears to provide the required privilege to protect the researcher and the subject (9). The applicability of this statute to drug research and countermeasure programs conducted under the sponsorship of agencies other than DHEW or DOJ is not known.

The following sections examine the impact of the present state of the law on situations likely to arise in research and countermeasure programs dealing with drugs and driving.

6.2 Experimental Studies

While many aspects of research are experimental, the focus of this section is on those activities that involve giving a subject a drug and measuring the effect. The measurements may be to identify and quantify the drug's level or to determine its behavioral effects. This type of research is commonly performed in laboratories. A similar situation could arise in countermeasure programs where a drug was given as a part of treatment. The administration of Antabuse® as part of an alcohol rehabilitation program and subsequent testing of the subject would be an example.

Researchers and managers face two basic legal issues. First, they must fully advise the subjects of *all* risks that are faced. Second, they must ensure that informed consent is obtained. These legal issues in turn raise a series of practical issues that turn around the definition of risk and the ability of the subject to consent.

In a research setting the first obstacle encountered may well be the review committee responsible for ensuring that the DHEW guidelines are met. It is unlikely that researcher protocols that wish to test the effects of drug levels significantly above those used therapeutically will be approved. Thus, one may not be able to test in the laboratory the effects of drug levels that may be found in accident victims. The effects may be inferred from lower dosage levels, so that such an obstacle may not be extremely significant and may well be firmly grounded in sound application of ethical standards.

Animal studies become significant in this regard. First, the results of animal studies

provide information about the expected pharmacological action of a drug and lay the foundation for the assessment of the risk of human studies. Second, acute dosages greater than those that may be ethically used in humans may be administered to animals. Chronic dose studies can also be conducted that could not be ethically completed in a human testing program. Because of species differences among animals and between animals and humans, no absolute extrapolations to predict human responses can be made.

It must be understood that the combination of sound ethical constraints and the limitations of animal studies make the simple testing of all drugs to determine all effects an impossibility.

Another practical obstacle is likely to arise as basic information is sought from the subjects. Clearly, knowledge of physical condition, psychological state, and other drug use are necessary for assessment of the risk to the subject as well as the conduct of the study. In the absence of a researcher-subject privilege, those seeking the information will have to advise subjects that the information may be disclosed. This is likely to have an adverse effect on cooperation and is likely to increase error within the data provided.

Other practices or negligence may give rise to legal problems but they cannot be viewed as particularly unique to drugs and driving and can adequately be dealt with by observing usual standards of clinical practice.

One particular aspect of drug/driving experimental studies may pose a problem. This arises in those studies which involve a subject operating a motor vehicle on a public street after taking a drug believed likely to impair driving ability. Klonoff recently reported on such a study involving marijuana, which was conducted in Canada (10).

Studies of this nature place other individuals at risk in addition to the subject. Thus, some provision must be made for obtaining "informed consent" either by or on behalf of these individuals, who would include other drivers, passengers, and pedestrians. At a minimum it would seem that permission should be sought from public officials who might be able to consent on behalf of the public. Even with such consent the legal issues are not clear. Without consent it would appear that the subject and the investigator might both be civilly and criminally liable. The risks inherent in the class of research make it appear unlikely that the review committees of major U.S. research organizations would approve such a study.

6.3 Field Studies

In the prior section, legal issues arising from giving a subject a drug and observing the results were discussed. In this section, the cases where the subject has taken (or may have taken) a drug prior to coming in contact with the data collector are considered.

This does not include the situation where a researcher invites subjects to take a drug on their own and then appear for testing. This would be quickly disposed of as a sham and all the standards applicable to experimental studies would apply.

This discussion focuses on those instances commonly encountered in epidemiological research and countermeasure efforts. Investigators may be concerned with the nature and extent of drug presence in the driving population and the accident population. In the same sense, managers of countermeasure programs may be concerned with determining drug use among participants in the program. In either instance, the data collector needs to obtain information from an individual. The information may be provided by simply answering questions, or more intrusive methods, such as extraction of a blood

sample, may be required. In each instance, the data collector is dealing with a subject who must give informed consent. The subject must be advised of the use of the information requested as well as the potential for disclosure.

In a practical sense, this poses significant problems for any inquiry. The information sought, if revealed, may well subject the individual to criminal prosecution and/or civil liability. Even if legal action is unlikely to result, the potential social stigma associated with disclosure may cause an individual to refuse to participate. In many cases, the use of prescription drugs is a very private matter which the user may not wish disclosed.

It is unlikely that a representative sample of the general driving population or accident population can be persuaded to cooperate with researchers unless adequate legal protection ensuring the confidentiality of the information provided exists. Until a privilege exists, no reputable researcher will seek to collect data without fully advising a subject of the risks of disclosure. Such a warning is most likely to result in refusals to cooperate, so that the study results are biased.

In the same sense, it is unlikely that adequate cooperation can be developed in countermeasure programs until the confidentiality of communications can be assured.

It has been suggested that the issue of disclosure can be circumvented by the use of record systems that are designed to prevent retrieval or are in scattered locations. Unfortunately, these suggestions fail to consider that someone must collect the basic information. This individual could be compelled, under existing law in most jurisdictions, to come forth and testify. While the data collector's recollection might not be perfect, it cannot be assumed that in every case critical elements would have been honestly forgotten. It is often the unusual case that comes to trial with the very fact situations that remain in the mind of an observer.

Thus, reliance on loss of memory or complex filing systems is unlikely to meet ethical standards of the professions regarding the duty owed individuals.

A researcher or manager who knows that information may possibly be disclosed and does not advise a subject of the potential for disclosure may be held legally liable for the consequences of disclosure. In addition to civil liability, in some cases criminal liability may exist under provisions of the Right of Privacy Act of 1974. Censure or other disciplinary action is likely for those who are members of a profession.

The lack of privilege for researchers and program managers is a significant constraint that precludes adequate investigation of the drug and driving problem. Serious consideration must be given to legislative protection such as that afforded drug researchers and drug treatment programs funded through DHEW and DOJ.

6.4 Summary

Research and countermeasure efforts are subject to significant legal and ethical constraints that, at present, impair adequate understanding of the drugs and driving problem.

Ethical constraints are likely to preclude testing of a full range of dosage levels of all drugs because of the potential risk to human subjects.

The lack of privilege ensuring the confidentiality of research data or countermeasure program records is a serious barrier. Investigators must now inform subjects that the information may be disclosed. This is likely to result in limited participation and raises serious questions about the validity of responses from subjects who do cooperate.

Legislation creating a privilege is needed.

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7.0 EXPERIMENTAL STUDIES

This chapter presents a review of selected research studies that examine the effects of drugs on human behavior. Seemingly, there are as many different types of experiments designed to test the effects of drugs as there are experimenters.

Several basic issues associated with this area of inquiry must be understood to place the experimental findings in perspective. The following sections discuss the research issues, present illustrative findings from a selected group of studies, and summarize the relevance of existing experimental research in defining the problem of drugs and driving.

7.1 Experimental Research Issues

7.1.1 Types of Experimental Research

An examination of the research literature reveals a diverse group of studies utilizing widely varying experimental designs to determine the effects of drugs on human behavior (or in some cases animal behavior). The object of a study may be to examine and measure effects solely of a physiological nature or solely of a behavioral nature. In some cases, the object is to measure and correlate the effects of both physiological and behavioral effects.

Studies may examine the effect of a single drug, or multiple drugs may be evaluated comparatively. Additive, synergistic, and antagonistic effects may be examined.

The drug or drugs can be administered in various dosage regimens. *Acute dosage* studies are more prevalent because they are simpler and less costly, although *chronic dosage* studies have also been conducted.

Acute dosage refers to a single administration or dosage form. Acute dosage studies reflect the results of limited use of a drug. Thus, tolerance or compensation effects are usually not examined in acute dosage studies. The results may not reflect the effects that would be seen in an individual who had been using the drug for some time.

A chronic dosage study attempts to measure effects that develop from repetitive drug usage. For most drugs, multiple-day administration of a given daily dosage would be used. Administration over several days allows the development of drug levels comparable to those found in patients who are long-time therapeutic users of the drug.

Many chronic studies have involved subjects who are patients using the drug therapeutically. The fact that these individuals constitute a readily available population is not the only reason for their selection as subjects. Ethical constraints prevent administering some drugs to subjects for whom the drug is not therapeutically indicated. Chronic studies have the potential for generating very useful data, since they tend to examine a population (chronic users) which may be more representative of the population at risk.

The use of normal subjects for drug studies may produce questionable results. Legg, Malpas, and Scott (1) argue that the pharmacological effects of a drug on a patient taking the drug for its therapeutic action are very likely to be reflected in improved behavioral performance. In contrast, the same drug taken by a normal subject may have no effect or may adversely affect behavioral performance. Such a case is demonstrated by the action of those compounds classified as tricylic antidepressants. When administered to normal subjects at therapeutic levels, virtually no effects are observed. Higher dosages produce sedation. When the same drug is given to individuals suffering from

endrogenous depression, the therapeutic action of the drug causes a dramatic reversal of the symptoms of depression.

A common type of drug study administers varying levels of acute dosages and measures the magnitude of the response associated with each dose level. This procedure is known as a *dose-response* study.

The simplest form of a dose-response study involves a single subject who is given varying dose levels of the drug and the responses recorded. These data allow the derivation of the relationships between dose level and magnitude of response.

Another approach to dose-response studies uses a number of subjects, each receiving a different dose level of the drug. This design suffers from a serious disadvantage, in that individual variation may not be adequately controlled.

All experiments to determine dose-response relationships are plagued by problems of variables. The variance in response among individuals to the same level of a drug is one example. Other issues include participant bias and observer bias.

A *placebo,* or non-active substance, may be administered in the same mode as the test drug. This may be done as a *blind* study, wherein the subject does not know whether the test drug or the inactive placebo is administered. This is designed to reduce participant bias. Another method uses a *double-blind* approach, wherein neither subject nor the observer is aware of whether the drug or the placebo has been administered. This is designed to control for both participant and observer bias.

The problem of individual variation may be approached by the use of placebos in double-blind experimental designs. All subjects receive the drug and the placebo at different times. The responses generated can be examined by standard statistical techniques to test for significant differences in responses between the placebo and the drug as well as among dosage levels. While this design represents a deliberate attempt to control for intervening variables, the problem of variance in the response of a single subject, depending on individual physiological and psychological states, may not be adequately solved. Moreover, the prior administration of the placebo may result in a physiological or psychological response that will modify the response to the test drug, or vice versa.

The problems of variation in settings and state are addressed by the use of a *crossover* design. Commonly, the subjects are divided randomly into two groups. One group receives the placebo and then the test drug; the other, the test drug and then the placebo. More complex crossover designs systematically balance all variables (drugs, order of administration, dosage, route of administration, etc.).

The following section presents some of the methodological problems that are characteristic of the research literature and limit its validity and applicability.

7.1.2 Methodological Problems

One of the foremost problems with existing studies is their weak design. One commonly finds significant errors in the design of experiments. That renders their results questionable at best. The weak designs may explain some of the variance in results reported in the literature. A number of key problems have been noted that tend to be repeated in various studies. A reader must be sensitive to these problems to evaluate existing research.

Dosage: Many studies report effects observed after administration of a drug in a

dosage that was undetermined or cannot be determined from the report of the study. Such a problem was common in early studies of illicit drugs such as marijuana. Without knowledge of the dosage, little can be said validly about the response.

Difficulty has been encountered because dosages believed known at the time of the experiment were later found to be erroneous. For example, Manno *et al.* (2) report that some of the discrepancies between their findings and those of Crancer *et al.* (3) may well be the result of unreliable analysis of the marijuana supplied to the Crancer group.

This emphasizes the desirability of measuring drug concentrations in the subject's blood or other body fluid. Adequate understanding of the drug's pharmacological action is also required. Some studies report testing that has been accomplished without consideration of the drug's metabolism within the body. Thus, tests have been run before or after the drug could be expected to have maximal effect.

Placebo Contamination: The use of a placebo may present a problem if it contains an active agent. For example, it is not totally agreed that delta-nine-tetrahydrocannabinol (THC) is the sole active component of marijuana. Yet many studies have reported use of a placebo substance which has been processed to be mainly or only THC-free. It is not clear that this results in a true placebo. Thus, studies that report no differences must be examined with care. This points to the necessity for investigators to carefully determine the pharmacological characteristics of substances used as placebos in the same independent manner that the dosage of the drug to be tested should be determined.

Subject Selection: One of the major problems with existing studies lies in the method of selection of subjects. Many studies represent experiments of convenience. The negative aspects of the tendency to perform acute rather than chronic dosage studies are enhanced when one finds that most acute studies are done on samples of convenience, often a few healthy college students who were easily accessible for the researcher. It is unlikely that such a sample is representative of the drug using or driving population. Thus, the validity of the results of these studies must be questioned and generalizations avoided.

The practices of some researchers who deliberately screen subjects, using psychological tests to eliminate "non-normal" subjects, merely intensifies the problem of sample bias. Subjects selected by such a method are unlikely to be representative of any general population.

One researcher advised that psychological screening resulted in the elimination of 70-90% of all volunteers. The screening was defended on the basis that testing without the screening did not produce statistically significant results. Regardless of the statistical significance of the results obtained from a screened group, the screening process makes it doubtful that the results have general validity.

Subject Control: Few researchers report adequate measures to determine if the subjects are using other drugs. Objective testing measures involving analytical measurement of body fluids to determine if other than the test drug(s) is present is most desirable. The use of paid subjects and/or subjects from a drug-using population increases the probability that other drugs may be present.

Equal concern must be devoted to ascertaining variations in physiological or psychological state. Sleep deprivation, emotional strain, or other influences on a subject's state may significantly affect responses to some drugs. In the absence of any control for these variables, one must be concerned about the validity of the reported results.

Sample Size: Most experimental studies utilize relatively few subjects. The limited sample size may not detect drug effects that will occur in the general population. An unusual sensitivity that may occur in one out of 20 people may go undetected. Such responses become significant when a drug is used widely. Even a low frequency of adverse reactions may result in a significant number of absolute cases when use is widespread.

The limited sample size of many studies produces an interesting yet disturbing pattern in the drug literature. Initial reports of drug testing may reflect inconsequential dysfunctions or side effects. This should be no great surprise, because few drugs appear on the market if evidence exists of significant dysfunctions. After a few years' use of the drug therapeutically, reports of side effects are accumulated from clinical reports. This often starts a new round of testing, using procedures that are sensitive to the side effects noted clinically. This then generates reports of impairments in the experimental literature.

One example of this pattern is the drug meprobamate. Early clinical reports of this drug (4, 5, 6, 7) indicated minimal problems with side effects. As the therapeutic usage of the drug increased, additional side effects were identified. This led to additional experimental studies using different measurement techniques that more fully defined the drug's properties (8, 9, 10, 11). This phenomenon is common to many drugs and often reflects clinical usage in a manner different from that carefully delineated in the original studies. It may also reflect the interaction of the drug with other agents. It highlights the need for careful selection of measurement methods to maximize detection of drug effects during the testing phase.

Thus, careful statistical designs are required and sample sizes should be generally increased. Only limited confidence can be placed in the results of limited testing. In this regard, prior animal studies are most significant. Drugs that demonstrate pharmacological actions in animals similar to actions of drugs that have been shown to produce impairment in humans should receive extensive testing before one concludes that they do not present potential problems.

Statistical Analysis: It is an adage that no statistical method can turn bad data into good results. The prior comments have focused primarily on problems that result in the generation of bad data. Unfortunately, the literature also contains problems with the analysis of good data. These problems may stem from ignorance of quantitative methods, ethical concerns that require that the minimum number of subjects be exposed to a drug or, possibly, in some cases other pressures that are less excusable.

One generally finds that a researcher has simply run a sufficient number of subjects to produce a particular (perhaps desired) result at a specific level of confidence—usually .05. This simply means that the observed effect has less than five chances out of 100 of having occurred by chance.

The logic of conventional statistics does not allow the continuous analysis of data. The number of times data are to be analyzed and the nominal level are to be established before the experiment starts.

Other methods such as sequential trial designs with accompanying tailored data analysis have been developed to overcome the problems of analyzing accumulating data. Unfortunately, some researchers have resorted to the use of conventional statistics in an unconventional manner and the reported conclusions are not supported by the analytical methods used.

The foregoing has been a brief discussion of problems observed in the reports of experimental studies. Other problems encountered in reviewing the studies were created by the state of the literature. These are discussed in the following section.

7.1.3 Research Review Problems

Examination and review of the experimental literature related to drugs and driving is particularly frustrating because so many of the reports are incomplete. The archival literature in this research area is not well developed. Some studies are well reported, meeting the standards of the best scientific literature, but many more are not. Our all too frequent experience during this literature review involved carefully reading a research report, examining it with a view to the key problem areas set forth in the previous section, and reaching the conclusion that no judgment could be made on the validity of the results because of the lack of information presented in the published report.

Typically the reports present one or more of the following problems: procedures are frequently not fully described, the data are reported in incomplete form, the analytical approach is not fully explained, or the conclusions are not adequately supported. If one wishes to infer that all experimental problems have been adequately dealt with and analyses correctly completed, some conclusions may be accepted. But such inferences are not consistent with scientific rigor. In sum, many of the reports fall in the category of being interesting but questionable.

The limited number of studies that are well executed and well reported are a comparative delight. Unfortunately, they are few in number and limited in scope.

The following section presents a brief review of selected studies that illustrate the findings presented in the experimental literature.

7.2 Reported Findings

This presentation of some classes of drugs that may affect driving ability is intended to be an illustrative rather than comprehensive review of a variety of efforts reported in the literature. The conclusions reached regarding drug effects are those of the authors under the conditions of their experimental design.

7.2.1 Analgesics and Antipyretics

Eleven popular nonprescription drugs were studied by Carter (12) in 1969 for their effects on some specific psychophysical driving skills. These drugs were multi-component preparations, a number of which contained analgesics and antipyretics or parasympatholytic agents. Eighteen subjects were tested for reaction time, depth perception, visual acuity, peripheral vision, glare recovery, and steadiness. The drugs were found to have no significant effect on driving skills; some were even followed by a trend toward the improvement of scores. Battig *et al.* (13) reported in 1966 that in a group of 29 students, three tablets of Saridon® (a nonprescription analgesic) or three tablets of placebo failed to have any significant effect on performance in six different psychomotor tests or on the results of a quantitatively measurable personality test.

7.2.2 Anesthetics

Nitrous oxide is a gaseous inhalation anesthetic commonly used in dentistry. Jarvis *et*

al. (14,15) reported, in 1971, the effects of inhaling 10, 20, and 30% nitrous oxide in oxygen as compared with those of pure oxygen in 12 normal subjects. Nitrous oxide prolonged reaction time and diminished all components of electroencephalograph-recorded responses in a dose-related manner. Forty male students were each exposed on two occasions to four hours of inhalation of either air or 500 ppm nitrous oxide with or without 15 ppm halothane, a very commonly used volatile anesthetic, in an experiment by Bruce *et al.* (16). Immediately following exposure a battery of tests of perceptual, cognitive, and motor skills was administered. Compared with responses after breathing air, those after exposure to nitrous oxide and halothane showed significant decrements in performance. Doenicke *et al.* (17) compared the recovery times after administration of a variety of injectable anesthetics which included methohexital, propanidid, thiobarbital, and thiopental. They found that the effects of propanidid vanished rapidly, although this was not the case with the other drugs. Even after 12 hours the potentiating effect of a small quantity of alcohol was discernible after methohexital, thiobarbital, and thiopental. They concluded that after intravenous barbiturate anesthesia for out-patient procedures, the patient should be cautioned about driving and drinking alcohol for 24 hours, but after propanidid a two-hour period is sufficient. Klebelsberg *et al.* (18) and Frey *et al.* (19) in experiments conducted in this area also reached similar conclusions regarding the expected diminished driving ability following administration of injectable anesthetics; and warned of alcohol potentiation.

7.2.3 Anorexics - Sympathomimetic Agents

The reported effects of dextroamphetamine and its congeners—d, l-amphetamine, and methamphetamine—on psychomotor skills range from an improved effect, through no effect, to a detrimental effect. Because of its stimulative capabilities it has often been investigated as a possible countering-agent to alcoholic intoxication. Again, the reports on this have been mixed. Lovingood *et al.* (20) in 1967 reported that 15 mg of d-amphetamine sulfate significantly improved performance but caused a significant increase in heart rate; he also reported that citrated caffeine, a psychostimulant, did not produce a significant change in either the performance tasks or the physiological parameters tested. Miller and Uhr (21) tested the acute effects in normal subjects of double the normal dose of d-amphetamine sulfate, meprobamate, meprobamate plus alcohol, and alcohol alone. While there was some evidence of unsteadiness under alcohol, no behavioral toxic effects were found with the d-amphetamine or the other two treatments. Hughes and Forney (22) tested eight subjects under the influence of d-amphetamine (20 mg) and/or ethanol (45 ml/150 lb.). They found that ethanol impaired performance and d-amphetamine had relatively no effect. When given in combination with ethanol, no clear evidence of antagonism by d-amphetamine was found; in fact, in a simple addition test, a synergistic effect was noted. Bernstein *et al.* (23) reported that amphetamine markedly overcame the nystagmatic effects resulting from the injestion of a moderate amount of alcohol. Bradl (24) has investigated the effects of ephedrine, another sympathomimetic agent, on the optical reaction time of man. Physiologically induced symptoms of fatigue considerably increased reaction time; this effect could be drastically enhanced by administration of the hypnotic, methaqualone, and could be completely suppressed by ephedrine.

7.2.4 Antidepressants

In a variety of experiments on humans and animals Milner (25, 26), *et al.* (27); Landauer (28), *et al.* (29); and Forney & Hughes (30) have all sought to determine the effects of a number of tricyclic antidepressants, alone or in combination with alcohol, on psychomotor skill tests related to driving. The drugs tested included amitriptyline, chlorimipramine, desimipramine, doxepin, imipramine, and nortriptyline. These authors, under a variety of different testing circumstances, found that no drug alone significantly impaired psychomotor skills. However, the co-administration of amitriptyline or doxepin increased the alcohol-induced impairment of psychomotor test responses. Patman *et al.* (31), on the other hand, found no such increased impairment over that of alcohol alone when amitriptyline was co-administered. These results are not, however, completely at odds with each other. In the first set of experiments, the drugs were administered acutely before the effects on psychomotor tests were measured, whereas in the latter set, amitriptyline was administered chronically before measuring psychomotor test effects. One of the most important tricyclic antidepressant side effects is cholinergic blockade with atropine-like "sedative" side effects, which obviously will increase alcohol impairment. At therapeutic dose levels the sedative side effects of the tricyclic antidepressants diminish (due to an acquired tolerance) after a few days of continuous treatment; the decrement in driving skills associated with alcohol consumption is not significantly added to by the antidepressant, as Patman demonstrated.

7.2.5 Antihistamines, Antinauseants, & Antivertigo Agents

Many antihistamines have antinauseant and antivertigo properties and are prescribed or taken for these properties in addition to their main one. Thus, a number of antihistamines are therapeutically employed for other than their antihistaminic property, or for both this property and the others mentioned. A number of researchers have investigated the effects of a wide variety of antihistamines, alone or in combination with alcohol, on mental and psychomotor tasks believed to be related to driving. Landauer & Milner (32) discuss the concept of grouping various types of antihistamines according to their alertness ratio (sedative dose/therapeutic dose), stating that evidence is now accumulating which indicates that the degree to which an antihistamine adds to the effects of alcohol is proportional to the alertness ratio of the drug. These authors outlined a double-blind experiment which investigated the joint effect of ethanol and three antihistamines (with high alertness ratios) on measures of skilled performance related to driving ability (33, 34). Subjects received either 50 mg of pheniramine, 4 mg of cyproheptadine, 1 mg of meclastine, or a placebo. After allowing time for drug absorption, the subjects completed a motor skill battery, then were given 0.95 ml per kg body weight of ethanol. A breathalyzer test was given, and the subjects repeated the test battery. Their results showed that none of the drugs, either alone or in combination with alcohol, significantly affected test performance; no drug potentiation due to alcohol was observed. They concluded that although many clinicians have warned that antihistamines may adversely affect a person's driving ability, either alone or in conjunction with alcohol, it does seem likely that this warning is based on experience with types of antihistamines which have a low alertness ratio.

Pearson, in 1957 (35), studied effects of some other antihistamines, which also serve as motion-sickness preventatives. Motor skill was tested after administering either diphenhydramine (50 mg, Benadryl®), dimenhydrinate (100 mg, Dramimine®), or placebo; both decreased psychomotor performance compared to placebo, leading to the conclusion that the effects of both of these drugs are such that they are not recommended for motion-sickness prophylaxis in situations where perceptual-motor skill is required of the individual. Linnoila (36) has studied the effect of diphenhydramine, meclastine, and chlormezanone, alone or in combination with alcohol, on psychomotor skills (a choice reaction test and two coordination tests) related to driving in 300 health volunteer subjects. Diphenhydramine caused sedation, partly independent of the dose, and slightly impaired psychomotor performance; it also enhanced the effects of alcohol. Some subjects were exceptionally sensitive to diphenhydramine-induced impairment of skills. Meclastine did not impair psychomotor performance. A 1.5 mg dose of meclastine did not enhance the effect of alcohol, but 3 mg did, although it was less potent than 50 mg of diphenhydramine. Chlormezanone (a tranquilizer) at 200 mg had a relaxing effect which became apparent as a shortened reaction time at 30 minutes. Chlormezanone 400 mg did not affect psychomotor performance, nor did it enhance the effects of alcohol on psychomotor skills. Both Molson *et al.* (37) and Large *et al.* (38) demonstrated that promethazine significantly impaired hand-eye coordination. The dose used (Molson 25 mg, Large 50 mg) was sufficient to produce subjective symptoms of central depression in all the subjects. Day *et al.* (39) found that clemastine, on the other hand, did not affect hand-eye coordination or visual function, at therapeutic doses. Hughes & Forney (40) have studied three antihistamines—clemizole, tripelennamine, diphenhydramine—alone and with alcohol, to determine their effects on motor and mental performance. No significant mental impairment was observed when the antihistamines were given alone, nor was the effect of alcohol significantly potentiated by them. When motor performance was measured, however, some of the antihistamines alone produced significant effects. In the presence of alochol, the action of diphenhydramine was potentiated.

7.2.6 Major [antipsychotic agents] and Minor [antianxiety agents] Tranquilizers

Many tranquilizers have been tested experimentally by more than as many researchers or research groups, as to their effects, alone or in combination with alcohol, on psychomotor skills related to driving. These psychomotor skills range from those as simple as reaction time tests to performance on simulators or in cars on closed-course tracks (41, 42, 43, 44, 45, 46, 47, 48). Chlordiazepoxide (Librium®), diazepam (Valium®), and meprobamate (Miltown®), are all minor tranquilizers, while chlorpromazine (Thorazine®), thioridazine (Mellaril®), trifluoperazine (Stelazine®) and haloperidol (Haldol®) are major tranquilizers. While barbiturates have in the past and to some degree are still being used as tranquilizers, they are best categorized as sedative/hypnotics, and as such mainly considered in that section.

Linnoila and co-workers (49) report on a study employing 400 healthy volunteers, in which the effects of diazepam, chlordiazepoxide, thioridazine, haloperidol, and flupenthixol, alone or in combination with alcohol, were investigated on psychomotor skills believed related to driving. A choice reaction test, two coordination tests, and an attention test were employed. The benzodiazepines (diazepam and chlordiazepoxide)

relaxed the subjects; the drugs had additive effects in combination with alcohol on reaction and coordination. Thioridazine had a more deleterious effect on attention than the benzodiazepines; it had slight additive effects with alcohol on coordination. Haloperidol and flupenthixol scarcely altered reactive or coordinative skills, although their effects on attention were deleterious; they did not interact with alcohol. The strong interaction of benzodiazepines with alcohol should be considered in medical practice, particularly in treating neurotic patients who often use drugs in combination with alcohol. Linnoila and Mattila (50, 51) in another experiment, done under double-blind conditions, studied the effects of combinations of diazepam (5 and 10 mg) and alcohol (0.5 and 0.8 g/kg) on skills related to driving in 200 volunteer students. These drugs either did not affect or even slightly improved the skills measured, but their various combinations definitely impaired the subjects' performances. This effect (at 30 min.) was greatest *before* the peak levels of blood alcohol (at 90 min.) or drug (after 30 min.) were reached. When 0.5 or 0.8 g/kg of alcohol was given with or without 10 mg of diazepam before the clinical test for drunkenness, diazepam did not alter the blood alcohol level nor the time in which it reached its peak (at 90 min.). Diazepam increased the effect of 0.5 g/kg of alcohol at 30 min. but not later. Linnoila and Hakkinen (52) have also employed the use of simulated driving. The effects of single oral doses of codeine, diazepam, and alcohol were investigated by using a modification of the English Sim-L-car. Diazepam (10 mg) increased the number of collisions and neglected instructions and generally enhanced the effects of alcohol. Linnoila and Mattila (53) have published a compilation of their findings in which they report the results of a number of studies they conducted to investigate interactions between centrally active drugs and alcohol on driving skills. The total subject population number 1,600; the drugs included: minor tranquilizers (diazepam, chlordiazepoxide, chlormezanone); major tranquilizers (thioridazine, haloperidol, flupenthixol); hypnotics (nitrazepam, ethinamate, bromvaletone); anticholinergics (atropine, glycopyrrhonium); isoniazid; and ethanol.

The results of Lawton and Cahn (54) at first seem to be contradistinctive from those of Linnoila and Mattila regarding diazepam-alcohol interaction. In this 1963 study 20 male subjects were given a battery of four psychological and psychomotor tests on the fourth day of medication with each of four treatment conditions: (1) placebo pill-placebo drink; (2) placebo pill-alcohol; (3) diazepam-placebo drink; and (4) diazepam-alcohol. A cancellation test, digit symbol test, addition test, and a pegboard test were administered. The results demonstrated a small but statistically significant tendency for psychomotor performance to be negatively influenced by the diazepam medication, whether with alcohol or placebo drink. There was, however, no evidence to suggest a potentiating decrement of performance with a combined dosage of diazepam and alcohol. One must keep in mind that this study was conducted under the conditions of semi-chronic drug dosage, whereas Linnoila's and Mattila's were acute dosage studies. As in the case of antidepressant (amitriptyline)-alcohol co-administration previously outlined (Antidepressant Section), chronic administration may lead to an acquired tolerance that lessens or eliminates the drug-alcohol additive effects.

Loomis and West (55, 56) have studied the effects of chlorpromazine, meprobamate, and secobarbital, among other drugs, in a simulated driving task. The results of this investigation indicated that chlorpromazine produced impairment of performance after a delayed onset. Meprobamate impaired performance two hours after the first dose and

one hour after the second. Secobarbital, a sedative/hypnotic, produced a prompt intense impairment of performance, which continued throughout the remainder of the day.

Betts, Clayton, and Mackay (57, 58, 59) have investigated the effects of certain tranquilizers and small amounts of alcohol on driving performance. A double-blind study of the effects of chronic administration of four tranquilizers upon performance of low-speed vehicle-handling tests was carried out. Three of the drugs (chlordiazepoxide, amobarbital, and trifluoperazine) produced significant changes in performance but there was little potentiation of the effect with alcohol (50 mg %).

Kielholz *et al.* (60, 61, 62, 63) conducted a series of investigations into the effects of tranquilizers and hypnotics, alone or in combination with alcohol, on direct road driving ability, employing either volunteers from the Basel police force or 200 different age healthy volunteers. Different doses of the tranquilizers (chlordiazepoxide and meprobamate) and the hypnotics (phenobarbital and methyprylon) were administered, as was placebo. Statistical evaluation of the results showed that lower doses of the tranquilizers did not significantly influence driving ability or the effects of alcohol. Larger doses, while not affecting driving ability, did significantly enhance the effects of alcohol. Both hypnotics led to a decline in driving performance, and both enhanced the effect of alcohol.

In 1957, Marquis *et al.* (64) reported a series of experimental studies on the behavioral effects of meprobamate on normal subjects. The primary finding of these studies was that meprobamate alone, even in double the usual dosage, produced no behavioral toxicity in the subjects as measured by tests of driving, steadiness, and vision. The study also indicated that while alcohol definitely impaired performance on some tests, combining meprobamate with alcohol did not significantly add to this unfavorable effect on any test. The authors concluded that the data gave no grounds for preventing persons under the usual dosage of meprobamate from driving automobiles, or even from driving under meprobamate after drinking alcohol in amounts that would not ordinarily affect driving ability.

7.2.7 Cardiovascular Preparations - Beta Adrenergic Blocking Agents

Tetsch *et al.* (65) evaluated the traffic-fitness and reaction times in patients upon whom minor surgical procedures under local anesthetics were undertaken. The elected reaction times with or without β-receptor blockers were determined and the results compared with those of subjects premedicated with diazepam and atropine. The results showed that the β-receptor blockers (propanalol, pronetholol) did not influence psychomotor capabilities.

Goldman *et al.* (66) investigated the effect of β-adrenergic blockade and alcohol on simulated car driving. Their study was designed to determine whether alprenol, a β-adrenergic blocking agent, would affect cardiac action precipitated by the stress of driving, and whether it would impair driving, alone or in combination with alcohol. Six healthy volunteers took part in the trial, which was designed as a double-blind cross-over comparison with placebo. Alprenolol (100 mg) and placebo were given in random order in a single oral dose, following a light breakfast on two subsequent days. Ninety minutes later the subjects performed in a Link Trainer for simulated driving. Between the first and second run, 100 ml of whiskey diluted in soda water was taken during 15 minutes. The second run was performed using a different film. The results indicated no

significant differences in driving errors between drug and placebo, either with or without alcohol. Thus, the authors concluded that alprenolol may be of benefit to drivers with ischemic heart disease, for it does not significantly impair performance nor potentiate the effects of alcohol.

7.2.8 Parasympathomimetic Agents

Twenty subjects in different age groups were examined by Lindstrom *et al.* (67) in studying the effects of topical 2% aqueous pilocarpine on normal occular dynamics. Considerable individual variability in response was noted. Maximum effects on visual acuity, accommodation, and refraction were produced in younger subjects, with older subjects exhibiting less marked changes. The most significant change was an initial decrease in visual acuity for distance. All subjects demonstrated characteristic miosis without significant reduction in peripheral fields; in addition, they all experienced some reduction in dark-adaptive ability.

7.2.9 Parasympatholytic Agents

Linnoila (68) has conducted an experiment in which atropine 0.5 mg and glycopyrrhonium 1.0 mg in combination with alcohol or a placebo drink were administered double blind to 170 healthy volunteers, and certain motor skills were measured (a choice reaction test, two coordination tests, and an attention test). The agents were administered 30 min. before the motor skill tests and the tests were repeated 90 and 150 min. after dosing. The experimenter reported that both atropine and glycopyrrhonium, at these doses, shortened reaction time and left coordination either unaffected or slightly improved. However, these agents, or alcohol alone, impaired attention. The combination of the parasympatholytics and alcohol further impaired attention, leaving reaction times and coordination unaffected. Moylan-Jones (69) has assessed the effect of a large parenteral dose of atropine sulfate (6 mg) in 23 adult male volunteers on tasks including hard labor, skilled work, the use of instruments and tools, and shooting. Impairment of performance was seen in these tasks under the influence of the drug; this effect was statistically significant only in some of them. Drowsiness occurred in 21 men and perceptual disorders were common, but two men were almost completely resistant to the effects of the drug.

7.2.10 Psychostimulants

Caffeine, nicotine, methylphenidate, and magnesium pemoline can all act as psychostimulants, with the first two agents being in widespread use through the consumption of coffee (or tea, soft drinks, etc.) and tobacco. Orzack *et al.* (70) have compared the effects of three of these. The effects of magnesium pemoline (20 or 50 mg) on the performance of a nonmotivated task which required continuous attention were compared to those of caffeine (100 or 200 mg), methylphenidate (15 mg), or placebo. Ten unhospitalized volunteers were tested six times, once for each treatment. The investigators reported that the significant increase in errors which occurred under placebo conditions did not occur with 50 mg magnesium pemoline, with 200 mg caffeine, or with 15 mg methylphenidate. Regina *et al.* (71) have investigated the effects of caffeine on alertness in simulated automobile driving. Thirty minutes after ingesting 200 mg of caffeine or a placebo, each of 24 male subjects operated an automobile simulator for 90

minutes. Immediately thereafter, the subject ingested a supplemental dose of the medication taken initially (200 mg of caffeine or placebo), and then drove for another 90 minutes. The investigators reported that both the initial and the supplemental doses of caffeine significantly enhanced performance, beyond that found with placebo, on each of four alertness measures.

Alcohol-caffeine interaction studies have yielded mixed results. Rutenfranz *et al.* (72) reported, in 1959, that the combination of 500 mg/kg of ethanol with 9 mg of methamphetamine or 200 mg of caffeine had no effect on the metabolism of ethanol in humans, although some of the adverse behavioral effects of the ethanol were reversed. Forney & Hughes (73) in 1964 reported that caffeine (500 mg) was ineffective in antagonizing alcohol, and, in some of the tests they administered, alcohol and caffeine combinations caused a greater impairment than could be expected from the individual actions of the drugs.

Frankenhaeuser *et al.* (74) have investigated the behavioral and physiological effects of cigarette smoking in a monotonous situation. Sustained performance in a visual reaction time test was examined in 12 moderate smokers. In a control condition without smoking, efficiency decreased over a time. This is an example of a withdrawal or letdown effect. In a condition where three cigarettes were smoked at 20-minute intervals, the subjects were able to maintain their initial level of performance throughout the session, mean reaction times being significantly shorter in the smoking situation than in the control condition. Myrsten *et al.* (75) in a subsequent study examined performance of simple visual and choice-reaction time tests by six healthy habitual smokers. Results from a non-smoking condition and a condition in which each subject smoked four cigarettes indicated that smoking had a beneficial effect on performance efficiency in both tasks for these subjects, presumably demonstrating a letdown or withdrawal effect when habitual smokers are not presently engaged in smoking.

7.2.11 Psychotropic Agents

Weil *et al.* (76) reported, in 1968, their attempt to discern some effects of marijuana in man. In a controlled laboratory setting, employing a double-blind crossover (Latin-square) experimental design, the experimenters concluded that in a neutral setting persons who are naive to marijuana do not have strong subjective experiences after smoking low (.5 g; approximately 4.5 mg THC) or high (2.0 g; approximately 18 mg THC) doses of the drug; the effects they do report are not the same as those described by regular users of marijuana who take the drug in the same neutral setting. Marijuana-naive persons did demonstrate impaired performance on simple intellectual and psychomotor tests after smoking marijuana, the impairment being dose-related in some cases. Regular users of marijuana did get "high" after smoking marijuana in a neutral setting but did not show the same degree of impairment of performance on the tests as did the naive subjects; in some cases their performance even appeared to improve slightly after smoking marijuana. Marijuana increased heart rate moderately, with no change in respiratory rate. No change in pupil size occurred in short-term exposure to marijuana, although there was some dilation of conjunctival blood vessels.

Isbell *et al.* (77), in 1967, administered synthetic THC [(-)Δ^9-trans-tetrahydrocannabinol] to chronic users. At doses of 120 mg/kg orally or 50 mg/kg by smoking, subjects reported this drug to be similar to marijuana; at higher doses (300 to 400 mg/kg orally or 200 to 250 mg/kg by smoking, psychotomimetic effects occurred in most

subjects. The investigators characterized these effects as marked distortion in visual and auditory perception, depersonalization, derealization, and hallucinations.

Kielholz *et al.* (78) conducted a double-blind study employing 54 volunteers who were tested for their car-driving ability before and after taking THC at doses of 350, 400, or 450 mg/kg and a placebo. They reported that THC changed (worsened) adaptability, especially if there was simultaneous stress when rapid decisions and actions were required; prolongation of reaction time and an increased frequency of wrong and inadequate reponses were also observed. The authors concluded that the degree of impairment depended in part on the initial personality structure and individual effects of the drug on basic mood and attitude.

In a double-blind study conducted by Tinklenberg *et al.* (79), time production tasks and clinical tests of memory funtion were performed by 15 normal subjects given placebo and "social" doses of ethanol and marijuana with a calibrated THC content. Using the subjects as their own controls, it was found that, compared to alcohol and placebo, marijuana induced a significant underproduction of time intervals (i.e., a few seconds felt like many seconds), suggesting an acceleration of the internal clock. At these dose levels, there were no significant changes in memory function, but during marijuana intoxication, some consistent trends toward greater impairment of tracking information over time were noted.

Manno and Forney *et al.* have conducted a series of experiments on marijuana's behavioral and physiological effects. In one of these (80) it was found that the high dose (5.0 mg) of the THC-calibrated marijuana produced significant impairment in performance of both mental and motor tasks; alcohol induced an additional effect. Various subjective effects were noted here, and in another experiment (81), and were dose dependent. Impairment of performance with low doses of marijuana was also noted by this team (82) in an experiment reported in 1973.

A series of experiments to examine marijuana effects on driver performance have been undertaken by Moskowitz *et al.* In one experiment (83) performance in a complex driving simulator under four marijuana dose levels was examined. Car control and tracking appeared to be uninfluenced, but significant dose-related impairment was found on a visual recognition task simulating the search-and-recognition aspects of driving. The investigators felt an additional study (84) of sensory signal detection supported the view that the perceptual deficit induced by marijuana involves a decrease in discrimination sensitivity. In this study detection of peripheral light stimuli was examined with 12 subjects under four treatment levels of smoked marijuana. Marijuana, they concluded, severely impaired detection performance; the decrement was linearly related to dose. The visual autokinetic phenomena were also examined (85) and the amount of apparent movement was greatly increased under the two highest doses. In another set of papers, the authors report that marijuana does impair visual perceptual performance; Moskowitz has hypothesized that marijuana may produce brief drop-outs of attention (86).

Rafaelson *et al.* have outlined his team's experimentation with cannabis and ethanol on simulated driving in a series of papers (87, 88, 89, 90, 91). Simulated car driving was studied with oral administration of cannabis resin containing 4% THC in three doses equivalent to 8, 12, and 16 mg THC. Alcohol was given orally in one standard dose of 70 g. Both cannabis and alcohol increased break time and start time, whereas alcohol increased, and cannabis decreased, the number of gear changes. Mean speed was un-

changed, but bigger variations in actual speed were observed with both drugs. The investigators reported that cannabis showed a stronger effect than did alcohol on the estimation of time and distance. The effect of cannabis was more marked on the "subjective" than on "objective" estimation. A dose-response effect of cannabis was seen. They concluded that cannabis has pronounced effects on some skills and judgments essential for driving and that cannabis and alcohol produced two different kinds of intoxications.

A five-minute contour tracking task was performed before and after receiving placebo or orally administered marijuana calibrated to a THC content of 20 mg in a study conducted by Roth *et al.* (92). The error patterns of 19 young male subjects who received placebos and 18 who received marijuana were compared. After marijuana there was an increase in total errors as measured by the standard deviation ($P<0.01$) and the mean deviation ($P<0.02$) error scores. The investigators reported that although marijuana is reputed to create a fluctuating effect, under the conditions of this experiment the variability of error scores between 15-second time periods in the marijuana group was not significantly greater than in the placebo group. In addition, the marijuana deficit did not show significant time trends during the task.

Ling (93) has studied the effects of cannabis, alone or in combination with alcohol, on certain perceptual-motor skills related to driving. Preliminary results indicate that alcohol alone at 50 mg% BAC has little effect on performance, but there was a marked inter-subject variation in performance after smoking the low cannabis dose. The high dose of cannabis induced an increased reaction time, acquisition time, and settling time. The combination of alcohol and either dose of cannabis resulted in much worse performance times than those observed with either agent alone. The author concluded that cannabis and alcohol can enhance the effects of the other drug, and the combined use of these agents can result in decreased psychomotor performance.

Binder (94) has studied the effects of marijuana smoking and various levels of blood alcohol upon several components of the driving task. To gain certain advantages of the epidemiological method in the experimental setting, subjects were recruited from bars and parties where they had been drinking alcoholic beverages or smoking marijuana in a manner and amount that was customary in that context. The investigator reported that performance decrement increased with blood alcohol content, that differences in performance found under alcohol were in evidence among the same subjects in non-alcohol trials, that marijuana produced performance decrement but apparently to a much lesser degree than alcohol, and that experimenters could predict the motor performance of the drinking subjects by observation of their behavior just prior to the experimental run.

The effects of marijuana, alcohol, and no treatment on simulated driving performance was investigated in experienced marijuana smokers by Crancer *et al.* (95). The experimenters reported that subjects experiencing a "social marijuana high" accumulated significantly more speedometer errors than when under control conditions, whereas there were not significant differences in accelerator, brake, signal, steering, and total errors. The same subjects intoxicated from alcohol (BAC 0.10 percent) accumulated significantly more accelerator, brake, signal, speedometer, and total errors than under normal conditions, whereas there was no significant difference in steering errors. The investigators concluded that impairment in simulated driving performance did not seem to be a function of increased marijuana dosage or inexperience with the drug.

Dott (96) has studied the effect of marijuana on risk acceptance in a simulated passing task. Twelve male marijuana users operated an optical driving simulator under a control condition and after smoking crude marijuana leaf at estimated dosages of THC of 0 mg, 11.25 mg, and 22.5 mg. During each test session, each subject was given the opportunity to pass a lead car with the assistance of a passing aid device under conditions of varying risk. During several of these passing trials, there arose an emergency condition that required immediate response in order to avoid an accident. No differences in performance were noted between the non-smoking and placebo (0 mg THC) conditions. Subjects under the influence of marijuana (11.25 or 22.5 mg) completed fewer passes and took more time to make the elective decision as to whether to pass, but did not have more accidents. It was concluded that chronic users under the influence of marijuana are less likely to accept risks than users not under the influence of marijuana.

Smiley (97) examined the combination of alcohol (0.06% BAC) and marijuana, in comparison to that level of alcohol alone or a placebo, using an instrumental car and young drivers (age 19–27). Mean driving speed decreased in the order: placebo - alcohol - alcohol + marijuana, while mean steering movements increased in the same order. Peak frequency increased in the order: alcohol - alcohol + marijuana - placebo. The author concludes that alcohol plus marijuana can influence various aspects of driving in different ways.

Klonoff (98) has reported the effects of low and high doses of marijuana on driving performance in both a restricted, traffic-free area (i.e., a driving course) and on the streets of Vancouver (British Columbia, Canada), including the downtown area, during peak hours of traffic flow. He reported that the smoking of marijuana by human subjects had a detrimental effect on their driving skills and performance in a restricted driving area; this effect was even greater under normal conditions of driving on city streets. The effect of marijuana was not uniform for all subjects, however, but was in fact bidirectional; whether or not a significant decline occurred in driving ability was dependent both on the subject's capacity to compensate and on the dose of marijuana. He concluded that for those subjects who improved their performance, the explanation may lie in overcompensation, and possibly the sedative effect of the drug.

7.2.12 Sedative/Hypnotic Agents

As mentioned in Section 7.2.6, many sedative/hynotics, particularly the barbiturates, have been employed as tranquilizers. Thus, some experiments involving secobarbital (Loomis and West (99, 100)), amobarbital (Betts, Clayton, and Mackay (101, 102, 103)), phenobarbital and methyprylon (Kielholz (104, 105, 106, 107)) have been outlined in that section.

Siegler *et al.* (108) compared the effects of several commonly used hypnotic drugs on psychomotor performance in the pursuit rotor test. Six medical student volunteers received each of the following at bedtime: 500 mg and 300 mg ethchlorvynol, 100 mg secobarbital, 500 mg glutethimide, 1,000 mg chloral hydrate, and placebo. The drugs were taken in a varied but systematic sequence for a total of six test nights per subject. Ten trials of the pursuit rotor at both 30 and 60 rpm were given to the students at bedtime (immediately before taking the medicine), two or three hours later (awakened from sleep), and the following morning after natural awakening. A two- or three-day "washout" period was used between test nights. The midnight test results indicated

that 500 mg glutethimide, 500 mg ethclolrvynol, and 100 mg secobarbital caused significant impairment of psychomotor function; 300 mg ethcholroynol and 1,000 mg of chloral hydrate were tolerated without impairment. The morning test results indicated that 100 mg secobarbital, 300 mg ethcholrvynol, and 1,000 mg chloral hydrate significantly enhanced performance, while 500 mg glutethimide significantly impaired it. The investigators concluded that if fine-movement coordination is required during nocturnal awakening and in the morning, chloral hydrate and 300 mg ethchlorvynol proved to be superior by this testing technique to the other hypnotic dosages used.

Walters and Lader (109) reported a double-blind study of ten normal subjects, in which hypnotic doses of butabarbital (100-200 mg) and nitrazepam (5-10 mg) caused a definite hangover 12 hours after the administration of the drug, accompanied by psychological impairment and electrophysiological changes.

The relative effects of ethchlorvynol, glutethimide, secobarbital, and placebo on mental and motor performance were measured in subjects aroused after four and eight hours of drug-induced sleep, by Kaplan *et al.* (110). Mental performance was measured with a delayed auditory feedback system utilizing nine separate tests. After four hours there was some impairment of mental activity with glutethimide, compared to each of the other three drug treatments; less variation in mental performance was found with these drugs. After eight hours, mental acuity was generally better after placebo than after ethchlorvynol, glutethimide, or secobarbital. Attentive motor performance was measured with a Pursuit Meter. After four hours there was significant motor impairment in two tests with glutethimide compared to secobarbital, and in one test compared to ethchlorvynol. After eight hours, there was a trend towards greater impairment of motor performance by secobarbital than with the other drugs.

Sambrooks *et al.* (111) have investigated the effects of two hypnotic drugs, nitrazepam and flurazepam, on performance of visuo-motor tasks. They reported that accuracy of the tests was not impaired, although nitrazepam caused a significant increase in response latency one hour after ingestion compared to flurazepam and placebo conditions. Flurazepam was found to have a more consistent effect on the response times of individual subjects than did nitrazepam.

In an experiment discussed earlier, Bradl (112) investigated the effects of a hypnotic, methaqualone, and sympathomimetic agent, ephedrine, on the optical reaction time of man. Physiologically caused symptoms of fatigue considerably lessen the reaction response; this effect could be drastically enhanced by administration of methaqualone.

Nine healthy male subjects were given 200 mg of phenobarbital, 200 mg of methyprylon, or placebo, in combination with alcohol (0.72 gm of pure alcohol per kg body weight) in an experiment conducted by Servais *et al.* (113). The subjects were studied over five-hour periods using a test battery consisting of various physiological recordings, performance tests, and self-ratings. The results showed that both of the hypnotic agents acted synergistically with alcohol.

Kornetsky and Orzack (114) have reported that on self-paced performance tests where sustained attention is not necessary, secobarbital caused more decrement in performance than did chlorpromazine, a major tranquilizer. In contrast, chlorpromazine caused more decrement in performance than did secobarbital on experimenter-paced performance tests where sustained attention is necessary.

7.2.13 Miscellaneous Agents

A few agents, because of their actions, use, or occurrence, deserve mentioning, although they are not part of the major categories of drugs most often investigated with regard to driving safety.

Seewald *et al.* (115) reported in 1970 that in a study of 235 women, ages 20-40, taking oral contraceptive medication on a chronic basis, reaction time was significantly increased.

Codeine is a narcotic antitussive agent employed in many "cough and cold" preparations. The effects of 25 mg and 50 mg of codeine on simulated driving have been investigated by Linnoila and Mattila (116) and Linnoila and Hakkinen (117), respectively. Both doses increased collision frequency, with 50 mg of codeine resulting in a measurably greater increase than 10 mg of diazepam. Codeine given in combination with alcohol was found to further increase the number of collisions, cause negligence of the rules (instructions), and serious steering errors—a new phenomenon.

A number of experimenters have investigated the effects of carbon monoxide on driving ability, employing a variety of tests ranging from simple behavioral to simulated driving to actual driving on a closed or open course. This environmental toxicant (pollutant gas) is felt to cause detrimental effects by some investigators at approximately the same level that others feel it is exerting no deleterious or compromising effect.

O'Donnell *et al.* (118, 119) using carbon monoxide (CO) levels of 0, 50, 200, and 250 ppm, which yielded carboxyhemoglobin (COHb) levels from 0.96 to 12.37%, found that low-level exposure did not result in a performance decrement of the psychomotor tasks they administered.

In a study by McFarland (120) subjects were exposed to low levels (700 ppm) of carbon monoxide until COHb levels of 6%, 11%, and 17% were reached, and then were tested as to their ability to perform both selected driving laboratory tests of visual response and control reactions and over-the-road vehicle driving. He reported that the results indicated that a 6% COHb level had no effect on driving ability, and that COHb levels of 11% and 17% did not appear to seriously affect the ability to drive motor vehicles, as measured by the tests administered in this study.

Mikulka, O'Donnell *et al.* (121) found no functional impairment of simple applied performance tasks after low-level carbon monoxide exposure.

An article in *Eye, Ear, Nose and Throat Monthly* (122), 1973, reported on research being carried out at Ohio State University with high levels of COHb. Carbon monoxide blood levels of 7 to 14% produced mild variations in eye movement patterns, car-following spacing, steering wheel reversals, and gas pedal usage, and the effects did not necessarily become more pronounced at these high levels. It was concluded that the subtle performance variations observed in the study did not create safety hazards during test runs conducted at speeds of 30 and 50 mph.

In an experiment conducted by Wright *et al.* (123), 80 ml of CO or air was administered double blind to 50 adults. Blood COHb levels increased by 3.4% in those receiving CO. Brake reaction time, night vision, glare vision, glare recovery, hand-steadiness, and depth perception all showed small and individually insignificant deterioration in the group receiving CO. During operation of a driving simulator, the CO-exposed group showed a highly significant deficit in "careful driving" skills, with a statistically insignificant facilitation of emergency-type movements. It was concluded that since a

3.4% increase of COHb level was sufficient to prejudice safe driving that there is a need to revise the permitted eight hour industrial CO exposure level of 50 ppm.

Ray and Rockwell (124) reported that estimated automobile concentrations of CO result in 8% of the nonsmokers having blood COHb concentration levels greater than 7%, and 4% having greater than 14% COHb, assuming they were exposed for 2 hours or more. Smokers would have COHb levels up to 15% higher than these, depending on their smoking habits. They concluded that several of the effects of the COHb studied, such as increase in response times to sensory detection-tasks of relative velocity and taillight brightness discrimination, and increases in the variance of several performance measures including velocity, headway, gas pedal reversals, and gas pedal deflection, were detrimental to driving performance.

Human volunteers were exposed to CO at concentrations of <1, 25, 50, 100, 200, 500, and 1,000 ppm for periods of 1/2 to 24 hours in an experiment conducted by Steward (125) *et al.* No untoward effects were observed in sedentary males exposed to 100 ppm for eight hours. Exposures producing COHb saturations greater than 15% to 20% resulted in delayed headaches, changes in the visual evoked response, and impairment of manual coordination.

Haider *et al.* (126) have emphasized the potential deleterious effects of low doses of CO (50, 100, 150 ppm) on human psychomotor functioning. In a test of time estimation, subjects had to estimate the duration of repeatedly presented tones. The results indicated that at 50 ppm CO the number of ignored signals was greater than in normal air. At 150 ppm CO the number of ignored signals was almost twice as high as at normal air.

Weir and Rockwell (127) have conducted an investigation of the effects of COHb on human performance which has involved the testing of 40 subjects on the highway with a battery of driving situations and/or laboratory tasks related to driving skills. Twenty-four tasks were developed and over 130,000 observations taken to study human performance at COHb levels of nominally 0, 7, 14, and 20%. The investigators reported that the results suggested that consistent patterns of performance change with increased COHb levels. Differences observed with 20% COHb levels were directionally preserved with lower (7 and 14% COHb) levels but with smaller magnitudes. The results, however, did not suggest a low COHb level where all performance measures are first affected. *Rather, the magnitudes and directions of performance changes appeared to be highly dependent on the particular task and protocol employed.* As expected, laboratory dual tasks (where the subject is required to perform two tasks simultaneously) exhibited performance differences at lower COHb levels than more simple tasks. The researchers suggested that since accidents are probably more prevalent when the attention and control demands on the driver are greatest, the dual task results may be more important than results in routine, over-learned situations. Strong correlations between performance on simple laboratory tasks and COHb levels were not observed. The authors categorized driving performance into three levels: visual, control and dynamic response. The results of this research, they concluded, suggest that the largest-magnitude effects with increased COHb levels occur at the early stages of information processing. Visual and psychomotor control levels were, in general, the first measure to be affected by COHb.

Ettema *et al.* (128) have investigated mental performance after exposure to certain chemical agents. Their results indicated that exposure to CO (175 ppm) for three hours,

producing a COHb level of 10%, or to trichloroethylene, a common industrial solvent (175 or 300 ppm) , for three hours, did not decrease mental performance.

Vernon *et al.*(129) have evaluated the effects of breathing 0, 100, 300, and 1,000 ppm of trichloroethylene on visuomotor performance, as measured by six standard tests. The results indicated that trichloroethylene, under the experimental conditions, adversely affected three tests of visual perception and motor skill at the highest concentration, but had no significant effects at the lower concentrations.

The effects of dichloromethene (0.03 and 0.08% by volume), another industrial solvent, were studied in three experiments on 42 subjects conducted by Winnere (130) *et al.* Both concentrations impaired vigilance and critical flicker frequency. The inhalation of 0.08% dichloromethene, they reported, resulted in a pattern of generalized impairment of psychomotor performance. Motor speed of gross hand and arm movements was reduced, reaction times for simple and complex responses were lengthened, coordination and precision of complex movement patterns as well as the ability to react quickly to changing stimulus configurations were impaired, and steadiness and control precision of static as well as dynamic positioning movement was disturbed.

7.3 Relevance of Experimental Research Studies

The body of experimental literature, taken as a whole, may be said to demonstrate that drugs do affect human behavior and performance. The literature on drug effects is extensive. While drug effects can be defined in operational terms, confounding variables such as motivation, set, and setting are modifying influences on the reliability of tests and the validity of the results.

It is not clear that the test results are valid indicators of drug effects in real-world situations. Further, it is not clear what relationship exists between test performance, driver performance, and traffic crash causation.

The experimental evidence points to the conclusion that a pure and simple predictive measure of drug effects on human performance cannot be obtained.

The experimental results, taken by themselves, do not establish that a particular drug is, in fact, a causative factor in traffic crashes.

The experimental evidence represents a set of indicators suggesting the need for further examination of drug effects in the highway safety setting. The experimental results may be useful in establishing priorities for epidemiological inquiry and suggesting the dimensions of investigations.

Experimental evidence of significant behavioral impairment arising from the pharmacological action of a drug, coupled with the knowledge that the drug is in common use by the driving population, does suggest that investigation should be undertaken to determine the role the drug may play in traffic crashes. Experimental results can also assist in explaining the relevance of epidemiological findings by relating drug presence to behavioral responses.

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8.0 EPIDEMIOLOGICAL STUDIES

This chapter presents a discussion of selected recent studies that examine relationships between drugs and traffic crashes.

A brief examination of the available literature quickly reveals several major limitations of existing research. First, there is a relative paucity of hard data; less than 30 reports appear in the indexed literature in the last 10 years. Second, the vast majority of these reports represent very limited efforts, so that it is unlikely that extrapolations to the general driving or accident population can be made. Third, the methods employed in some of the studies raise significant questions about the overall validity of their data and conclusions.

The following sections discuss methodological issues, present illustrative findings reported in a selected set of studies, and summarize the relevance of existing epidemiological research in defining the problem of drugs and driving.

8.1 Epidemiological Research Issues

8.1.1 Types of Epidemiological Research

The basic goal of epidemiological research, in this area, is to define the role that drugs play in traffic crash causation. To this end, studies have been undertaken to determine the nature and extent of drugs present in the crash population and in the general driving population. Some studies attack the problem directly by selecting a sample of drivers from the crash population and from the driving population and objectively determining drug presence through the analysis of body fluids. The number of these studies is extremely limited. More commonly, researchers have attempted to obtain data on drug use (and possible presence) indirectly. This may involve the use of questionnaires to determine drug use patterns and/or reliance on secondary sources for information about drug use patterns of drivers.

Another indirect approach has been to retrospectively examine the driving records of individuals known to be drug users and compare their records with other drivers.

Each of these approaches has methodological problems. The following section discusses common methodological issues to establish a frame of reference for review of existing research and the design of future efforts.

8.1.2 Methodological Issues in Epidemiological Research

A basic problem that characterizes most epidemiological research in this area is that existing knowledge of experimental design has not been rigorously applied. In some cases this may reflect the pressures that limited funding places on the researcher. Many of the studies use existing data sources which contain errors. Studies which collect data independently are frequently unable to obtain "clean samples" because of practical real-world constraints such as the lack of cooperation of the driving public. The combination of lack of rigor in design, implementation, and interpretation, coupled with the real-world constraints endemic to this area of inquiry, have resulted in a body of literature that is of a far lesser quality than desired.

Some of the major methodological problems encountered in the existing literature are set forth below as illustrative of matters that must be considered in reviewing research reports.

Sample Selection: The nature of the research problem dictates that a sample of drivers be used, as opposed to a complete census. In most studies reported in the literature, significant questions can be raised about the validity of the sampling procedures used. Samples of convenience are common and clearly random samples almost non-existent. This initial bias of the data must be examined in assessing the validity of the results. The problem of sample selection is not limited to the selection of the study group but applies to the selection of control groups as well.

Studies that have examined the driving records of drug users and compared them with the driving population have reached differing conclusions. The method of selection of the comparison population can account for these differences. Similar problems arise when a general driving population sample is selected for comparison with a sample of accident-involved drivers. Samples from different population universes should not be compared.

It is common for researchers to present a warning of sampling problems. The data, however, are then examined using conventional statistical techniques which presume a random sample. Extreme caution must be exercised in evaluating such research studies.

Data Collection: A series of problems accompanies the collection of data in the reported epidemiological studies. First, the basic methods of collection may not be reliable. Studies that rely on self-reporting or questionnaires have been shown to be of unknown validity; generally under-reporting occurs. While this criticism is generally made of questionnaire approaches, it has special importance in this area. Many subjects are not aware of the nature of drugs they are taking and have no comprehension of dosage or potency. Illicit users may be expected to face some pressure to report incorrectly.

This results in the second problem, which is that of missing data. Almost all the studies report dropping subjects because of missing data. This may arise from an initial failure to cooperate or some problem in data collection or reporting. In the absence of clear evidence that the non-participants are identical to the participants it cannot be assumed that the data are representative.

A third problem, which is associated with studies using analytical methods to determine drug presence, relates to the collection of the specimen to be tested. Many of the studies have relied on data collectors (often untrained) who are not under the direction of the individuals performing the drug analyses. It is not unusual to find a variety of methods used to collect specimens and for contamination to occur. Lack of rigorous control over the collection of analytical specimens can result in either false positives or false negatives, thereby reducing the validity of the data.

Drug Detection: Studies that use analytical methods to objectively determine drug presence present special methodological problems. The wide diversity of agents that have the potential to impair driving behavior makes it unfeasible, because of many considerations, to test for every potential drug. Thus, studies invariably limit analytical testing to a selected set of drugs. This decision means that negative results, or reports that drugs are not present, are valid only for a limited number of drugs, at best. Other drugs, not tested for, may or may not be present in the sample population.

This defect would not be significant if there were a wide variety of studies that had examined diverse driver populations for a broad spectrum of agents. Unfortunately, the studies are very limited in number, scope, and range of drugs examined.

An examination of the methods used in some of the studies raises further questions

about the validity of the data reported. In some cases, the testing methods used would not detect the most likely form of the drug; the fact that some drugs act through a metabolite has been previously noted. Several studies that purport to test for drugs made no provision for testing for metabolites. Thus, negative findings cannot be presumed to be conclusive.

Other studies have used tests that are quite unsophisticated and that may result in false positives. These limitations make it necessary to carefully examine each study and the findings.

Data Analysis and Interpretation: Frequently, the problems noted in the preceding paragraphs are compounded during the analysis phase of a study. Biases created by sampling error, missing data, test selection, or other factors may be acknowledged by authors, then ignored in the presentation of the results. Perhaps the most consistent problem appearing in the reports is the implication that the fact that no drug was detected in a particular case means that no drug was present. This inference usually develops through the presentation of data in what is an apparently straightforward manner. The inference may not be intended by the authors but it is frequently drawn by readers and reviewers.

A second problem arises when standard statistical procedures intended for use with random samples are utilized to examine data generated from a non-random sample. The tests may be applied and results stated in standard statistical nomenclature. This tends to lend an aura of credibility to the results that is unwarranted because of the initial validity problems. Before any statistical results are accepted, the data base should be examined for validity. While many of the studies have not utilized statistical testing, data have been presented using quasi-scientific notation. Frequently, sample sizes have been very small (less than 100 cases) and the results cited in percentages. Extreme caution must be exercised in interpreting such data, as it is unlikely that they can be generalized to a percentage of the total population.

A third problem arises in the reporting of findings when drugs are improperly categorized. One finds anxiolytic agents such as chlordizepoxide, diazepam, or meprobamate lumped with antipsychotic agents such as chlorpromazine under a general heading such as "tranquilizers." One study classified an antihypertensive agent with no central nervous system activity as a "tranquilizer," an antianginal agent and digitalis as "stimulants and anoretic agents," an antihistamine as a "sedative and hypnotic," and colhicine (an antigout drug) as an "analgesic and antipyretic." This lack of rigor in reporting contributes to confusion in the interpretation of results.

Finally, in some studies researchers have sought to present their findings and concerns in a most positive fashion. The result has been summary or conclusionary statements that go beyond the data actually developed in the course of the study. This phenomenon is not limited to this area of inquiry. It is illustrative, however, of the need to carefully examine the methods, data, and findings of each study before adopting the conclusions.

8.1.3 Research Review Problems

As in the case of the experimental literature discussed in Section 7.1.3, considerable frustration was experienced because of the incomplete reporting methods, data, and analytical approaches used in the epidemiological studies. In many cases it could not be

determined if the analytical procedures used were adequate to achieve the stated objectives of the particular study.

The literature base in this area is difficult to examine. Many major studies have been conducted over a period of several years. Interim reports and final reports have been published that differ factually. Reports of the same studies have appeared in the archival literature and the more popular literature. Results are frequently not reported consistently. This may be due to the fact that different time periods of the study are the subject of different reports, the findings may have been simplified for a general presentation, or some particular aspect of the study may have been emphasized for a special audience. The variances do not reflect reversals of position but produce the type of confusion that is usually avoided in other areas of scientific endeavor. The literature is neither neat nor well defined.

The original literature has been reviewed by a number of researchers who have compiled summaries of work in this area. Original difficulties in interpretation have been compounded in the reviews. Again, the most common problem is the way in which negative findings are reported. The strength of the negative seems to grow with each review, so that over time it appears conclusive that a researcher "did *not* find drugs except in X cases," when all that was originally reported was that the researcher did find a drug(s) in X cases. This is a subtle but critical distinction.

Another distinction that is implicit but needs to be stated explicitly is the maxim that "correlation is not causation." The finding that a drug is present in a crash victim or driver does not, by itself, establish a causal relationship between the drug's presence, driver impairment, and crash causation. This fact is generally understood by the research community but is seldom explicitly stated in the research reports. The lack of a relationship is less well understood by the lay community and general reports of research studies often equate correlation (positive findings) with causation.

In contrast, some research reports have noted that drugs were found in crash-involved drivers but "only at therapeutic levels." Such statements are often set in a context whereby a reader would be led to believe that no impairment would exist if only a therapeutic level was present. This inference is not justified, in many cases, because therapeutic levels have been shown to have effects that impair physiological and psychological functioning.

Epidemiological research on drugs and driving is in its infancy. The state of the art of existing research is less advanced than desired. Many of the studies are fraught with methodological problems that render the findings less than conclusive. A few studies have been carefully executed and are well reported. These bright spots present hope for the future.

8.2 Epidemiological Research Findings

The following sections briefly summarize the findings of selected research studies which are illustrative of the literature. The findings and conclusions reported are those of the authors of the respective studies reached under the conditions of their experimental designs.

8.2.1 Alcohol, Road Traffic and Drugs in Denmark (1)

Wangel reported the results of a study conducted in 1960 in Denmark. The subjects

were 6,067 drivers who were required to give a blood sample as part of a medico-legal examination of a road traffic case. The blood sample was analyzed to establish a blood alcohol concentration (BAC). The subjects were asked to provide information on drug use. Comparisons of the subjects' reported drug use with BAC values suggest that drivers with BAC values in excess of .15% were significantly more likely to be acute or chronic users of analgesics/antipyretics/antirheumatics, hypnotics (especially barbiturates) and psychopharmacological agents (including meprobamate) than were drivers with lower BAC values. In contrast, no such differential in drug usage was reported for hormones, vitamins, antibiotics, sulfonamides, and other drugs not likely to have adverse effects on driving.

8.2.2 Psychotropic Drugs and the Motorist (2)

Rees reports a study that used police information to establish driving patterns of the patients of ten doctors in rural mid-Wales. The patient records indicated that of a sample size of 927 male and 263 female drivers, 3% of the males and 5% of the females had been prescribed psychoactive drugs (sedatives, tranquilizers, antidepressants) for periods exceeding 90 days, while they were reported to be operating motor vehicles. Patient records for a five-year period were reviewed. The study was published in 1966.

8.2.3 Toxicological Statistics for Ontario (3)

Gupta and Kofoed reported data compiled by the Attorney-General's Laboratory, Toronto, Ontario, Canada, for the period 1958-64. The number of persons charged with driving a motor vehicle under the influence of barbiturates increased from one per year to 18 per year; the number charged with driving while under the influence of tranquilizers increased from zero per year to seven per year. These represent cases in which the blood samples contained a drug but no alcohol.

8.2.4 Dade County Fatal Accident Study (4)

Davis and Fisk report the results of a study conducted by the Dade County Medical Examiners office during the period 1962-1966. One hundred seventy-nine fatally injured drivers were tested for drug presence, using only routine ultraviolet spectrographic analysis. Of the eight drug-positive cases, three were caffeine, one aminophylline, one an unknown barbiturate, one glutethimide, one phenobarbital, and one a secobarbital/amobarbital mixture. In four of the cases where drugs were detected, a BAC of .08% or greater was also detected. Carbon monoxide was detected in more than trace amounts in three of the drug-positive cases.

8.2.5 California Drug Study (5)

A cooperative study of the roles of alcohol, drugs, and organic factors in fatal single-vehicle accidents was conducted by several California agencies from November 1, 1963 to Ocober 31, 1965. Study cases were 1,474 single-vehicle accidents in which the driver died within 15 minutes of the crash. Of the 1,474 cases submitted for analysis, 155 were attributed to natural causes. The remainder, 1,319 cases, were attributed to injuries received in the course of the crash. In 448 of the 1,319 cases the blood for the test was contaminated or insufficient or no blood was submitted for testing. This left 871 cases

from which 99 out-of-state residents were deleted, leaving 772 cases (662 men and 110 women), who were the focus of the study.

Of the 772 drivers, 84 men and 18 women had been taking drugs. The percentage of drivers using drugs increased with age for both men and women. Women used drugs more than men, although the difference was not great. Sixty-two of the 102 drivers who tested positive for drugs had a BAC of .10% or higher.

Blood samples were screened for 12 common drugs; detections were reported as follows: phenobarbital - 32, caffeine - 29, meprobamate - 8, pentobarbital - 7, non-specified barbiturates - 6, amobarbital - 5, secobarbital - 4, butabarbital - 2, diphenylhydantoin - 2, chloridiazepoxide - 1, sulfonamide - 1, and non-identified agents - 23.

In addition to the technical report cited above, the study has been reported in other publications (6, 7).

8.2.6 Cleveland/Philadelphia Fatal Crash Study (8)

Sunshine *et al.* report a study based on the examination of blood and urine samples from 75 victims of fatal crashes in Philadelphia in 1965 and 82 similar deaths in Cayahoga County, Ohio in 1965-66. The author states that urine samples were not obtained from many of the victims. In the Philadelphia data set, 1.3% had blood carboxyhemoglobin greater than 10%, 17.3% had 5-10%, and the remainder had less than 5%. In the Cayahoga County set, 14.6% had greater than 10% blood carboxyhemoglobin, 22% had 5-10%, and the remainder had less than 5%. The only drugs reported as detected were two cases in Philadephia where barbiturates were present. Thirty-one of the subjects had BAC equal to or greater than .10%.

8.2.7 UASEUR Fatal Motor Accident Study (9)

This study examined 540 fatal crashes involving military personnel in Europe during the period 1965-67. Blood samples were obtained from 90 deceased drivers. Two-thirds of the blood specimens tested positive for ethanol; one-third had a BAC of .15% or greater. Carbon monoxide was detected in 2.2% of the cases in an amount greater than 15% saturation; in 26.6% of the cases a 1-15% saturation was reported. The remainder were free of carbon monoxide (less than 1% saturation). While chemical analyses were performed for blood levels of amphetamines, antihistamines, barbiturates, narcotics, and tranquilizers, the only reported information is that "In no case was a blood concentration greater than that considered the 'therapeutic level' found . . . "

8.2.8 Australian Patient Drug Use (10)

Milner reports a study that examined prescribing practices for 4,584 adult patients in Perth, Australia, in 1967. Patient records were examined. Patients were asked about driving and drinking habits. Milner reports that 753 of the 4,584 patients were prescribed psychotropic drugs. Of those prescribed psychotropic drugs, 85% of the men reported using alcohol and 60% were licensed to drive. The corresponding figures for women were 71% and 42%. The numbers of patients for each class of drug prescribed were as follows: tranquilizers - 335, sedatives - 280, antianxiety drugs - 188, tricyclic antidepressants - 181, stimulants - 18, and other drugs - 59. Milner concluded that 57% of the men and 35% of the women were at risk of drinking and driving while taking the drug prescribed.

8.2.9 New York State Addict Driving Study (11)

A joint study effort by two New York State agencies examined the driving records of the 6,000 certified opiate user admissions to the Narcotic Addiction Control Commission, during the period of April, 1967, to March 31, 1969. Of these, 1,245 or 20% had a driver's license or a driving record with the New York State Department of Motor Vehicles. Analyses of these records indicated that 77% of the males and 73% of the females had one or more accidents, or convictions for violation of the Vehicle and Traffic Law. The records of the male addicts showed a total of 4,465 accidents and traffic convictions, with 402 accidents involving injury or death. None of the addicts was ever convicted of driving under the influence of drugs. The study noted that only about 20% of the general driving population have any accidents or traffic convictions on their record.

8.2.10 Psychoactive Drugs and Traffic Accidents (12)

Smart, Schmidt, and Bateman report a study of the accident rates of 30 psychoactive drug abusers seen at a clinic in Toronto in 1967. Driving histories were obtained by interview for 1961-66. Accident data for 1965-66 were verified. The group included persons addicted to or dependent upon barbiturates, tranquilizers, and stimulants; half were also dependent upon alcohol. Expected accident rates per mile driven were computed for each age and sex group and the reported rates compared. The psychoactive drug abusers had accident rates about twice as high as expected for age, sex, and driving exposure. Most of the excess was contributed by those addicted to amphetamines (alone or in combination with other drugs). Those addicted to alcohol and barbiturates, barbiturates only, or tranquilizers only had lower rates than expected.

8.2.11 Santa Clara Drug Study

Finkle, Biasotti, and Bradford have reported on this detailed study in a series of publications (13, 14, 15). The study examined drug use among drivers arrested in Santa Clara County, California, during 1966-68. A total of 10,436 subjects formed the study population. Data on drug use were obtained in several different ways. First, drivers were questioned on drug use by the arresting officers. Second, blood or urine samples were screened for drugs when the subjects exhibited overt signs of intoxication but had BAC levels less than .15%. A relatively small number of cases in which the BAC was greater than .15% were screened at the specific request of the police or District Attorney because of peculiar or exacerbating factors associated with the case.

Almost 25% of the cases (2,559) had a drug involvement reported by the arresting officer or by chemical analysis. A total of 273 different drugs were encountered on 2,688 occasions. A breakdown by class of drug involved is presented in table 8-1. In 1,406 cases (13% of the total) the drugs involved were legally defined as "dangerous drugs."

In addition to the results from request by the police for alcohol and/or drug analyses, the analytical data were compiled from the fraction of cases in which BAC levels were less than .15% and evidence of intoxication existed. A total of 700 analyses were performed; 22% (159) were positive. This included 52 cases in which no drugs were indicated during the initial questioning by the arresting officers. Twenty-four different drugs were detected, as shown in Table 8-2.

TABLE 8-1

Drugs Encountered and Frequency of Occurrence

Type of Drug	*Frequency of Occurrence*
Ataractic & Ataxic Agents (Tranquilizers)	518
Analgesics & Antipyretics	315
Stimulants & Anorectic Agents	309
Hormones & Steroids	158
Sedatives & Hypnotics	193
Anti-infective Agents	143
Vitamins & Minerals	139
Antidiabetic Agents	111
Antihistamines	145
Anticoagulants	29
Analygesic Narcotics	93
Anticholinergic Agents	43
Diuretics & Uricosuric Agents	66
Antiasthmatics	62
Antiarthritic Agents	25
Antispasmodics	53
Antacids & Intestinal Absorbents	57
Laxatives	4
Miscellaneous	225

TABLE 8-2

Positive Analytical Findings

Drug	*Total Occurrences*	*Indicated By Questioning*	*Not Indicated By Questioning*
*Secobarbital	44	7	19
*Phenobarbital	35	10	11
*Pentobarbital	31	9	11
*Meprobamate	25	10	7
*Amobarbital	19	5	10
*Glutethimide	10	1	3
*Tuinal®	7	2	3
*Caffeine	7	2	2
*Salicylate	6	2	1
Butabarbital	5	3	2
Chlordiazepoxide	4	4	—
Amphetamine	3	2	1
Methamphetamine	3	—	3
Phenacetin	2	2	—
Methyprylon	2	2	—
Sandoptal®	1	1	—
Dilantin®	1	1	—
Chlorpheniramine	1	1	—
Metabolite of diphenhydramine	1	1	—
Toluene	1	1	—
Dicoumarol	1	1	—
Sulphathiazole	1	1	—
Tybamate	1	1	—
Terpin hydrate	1	1	—

*The balance of occurrences for these drugs is made up from cases in which the arrestees stated they were using a different drug than that found by analysis.

The analytical screening procedure was limited to a blood sample which ranged from 7 ml to not more than 8 ml, of which 2 ml was used for alcohol determination. The analytical scheme was designed to detect volatile drugs, strong and weak acids, and chemically neutral materials, as well as many miscellaneous drugs which are extractable into chloroform at physiological pH. The authors report that the analytical procedure would not detect a number of common drugs, including Librium®, Valium®, Thorazine®, Compazine®, Darvon®, Elavil®, Dexedrine®, Preludin®, Eskatrol®, cortisone, insulin, Dristan®, Contac®, Coricidin®, codeine, heroin, morphine, and Demerol®. Usage of these drugs is reported in the study as the arrested drivers reported use to the arresting officers.

In 77% of the cases where drugs were detected, the District Attorney issued complaints under the California Vehicle Code. Eighty-four percent of these complaints were for driving under the influence or reckless driving. The remainder were for less serious infractions. In more than 90% of the cases in which a complaint was issued a conviction resulted. Most defendants pled guilty.

8.2.12 Driving Records of Illegal Drug Users (16)

Crancer and Quiring report a study conducted in 1968 by the State of Washington Department of Motor Vehicles that examined the driving records of 302 individuals who had been arrested for use of dangerous drugs and whose police records indicated drug use since 1963. The subjects' driving records for a six-year period were examined and compared with the driving records of 687,228 persons living in the same general area.

Three groups of illegal drug users were studied: (1) narcotic users; (2) dangerous drug users; and (3) marijuana users. Accident and violation rates for each group were higher, some statistically significantly so, than those for the general population which was used for comparison. Considerably fewer of the illegal drug users had driving records free from violations and accidents than did the general population. Each of the groups studied had a larger proportion of reckless, hit and run, and negligent driving convictions than did the general population. The groups, however, had fewer violations for speeding, failure to stop, and failure to yield than did the general population. The proportions of injury and property damage accidents were comparable to the general population. No one in any of the illegal drug groups had been involved in a fatal traffic crash.

8.2.13 Trends in Drunken Driving in Finland (17)

Alha reports a study that examined urine from 110 subjects arrested for drunken driving in Finland in 1969-70. Positive findings were as follows: barbiturates - 26, benzodiazepines - 26, meprobamate - 10, solvents - 7, phenothiazine derivatives - 6; 11 other drugs were detected in 21 cases.

8.2.14 Alcohol & Drugs in Denmark Road Fatalities (18)

Naess-Schmidt reports the results of a study covering the 12-month period from July 1, 1967, to June 30, 1968, of the range of occurrence of alcohol, carbon monoxide, and drugs in 301 autopsied victims of 288 road accidents in Denmark. Presence of carbon monoxide and barbiturates was found in only a few percent of the subjects. Meprobamate, in small quantities, was seen in a few subjects, and the presence of other drugs was not demonstrable. BACs of .10% or greater were seen in 21% of the accidents.

8.2.15 Influences of Licit and Illicit Drugs (19)

Berg *et al.* reported a study conducted in Monroe County, Indiana, in 1971. Drug usage information among 24 accident-involved drivers who were college students and a control group of nonaccident-involved college student drivers was collected through interviews. Blood specimens were obtained from the accident-involved drivers and analyzed. Only two positive results were obtained, one each for protoptyline and morphine. Drug usage was statistically unrelated to the number of traffic accidents that the subjects had incurred in their driving lifetime.

8.2.16 400 Fatal Crash Study, Australia (20)

Hossack reports a study that investigated 400 accident victims dying between June, 1970, and May, 1971. Autopsies were the primary data source. Of these, 100 drivers were selected for further examination to determine the presence of drugs. Eight of these drivers were shown to have drugs present through blood testing. The results were: amphetamines - 4, barbiturates - 2, bromureide - 1, and chloroquine - 1. Seven of these eight victims had a blood alcohol level such that this alone would significantly contribute to the accident.

8.2.17 Research Triangle Study (21)

Moser, Bressler, and Williams report a study conducted by Research Triangle Institute in 1971 that examined the frequency and amount of use of drugs among 1,889 arrestees for serious crimes. The driving records of drug users were compared with the driving records of non-drug users among the group of arrestees. For this select population, the authors report that drug-using drivers have no worse driving records, in terms of accidents and convictions, than the non-drug-user drivers.

8.2.18 Dunlap Study (22)

Blomberg and Preusser report a study conducted by Dunlap and Associates of 1,562 methadone maintenance patients in New York State. Data were collected through interviews. A control group of 1,059 people was constructed by asking the subjects to volunteer names of non-addicted friends. State driver records for 718 subjects and 579 controls were obtained and analyzed.

In general, experimental subjects were no worse drivers than the controls for the entire period covered by driver records. This was so despite the fact that the subjects estimated their mileage to be at or above the national average, throughout their abuse of non-narcotic and narcotic drugs and during their methadone treatment. The subjects' reports supported the conclusion that drug abusers who drive are likely to drive immediately after using drugs. The report cautions against generalizing these results to other groups.

In addition to the technical report cited above, this study has also been reported in the archival literature (23).

8.2.19 Boston Area Study (24)

Sterling-Smith and Fell report on a study of drivers involved in 50 fatality accidents in the Boston area in 1971-72. No positive test results were reported for: salicylates,

gutethimide, or organic bases. Barbiturates were detected in 12% of the blood samples. Clinical and/or laboratory judgments indicated that 42% of the operators had been under the influence of alcohol at the time of the collision.

8.2.20 Canadian Emergency Room Study (25)

Gilbert reports a study of patients admitted to the emergency room of the Royal Alexandria Hospital, Edmonton, Alberta, Canada, during a short period in 1972. The patients studied were those admitted because of accidental injury. Blood specimens were obtained from 460 patients and tested for the presence of drugs and alochol. Interviews were conducted to determine drug and alcohol usage. Blood analysis produced positive results as follows: salicylates - 35, barbiturates - 16, diazepam - 14, chlordiazepoxide - 12, and phenothiazines - 7. The author estimates that about 25% of patients attending the emergency room will have BAC levels in excess of 15%, will be using sedatives such as barbiturates or diazepam, and 8% will be taking salicylates. That is, about 40% in all will be on alcohol or medications at the time they are seen.

8.2.21 Causal Factors in Norwegian Traffic Crashes (26)

Haffner and Lunde studied the incidence of diazepam and alcohol in 74 hospitalized accident-involved motor vehicle drivers in Oslo, Norway, in 1973. Blood ethanol and plasma diazepam concentrations were detected in 46 out of the 74 drivers. Seven had diazepam and 31 ethanol alone, while both agents were detected in eight patients. Five of those with alcohol alone had BACs below .05% and four of the seven who had taken diazepam alone were within or below a defined therapeutic range. Diazepam in excess of 300 ng/ml was detected in four patients. The author reports that sales of diazepam represent 85% of the total sales of sedatives in Norway in 1973.

8.2.22 Marijuana and Driving Among Teenagers (27)

Waller, Lamborn, and Steffenhagan report a study that surveyed drug usage and driving habits of 1,271 incoming freshman and transfer students at the University of Vermont in September, 1972. They found that forty-nine percent of the 1,271 students reported using marijuana during the previous year. A majority of marijuana users simultaneously consume alcohol, at least on occasion, and many of them have enough alcohol at those times to be impaired by alcohol alone. Among users who smoke weekly or more often, one-quarter of driving while "high" occurs under the combined effect of marijuana and medium to heavy alcohol use. Most users reported marijuana effects on driving judged to be hazardous, such as altered attention, vision, or time perception.

In an estimated 15,000 driving trips while "high" on marijuana, two crashes occurred definitely attributable and two possibly attributable to marijuana use. Also 42 persons (13% of drivers) reported near crashes while "high." *Since this is not a comparison study, it is not known whether or not this reported experience is excessive for this age group.* [author's emphasis] Drivers who encountered trouble while driving after marijuana said 59% of the time that the incidents were caused by the marijuana, 27% of the time by alcohol, and in 14% that they could not assess which drug was responsible. Data were collected by questionnaires and the analyses are based on the reported information.

8.2.23 Drug Incidence in Fatally Injured Drivers (28)

Woodhouse reports a Midwest Research Institute study that analyzed specimens of blood, urine, and bile, as well as alcohol washes of the fingers and face of fatally injured drivers. The specimens were provided by coroners who cooperated by voluntarily supplying test material. Subjects were selected by the coroners and specimens collected under their control. The blood, urine, and bile were analyzed for 46 commonly abused drugs. The fluids were extracted and screened by qualitative thin-layer chromotography. If the screening indicated a positive, quantitative gas chromotography was used for confirmation. Mass spectrometry was used if additional qualitative information was desired. Alcohol washes of the face and fingers were examined for evidence of marijuana, using thin-layer chromatographic and colorimetric methods. Blood samples were assayed for alcohol content, using a gas chromatographic method. The analytical results indicated that 58% of the drivers had ingested alcohol and 47% had BAC level of .10% or greater. Blood (682 samples), bile (526 samples) or urine (517 samples) were assayed for the presence of 46 drugs. The percentage of positive test results (in blood, bile, and urine, respectively) were as follows: sedatives and hypnotics - 2.9, 4.6, 5.2; stimulants - 1.32, 0.57, 0.58; antihistamines and decongestants - 0.15, 1.14, 1.35; tranquilizers - 0.29, 2.09, 1.35; narcotic analgesics - 0, 0.57, 0.58; nicotine - 8.4, 17.3, 54.9; aspirin - 12.8, 19.8, 22.1; salicylic acid - 1.0, 3.8, 5.6; and miscellaneous drugs - 0.44, 0, 0.38. Tests for marijuana were performed on the swabs using two methods. The first method yielded positive results in 11.8% of the cases for the hand swabs and 38.4% for the nasal swabs. When a thin-layer chromatography test was used to examine the eluted swabs the positive incidence was 1.57% for 357 cases tested.

8.2.24 Marijuana and Driving Risk Among College Students (29)

Smart reports a study that used an anonymous questionnaire to survey 296 students between the ages of 18 and 23 in Canadian colleges about marijuana and driving. Of the 296 students, 246 were drivers. The study investigated the frequency of driving, accident involvement, and driving charges after marijuana use. While 42% of the licensed drivers had used marijuana, only 62% of those reported driving soon after that use. Few reported accidents or moving violations after marijuana use, especially in comparison to after alcohol use. The frequency of reported marijuana-driving occasions was only about 35% of the reported alcohol-driving occasions.

8.2.25 Drug Involvement in North Carolina Traffic Fatalities (30)

Turk, McBay, and Hudson report a study that examined fatally injured drivers and pedestrians for alcohol and drug presence. The subjects were all over the age of 15 years, and either died at the scene of the crash or were dead on arrival at the hospital. The results reported are for the first year (1973) of a three-year study. Sixty-seven drivers and 33 pedestrians were examined. Alcohol was present in 33 of the drivers and 20 of the pedestrians. Blood and urine analyses produced positive drug results for four drivers: phenobarbital - 1, propoxyphene - 1, salicylate - 1, and chlorpromazine - 1. Positive results were noted for pedestrians in seven cases. The drugs detected included: phenobarbital - 2, meprobamate - 2, amobarbital - 1, secobarbital - 1, salicylate - 1, and a slow-acting barbiturate.

8.2.26 Drug Use Among Drivers (31)

Glauz and Blackburn report a Midwest Research Institute study that examined drug presence in the driving populations in Lincoln, Nebraska, and Dade County, Florida, in 1972 and 1973. The researchers selected approximately 4 dozen sites in the two areas that were near the location of a previous fatal accident. About 1,500 drivers were stopped and asked to participate in an interview and to provide a blood and urine sample. Of those stopped, 78% agreed to the interview. Of those interviewed, 840 provided a blood sample and 1,029 a urine sample. Breath samples and lip swabs were also requested and were provided by a much higher percentage of those participating in the interview.

Breath tests indicated that 37% of those tested had been drinking. About 4% had BAC levels of .10% or greater.

Analyses were performed on blood specimens (66.2% in Lincoln and 47.4% in Dade County), urine (74.2% in Lincoln and 64.4% in Dade County) and lip swabs (81.6% in Lincoln and 72.6% in Dade County) for 41 selected drugs and marijuana residue. The results for Lincoln indicated 1 positive blood (phenobarbital), 16 positive urines at >1.0 ug/ml (meprobamate - 8, phenobarbital - 4, secobarbital - 2, and chlorpheniramine, diphenylhydantoin, morphine, and phenylpropanolamine - 1 each), and 10 positive urines at <1.0 ug/ml (meprobamate - 3, secobarbital - 3, phenobarbital - 2, and methamphetamine and codeine - 1 each). In addition, 2.92% of the drivers tested with lip swabs in Lincoln were positive for marijuana. The results for Dade County indicated 1 positive blood (phenobarbital), 10 positive urines at >1.0 ug/ml (phenobarbital - 3, phenylpropanolamine - 2, and amitriptyline, butobarbital, codeine, lobeline, and pentobarbital - 1 each), and 12 positive urines at <1.0 ug/ml (phenobarbital - 4, methaqualone - 2, secobarbital - 2, and chlorpheniramine, codeine, diazepam, and methylphenidate - 1 each). In addition, 9.2% of the drivers tested with lip swabs for marijuana in Dade County were positive. Testing of urine for nicotine indicated that 58.5% of the Lincoln drivers and 48.1% of the Dade County drivers were positive; in contrast, positive tests for nicotine in blood were found in only 2.12% of the Lincoln drivers and 2.44% of the Dade County drivers.

8.3 Relevance of Epidemiological Studies

The existing literature is limited in scope and quality and does not provide an adequate explanation of the relationship (presuming one exists) between drug usage and traffic crashes. The studies do establish the presence of drugs in the driving and crash populations.

Two problems exist, however, with the interpretation of these findings. First, the role the drug played in altering driving behavior or in traffic crash causation is generally undefined. The studies report drug presence but not drug effects. A very limited number of cases of extremely high dosage levels have been reported, where gross impairment can be reasonably inferred from the known pharmacological action of the drug. Such instances are very limited.

Second, the studies simply cannot be generalized to either the general driving or accident populations. The populations studied are not samples in a random or representative sense. Thus, the results must be viewed as indicators rather than proof of a drug/driving problem.

The studies, however, do present consistent evidence sufficient to justify the belief that drugs do play a role in traffic crashes. The nature and extent of that role cannot be defined on the basis of the existing literature.

This suggests that the problem should be examined further to establish the nature and extent of the relationship. Past efforts clearly indicate that future epidemiological research programs must be very carefully designed. Three key decision points must be considered in developing the experimental designs:

1. Data must be collected from a representative sample of the driving and accident populations. Missing data must be held to a statistically insignificant level.
2. A set of drugs believed to present the greatest potential for actual impairment must be chosen for study. Dose-response relationships should be known.
3. Analytical methods for objectively establishing the presence and concentration of *all* pharmacologically active forms of the drugs chosen for study must be used.

There are obviously a host of other decision areas that must also be considered. However, these three, taken together, seem to have been ignored most commonly in the past. Thus we emphasize them for future consideration.

The studies also present consistent evidence of polydrug use, in particular, alcohol/drug use. This, too, warrants further examination.

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9.0 CONCLUSIONS AND RECOMMENDATIONS

Existing research establishes that:

1. The adult population of the United States commonly uses many drugs that have the potential to adversely affect driving behavior.
2. Drivers involved in traffic crashes have been found to have drug concentrations sufficient to affect behavior.
3. Drivers involved in crashes or arrested for impaired driving have been found to have both alcohol and drug present in concentrations sufficient to affect behavior.

Existing research is not sufficient to establish:

1. The role that drug usage plays in traffic crash causation in the United States.
2. The nature and extent of drug usage by drivers involved in traffic crashes in the United States.
3. The nature and extent of drug usage by drivers at risk who are not involved in traffic crashes in the United States.

Past research efforts have been constrained by:

1. Lack of funds available for the support of large-scale research efforts such as those required for definitive examination of the relationship between drug usage, driver behavior, and traffic crash causation.
2. The "state of the art" of knowledge and technology for the detection and measurement of drug presence.
3. Lack of information relating the pharmacological aspects of drugs and driver impairment.
4. Legal restraints that impede the collection of information.

Research findings with regard to countermeasure programs suggest that:

1. Large-scale countermeasure programs focused on the drug/driving program do not appear warranted at this time. The nature and extent of the problem must be better defined before a large-scale response can be developed or supported.
2. In the light of the present lack of proven methods for effectively dealing with other drug-related problems, any countermeasure approach should be carefully developed and intensively evaluated before large-scale implementation is attempted.
3. Information on the pharmacological characteristics of drugs with the potential to affect driving should be widely disseminated. Information on the potential for impairment from polydrug use—in particular, alcohol and drugs—should also be disseminated.
4. Existing laws prohibiting driving under the influence of drugs should be enforced. Videotape records of driver behavior appears to be a highly persuasive evidentiary approach.

Future research efforts within the mission area of the National Highway Traffic Safety Administration should include:

1. Studies which examine drug usage patterns of the driving population. These efforts should focus on establishing exposure data for all agents, including prescription drugs, over-the-counter medications, recreational chemicals, and other chemical

agents. Survey approaches using interviews and questionnaires supported by separate verification systems appear the most feasible. Exposure information is needed to define the problem and form the basis for further epidemiological studies.

2. Studies which examine accident populations and the driving population for concentrations of specific drugs believed to be involved in crash causation or which are widely used and have significant potential for behavioral impairment. Such studies, to be effective, must be large-scale multidisciplinary efforts. Major emphasis must be placed on experimental design. Such projects should be planned to span several years. Provisions should be made for outside advisors to assist in the planning of such efforts, and outside reviewers to monitor technical performance of contractors. The review group should include individuals with expertise in chemistry, pharmacology, medicine, research methodology, survey design, and the collection of data in the highway safety environment.
3. Studies which examine the nature and extent of existing countermeasure efforts focused on drugs and driving. The literature is almost non-existent in this area. Field studies to document existing practices at the state and local level are required.
4. Studies which focus on the development and evaluation of countermeasure programs. Such efforts should be carefully integrated with the programs suggested in the paragraphs above.

The National Highway Safety Administration should facilitate and improve research on the problem of drugs and driving by:

1. Obtaining legal privilege for researchers and countermeasure program personnel as is provided for personnel operating under programs of the Department of Health, Education and Welfare (DHEW) and the Department of Justice (DOJ). Either separate legislation establishing a privilege should be sought or provision should be made to utilize the existing privilege provided DHEW and DOJ.
2. Establishing more extensive communications with other government agencies sponsoring drug research. Active exchange of information, technology, facilities, and expertise would enhance the effectiveness of NHTSA-sponsored research and action programs and increase fiscal effectiveness.
3. Establishing a Scientific Advisory Board to advise NHTSA on the design and implementation of research and countermeasure programs dealing with drugs and driving.
4. Supporting periodic scientific meetings of researchers and practitioners active in the drugs and driving area to facilitate communication. Rigorous planning should be required to ensure that the meetings have a "redeeming scientific value" of direct benefit to the highway safety community.

10.0 INSIGHTS

The prior sections of this report have examined the research literature on the topic of drugs and driving. The literature has been discussed and conclusions drawn by the principal investigators and the project staff in as objective a manner as possible. Our expectation is that other researchers reviewing the same material would agree that our findings are conservative and are fully supported by existing research.

It is impossible to review and examine the amount of literature encountered in this project without forming personal opinions. The principal investigators have personal views on this subject and state them below. Our objective in placing our opinions in this separate section is to distinguish our personal judgments, which may be more heuristic, from the prior conclusions and recommendations which we believe are firmly supported by fact.

10.1 Study Perspective

A brief word is in order to place this study in perspective so that the scope and approach of the effort is understood. This project is one of a family of projects within the drugs and driving research program of NHTSA. The basic objective of this study was to draw together the body of literature presenting information on the drug/driving problem to provide a baseline statement of existing knowledge. Thus, this report and the other workproducts focus on the existing literature, as opposed to the design of future research efforts.

Other NHTSA projects are examining the role that drugs play in accident causation. Future projects will continue and expand the scope of inquiry. As a part of the NHTSA research program, the principal investigators are engaged in a separate effort to develop research approaches for the future. That project reflects a logical continuation of the work reported here and will be the subject of a separate report in 1976.

10.2 The "Alcohol Analogy"

One of the most persistent problems encountered in the course of the project was the tendency of policymakers (and to a lesser extent researchers) to attempt to discuss the drug/driving problem by drawing analogies with the alcohol/driving problem.

As noted previously, alcohol is a unique drug with simple direct actions. The amount of alcohol in a driver can be determined simply and accurately and quite reasonably correlated with impairment. This is not true for many other drugs. Many drugs that have the potential to impair driving ability remain within the body long after their main effects have taken place. Thus, mere presence of a drug does not necessarily mean impairment.

The findings of many of the epidemiological studies that report drug presence cannot be interpreted to mean that driving behavior was impaired. Impairment can be inferred in the case of some drugs where the concentration within the body fluid can be quantified. This information is either not available or not presented in many studies.

Unfortunately, some individuals have seized the limited results of epidemiological studies, equated presence with impairment, and concluded that drugs are a major cause of traffic crashes. Present research does not support such sweeping conclusions.

In addition to the use of the "alcohol analogy" in the problem definition process, one

finds discussions of countermeasure development focusing on the alcohol experience. We do not suggest that one should ignore what has been learned in alcohol countermeasure programs. We believe, however, that the drug and driving problem has much broader dimensions; approaching it from an "alcohol perspective" is too narrow a view.

10.3 Research Limitations

A review of the research literature on drugs and driving is a frustrating experience. Many of the studies that appear most promising have serious methodological limitations that flow from the time and dollar constraints placed on the researchers. One finds experimental studies that use subjects that are atypical of the driving population. A reasonable inference is that in many cases the cost of obtaining a representative sample was beyond the scope of project funding.

Similar difficulties may be seen in epidemiological studies. Frequently, the population that forms the basis for a study is not representative of the general accident or driving population. This may occur as a result of the original subject selection process or flow from missing data as cases from a sample of the population are lost or incomplete.

Another and perhaps more serious problem with epidemiological studies is the drug detection and measurement techniques used. Often the availability of equipment and qualifications of personnel appear to dictate the choice of drugs that are tested for in the study population. Thus, one finds that many of the studies have failed to test for drugs that have the potential for impairment, are commonly used by the driving population, and have been anecdotally reported to be involved in crash causation. For example, we are unable to identify any major study in the United States that tested body fluids of accident-involved drivers for the presence of the active metabolite of diazepam. This psychoactive agent is the most frequently prescribed drug in the United States and has been shown through experimental studies to have the potential to impair behavioral skills believed related to the driving task.

We are sure that our frustrations are shared by the many researchers who are working in this area. The lapses noted above reflect, in most cases, the results of a research team doing the best they could in the face of time and dollar constraints.

There is a clear need to recognize that adequate research in this area will be costly and will require time and funding for planning and execution. An approach that does not take this into consideration is likely to prove more costly in the long run; the results of hastily executed projects are likely to be as inconclusive as similar past efforts have been.

If there is one lesson to be learned from the existing literature, it is to adequately fund projects, provide time for planning, require proper experimental design, and ensure that the design is followed.

10.4 The Drug/Driving Problem

Throughout this report we have set forth the limitations of existing knowledge and stressed the impossibility of drawing precise conclusions on the nature and extent of the drug and driving problem. We cannot state that drugs play a causative role in X percent of traffic crashes. We do not believe that any responsible researcher could make any such statement on the basis of existing research findings.

Yet, taken as a whole, the experimental and epidemiological research literature clearly indicates to us that drugs do play a role in traffic crash causation. We do not know the extent but believe that it is significant and that it warrants further careful investigation.

The drug/driving problem is a part of the larger problem of drug use and abuse in our society. This must be understood and considered as the drug/driving problem is studied and countermeasures developed.

At this stage in our state of knowledge about the drug and driving problem, we believe that the principal effort for the highway safety community should be to more precisely define the problem. At this time the implementation of large-scale countermeasure efforts does not seem advisable. Information about the drug and driving problem, however, should be deliberately disseminated to health professionals responsible for the prescription and dispensing of drugs.

Again the evidence is incomplete, but we believe that alcohol-drug interactions are a significant factor in traffic crash causation. This is a particularly troublesome area, because driver impairment may result from the use of a licit drug, as prescribed, plus ingestion of a limited amount of alcohol. Impairment can occur with an alcohol concentration far below the legal limit. The impairment may be insidious and unrecognized until too late. Drivers in this class are likely to be quite different from abusive users of either drugs or alcohol. This suggests the strong need for an awareness on the part of the physician and patient of the potential for drug-alcohol interactions.

In conclusion, we believe there is a drug and driving problem. Action should be taken to precisely define its nature and extent. This knowlege should lead to measures for the reduction of crash losses.