Report of an International Symposium on Drugs and Driving

Indiana University
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REPORT OF

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ON DRUGS AND DRIVING

Conducted by:

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16. Abstract

This report presents the proceedings of a Symposium on Drugs (other than alcohol) and Driving. Speaker's papers and work session summaries are included. Major topics include: Overview of Problem, Risk Identification, Drug Measurement in Biological Materials, Measurement of Drug Effects on Driver Behavior, Legal and Practical Constraints on Drug/Driving Research, and Recommendations for Future Research and Countermeasures.

The report summarizes the discussions of 30 leading researchers and practitioners who met to review existing research findings about the drug/driving problem. On the basis of current knowledge suggestions for research efforts and countermeasure actions are made.

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CHAPTER I

1.0 INTRODUCTION

This report presents the proceedings of an International Symposium on Drugs and Driving. The Symposium was held April 9-11, 1975 at Bloomington, Indiana. The Symposium was conducted by Indiana University under the sponsorship of the U. S. Department of Transportation, National Highway Traffic Safety Administration as a part of the efforts under contract number DOT-HS-4-00994.

Leading researchers and practitioners met to examine the nature and extent of current knowledge about drugs (other than alcohol alone) and driving. This examination led to an identification of research requirements as well as suggestions for countermeasure development.

2.0 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 drugs (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/driver problem that require further research and to suggest, insofar as present knowledge permits, possible drug/driving countermeasures that can be implemented in the immediate future.

In order to achieve these objectives a basic research plan was developed. The major steps in this research effort are as follows:

1. Conduct an initial literature search to identify published studies dealing with the drug/driver problem.

2. Circulate the 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 current knowledge and to develop directions for future action.

4. Collate and synthesize the information obtained from the literature search and the symposium and through an analytical process develop a series of reports which will include:

   A Report of the Symposium

   A Review of the Literature

   A Detailed Technical Report

   A Summary Report

Steps 1, 2, and 3 have been completed. An initial bibliography was provided participants in the Symposium and has been circulated to other researchers and research organizations for comment. Additional material was identified by the Symposium participants and will be included in the Review of the Literature.

This report is the Report of the Symposium referenced above. The other reports identified will be produced in September 1975.

3.0 TECHNICAL APPROACH

The Symposium was deliberately developed as a working conference with major emphasis on small group interaction and limited formal presentations. The participants (see Appendix A) are leading specialists in the field and provided logical structure for the analytical efforts of the working sessions. Pre-conference planning identified the scope and approach of group activity but deliberately avoided establishing a required structure for each individual group.

A limited number of formal presentations were made to all the conference participants. These presentations were intended to familiarize the invitees with the range of topics under discussion and to raise in summary form the major issues. (See Appendix B for the schedule of the Symposium).

The participants were divided into five working groups. These groups met during each working session to discuss existing information and to develop conclusions and recommendations.

Each working group was moderated by an individual from Indiana University who played a neutral role to facilitate discussion; an additional staff member from Indiana University was present as a recorder. Continuous tape recordings were made of the working sessions to assist the recorders and moderators in developing a summary report. Transcriptions were not made and statements of individual participants are not quoted.

3.1 Symposium Objectives

The primary objective of the Symposium was to examine the current knowledge about the problem of drugs and driving. This required an examination of the nature and extent of the problem as well as an identification of information needs for problem definition. The summarization of current knowledge and identification of information needs was expected to lead to suggested approaches to obtain the required information.

Further, the organization of existing knowledge was expected to present the known risk of drugs with more precision and lead to the identification of some countermeasures that could be implemented in the near term future.

A particular concern of the Symposium was to define research needs for the more precise identification of the risk posed by the driver who uses drugs as well as for the development of methods and countermeasures to manage such risk.

Each working group was asked to discuss existing research in an analytical framework and then turn to the examination of future action and research needs. Any action that was seen as currently feasible for dealing with the problem was emphasized. Information gaps that were identified were developed as research requirements with special emphasis on the needs that fall within the research mission of NHTSA.

3.2 Working Group Topics

The participants were divided into working groups to discuss in a focused manner specific topic areas. These areas were to be defined as follows:

Risk Identification-Examination of the risk posed by the drug impaired driver. The scope and extent of the problem and the risks created by specific drugs were examined. The problems associated with various research approaches were discussed.

Behavioral Measurement Methodology-Examination of the methods for identification of the effects of drugs on behavior, specifically, driving behavior.

Drug Measurement Methodology-Examination of the available analytical methods for determination and identification of drug presence in biological materials. Emphasis was placed on the evaluation of current analytical methods in terms of the real world constraints associated with obtaining and analyzing samples from drivers.

Legal and Practical Constraints-Examination of the practical constraints on research created by the law. The use of human subjects in drug/driving research was examined and legal constraints emphasized.

Countermeasure Development-Examination of existing countermeasure activity was undertaken to suggest approaches for the near term future and to establish research requirements.

The formal presentations developed summaries of these topics for the participants. The working sessions provided an opportunity for individual discussion of the topics and allowed participants to express opinions and make their own recommendations.

4.0 REPORT ORGANIZATION

This report has been structured to facilitate use by the reader. The chapters have been arranged so that the formal presentation of the speaker on a particular topic is immediately followed by the chapter containing the report of the working sessions on the same topic area.

The reports of the working sessions have been developed to provide a summary of the discussions. In order to present a coherent document for a reader, it was necessary to include background material that was accepted as a basis for the discussions. Frequently, this required the inclusion of definitions or the presentation of reference materials that were well known to the participants but may not be as well known to professionals from other areas.

Specific points that became the object of repeated emphasis are presented in both the speakers' papers and in the working session reports. Overlap among the sessions was expected. Thus, the same topic may be touched upon in several different sessions from slightly different perspectives.

A reader is encouraged to treat the document as a whole rather than seeking answers from individual chapters.

CHAPTER II

THE DRUG/DRIVING PROBLEM - A PERSPECTIVE

1.0 INTRODUCTION

The objective of this chapter is to provide a brief discussion of the drug/driving problem for the reader who is not familiar with the literature. The symposium participants were drawn from researchers and practitioners active in the field. Thus, the papers and discussions were presented to a group that shared a common knowledge base. A brief summary, as presented in this chapter, cannot replicate that knowledge base; however, it is intended to provide information for the reader to facilitate examination of the papers and working session reports.

More than 75 years have elapsed since the first reported motor vehicle death. In that time more than one million people have died as a result of motor vehicle crashes. Millions more have been injured and the costs of traffic crashes now exceed 40 billion dollars each year. The precise role that drugs play in this major social problem remains to be delineated.

In the last decade a number of reviews and reports have been produced that examine the drug/driving problem. Readers interested in a more detailed examination of the problem are urged to examine the following reviews and bibliographies: Goldberg and Havard (1), Poldinger and Sutter (2), Kibrick and Smart (3), Nichols (4), Milner (5), and the annotated bibliographies of the Addiction Research Foundation (6).

The following sections present a brief discussion of the ways in which drug use can increase the driving risk and a digest of studies examining the role of drugs in traffic crashes.

2.0 HOW DRUGS CREATE A DRIVING RISK

The driving task is a complex endeavor requiring the coordination of mind and body. We do not know all the parameters of the behavioral and psychomotor skills involved in the driving task. A valid testing system that replicates the driving task in the real world does not exist. Thus, information on drug effects is drawn inferentially from evidence that specific behaviors or psycho-

motor skills are altered by drug use.

Drugs may influence driving performance in a variety of ways. Some drugs may alter judgement, perception, cognition, and other psychological variables while other drugs may have physiological effects. The types of drug effects that are likely to interfere with motor vehicle operation may be discerned from behavioral testing of animals and humans. In terms of animal testing, drugs that cause sedation, reduction in spontaneous or individual motor activity, muscle flaccidity, or perturbations in performance on operant conditioned responding are likely to be problems when used by human drivers.

Laboratory tests on humans allow the identification of drugs that increase response time, impair visual acuity, cause drowsiness or ataxia, impair concentration or problem solving ability. Such drugs are likely to impair drivers.

The use of driving simulators may permit greater sensitivity in detection of impairment as such testing systems present multiple tasks for the subject. Simulators have been critized as lacking validity and reliability in approximating the driving task. Dual control vehicles on a closed test course have been used to measure drug effects although this test system is also artificial. In general, any test system other than actual highway driving can be criticized as only "approximating" the real world driving task. Studies which examine driver behavior on the highway have been criticized for placing human subjects at risk.

No coordinated approach for testing for drug effects exists. Thus, test results for all drugs on a particular test or set of tests believed relevant to the driving task do not exist. Even if such data were available, a risk assessment model which would correlate the data to allow objective risk prediction does not exist.

The most feasible approach, for the immediate future, would be to examine in a coordinated manner the frequency of use of specific drugs, in light of the known behavioral effects of such drugs, to develop a subjective assessment of risk.

For example, penicillin is a widely prescribed and used drug. Its pharmacology is such that it is highly unlikely that driver behavior would be adversely affected by its

use. In contrast, diazepam is also widely prescribed and has marked effects on behavior and performance. Thus, diazepam use may be viewed as a likely "risk" in terms of highway safety and should be the subject of further study.

A preliminary subjective assessment has been made of commonly used drugs based on available information of behavioral effects. A list of drugs that present potential risk profiles is set forth in Table 1. No attempt has been made to rank the drugs/drug classes in terms of relative risk, nor is the list believed to include all agents that may adversely affect driving behavior.

The previous comments have focused on some drug effects that are likely to result in driver impairment. It is well to pause for a moment and recognize that driver impairment may result from drug use or abuse. The impairment may flow from a deliberate act by an individual who is using a drug in a "recreational sense" seeking alteration of a psychological state. In an opposite sense, prescribed licit drug use may result in the unwitting impairment of an individual. Polydrug use may result in impairment which may be known or unknown to the user. The interaction of alcohol and drugs is an example of this case. The direct pharmacological action of a drug, alone or in combination with other drugs, can produce impairment. It appears probable that such direct impairments form the major components of the drug/driving problem.

Two other facets of drug use suggest potential problems that should be considered. First, drugs may be prescribed to alter an abnormal behavioral state (e.g., neuroses or psychoses). The drug may alter the individual's behavior beneficially, in a general social sense. The potential exists, however, that the driving decision patterns developed in the prior abnormal state will be adversely altered by drug use and result in an increase in risk in the driving task. Second, cessation of drug use by a chronic user may produce withdrawal effects that produce deleterious driving behavior.

While modest information exists about the direct pharmacological effects of drugs (and drug interactions), very little is known about the potential risk posed by the last two cases.

Unfortunately, absolute proof that any given drug adversely affects driving behavior must, by definition, be drawn from evidence of the drug's causative role in traffic

TABLE 1

Drugs with the Potential to Impair Driving

Pharmacological Class	Common Members
Antidepressants	amitriptyline desipramine imipramine nortriptyline protriptyline
Antihistaminics	diphenhydramine methapyrilene promethazine pyribenzamine tripelennamine
Antipsychotics	chlorpromazine haloperidol promazine thioridazine trifluoperazine
Anxiolytics	chlordiazepoxide diazepam meprobamate phenobarbital
Narcotics	codeine methadone morphine
Sedatives	amobarbital butabarbital fluazepam glutethimide methaqualone pentobarbital secobarbital
Stimulants	amphetamine caffeine methylphenidate
Miscellaneous	LSD phencyclidine THC

crashes. Prudence suggests that this level of proof may not be needed for reasonable decision-making in all cases.

3.0 THE DRUG/DRIVING PROBLEM

It would be satisfying to be able to state with precision the percentage of vehicle crashes that are caused by drugs, delineate the drugs involved and present comparative statistics describing the frequency of use of those drugs in the general driving population. Such data do not exist.

Information on drug use by the general population does exist and allows interpolation to the driving population. Such estimates are of unknown reliability.

Very limited information exists on the role of drugs in traffic crashes. The cost and difficulty of obtaining valid information has limited the number of studies that have been undertaken. Given the limited efforts, significant methodological questions related to representativeness of the samples exist. Other methodological problems, related to the ability to detect and quantify drug presence, suggest that underdetection is probable. The lack of information correlating drug presence with drug effects makes the interpretation of data difficult. Mere presence of a drug in a biological sample does not mean that the driver was impaired. Further, if the impairment is slight, it is extremely difficult to ascertain the precise role the drug played in the pre-crash sequence.

The subtle nature of drug effects and the methodological problems in detection of drug presence suggest that existing research has only touched the surface of the drug/driving problem.

The existing evidence is suggestive of a serious problem but is not definitive. It is sufficient to suggest the need for further investigation but not sufficient to support scientifically sound estimates of the magnitude of the problem.

Surveys generally show that 10 to 20 percent of drivers are using some drug at any point in time, 25 percent have used drugs within the past year, and 50 percent have used a psychotherapeutic agent at some time in their lives. About 7 percent of the population are actually using prescribed psychotherapeutic agents, driving and consuming alcoholic beverages.

Studies have reported that approximately 11 to 15 percent of accident-involved drivers (in the study populations) had taken a drug (other than alcohol) prior to the crash.

Key studies which discuss drug use and crash involvements are summarized in the following paragraphs.

In 1966, Rees (7) examined almost 1,200 patients in his practice. Eighty percent of the men and 22 percent of the women drank alcohol. Sixty percent of the men and 16 percent of the women were licensed to drive. Fourteen of the patients were on phenobarbital, 7 on diazepam, 12 on chlordiazepoxide, 12 on antidepressants - a total of 45 on different drugs.

In another study, Kibrick and Smart (3) reported that 35 to 50 percent of the population drive after drug use at least once a year, and that psychotherapeutic agents are especially likely to have been taken by drinking drivers who were killed in motor vehicle crashes.

Milner surveyed 4,584 patients of Australian physicians. Out of 753 patients who received prescriptions for psychotherapeutic agents; 85 percent of the men regularly drank alcohol, 66 percent would drink and drive, and 57 percent might drink and drive while using the prescribed drug. The corresponding figures for women were 71 percent, 42 percent, and 35 percent (9).

A California Highway Patrol Study examined 772 fatally injured drivers for alcohol and drug presence. Among male drivers, 13 percent were found to have taken drugs while 16 percent of the female drivers had taken drugs. Beginning at about 16 years of age, the drug usage increased proportionately with age. Alcohol/drug interactions were noted (8).

In 1960, Murray (10) showed that of 68 drivers on 10 to 100 milligrams of chlordiazepoxide there was, over a ninety day period, ten times the expected rate of traffic accidents (10 of them being minor and 6 major). Three other patients had serious falls and others had minor mishaps at home.

ImObersteg and Baumler (11) studied 328 subjects involved in traffic accidents and found that in 24 percent of the traffic accidents alcohol played a significant role, whereas other drugs played a significant role in 4 percent of the traffic accidents.

Smart found that cannabis users had twice the usual frequency of traffic accidents in the 6 to 12 months before they were convicted for cannabis use (12).

Turk found that 61 percent of single vehicle deaths involved alcohol; drugs and alcohol were involved in 5 percent. Of pedestrians, 54 percent were under the influence of alcohol, 15 percent were using drugs, and 6 percent had an alcohol-drug combination (13).

Smith (14) studied 772 drivers who had died within fifteen minutes of the crash. Seven percent were on barbiturates, 1 percent on tranquilizers, 4 percent on other identified drugs, and 3 percent on unidentified drugs - a total of 15 percent.

Woodhouse (15) studied the incidence of drugs in 710 fatally injured drivers. Fifty-eight percent had used alcohol (47 percent with a BAC over .10); 13 percent were on prescribed drugs (8 percent of the sedative-hypnotic type), and 5 percent of these had not been drinking at the time of their death. Thirty-eight percent of the drivers were said to have been "in contact with" cannabis.

In a survey by Finkle et al (16) of 129 drivers arrested for intoxicated behavior, but whose blood alcohol concentration (BAC) was less than .05, 85 were on barbiturates, 13 on meprobamate, 6 on amphetamines, and several others on sedatives.

In 1971, Waller suggested that we are in the same state now with drug research as we were with alcohol in the 1930's in that there is a lag in terms of epidemiology (17). He concluded after a review of a number of studies that available data indicate some crashes are attributable to impairment from drug effects. The effects of drugs, other than amphetamines, did not appear significant in terms of driving impairment. He believed that individuals using prescription or non-prescription drugs to cope with everyday stresses and young adults who use only marijuana probably do not have an increased risk of crashes or citations.

One cannot, based on this melange of studies, conclude that the probability of a drug or drugs causing a motor vehicle accident has a known value. One can infer, however, that there is a likelihood that drugs are involved in a causative role in motor vehicle accidents. This inference is supported by a wide variety of data from epidemiological studies and from both animal and human testing. The extent of the involvement is not known.

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DRUG/DRIVING RESEARCH REVIEW

SYMPOSIUM

APRIL 1975

CHAPTER III

Speaker's Paper

AN OVERVIEW OF THE DRUG/DRIVING PROBLEM

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1.0 INTRODUCTION

"My dear Watson, you see,
but you do not notice."
Sherlock Holmes

First, I wish to thank those responsible for arranging my invitation to address this Symposium and giving me the opportunity to meet again with old friends and colleagues.

I feel diffident about my trans-Pacific journey, but trust that the direct simplistic thinking of a denizen of Down Under (the new Wild West) is needed to help cut through the civilized Gordian Knot of doubt and indecision that has been tied about a new social problem - drugs and driving.

2.0 THE AUSTRALIAN EXPERIENCE

Although the first road death was recorded in England in 1896 and the next in the U.S., we in Australia have already gained a much higher road death rate: we drink half as much alcohol again as you do; use just as much in the way of major and minor tranquillizers, particularly drugs like Valium® (diazepam); issued the first report of a driver going to sleep under the influence of Librium® (chlordiazepoxide) and the first consistent reports of alcohol's interaction with other psychotropic drugs in laboratory experiments; and we have accepted legislation designed to control the inappropriate use of alcohol and other drugs by drivers. Throughout Australia we have accepted Breathalyzer legislation and the mandatory use of safety belts. My own state, Victoria, led the way in this legislation and in addition has legislation to provide for the compulsory blood testing of all those injured in motor vehicle crashes. As well as this we have legislation designed to provide for the compulsory assessment of all persons who suffer and/or cause others to suffer because of their inappropriate use of alcohol and other drugs; the legislation also provides for compulsory care and indeed treatment, but it has been used principally as a tool to establish major voluntary assessment, treatment, research and prevention programme facilities for the community as a whole.

It may be because we are poor compared to yourselves that we have been prepared to accept such strong legislation, which I am sure would cause a considerable outcry if you try to introduce it here. Certainly we are unable to tolerate the costs involved from our current drinking, driving and drug

use practices, but I would like to think also that Australians are socially conscious and are prepared to act accordingly.

3.0 EXTENT OF DRUG USE

None of us would deny that psychotropic drug use is commonplace and becoming more extensive. This is just part of the consumer culture, which is fast making us into cannibalistic communities. In the United Kingdom a psychotropic drug is taken by about one person in ten in every 24 hours and in Australia the figure is that one adult in three takes a prescribed course of some psychotropic drug in any one year. Ten per cent of the population take a course of an antihistamine in any one year. Each adult drinker in Australia consumes the equivalent of 100 gallons of beer per year and this is rising at 5 per cent annually. Thus, you can see that we have a greater drug use problem than your own, particularly if you take into account the fact that Australia's abuse of analgesics is some twenty times greater than your problem with these drugs in the U.S.A. We still use less in the way of cannabis and narcotics than you do, but we are coming along quite nicely.

The 12 million population of Australia in 1967 consumed 4 1/2 tonnes of barbiturates, but legislation restricting barbiturate prescribing has led to a drop in this quantity to a figure of 3 tonnes per year at present, with our population of 13 million. Unfortunately the prescription of diazepam (Valium®) went up 300 per cent between 1969 and 1972 and is still rising. More than twenty doses are being prescribed or issued for every man, woman and child in Australia in any one year. In the United States I believe you issue 7 million new prescriptions every year for diazepam and chlordiazepoxide and if prescribing trends continue you will all be permanently under the influence of these drugs by the year 2000. May I put it to you that there are traffic hazards implicit in this situation?

It is true that we cannot afford our current escalation in alcohol and other drug use. Drug combinations are especially dangerous, for as little as six capsules of a barbiturate taken together with a blood alcohol level of only .10 or .15% can readily result in death, as it did with Marilyn Monroe. Society cannot afford this sort of loss.

4.0 PROOF? HOW LONG?

It was in 1904 that the Quarterly Journal of Inebriety first brought to public attention the fact that the intemper-

ate use of alcoholic beverages made for traffic fatalities, but it took until the Grand Rapids Study in 1964 to really prove in scientific terms the way in which alcohol use was related to motor vehicle accidents. How long is it going to take for us to prove the role played by other drugs? A drug is any substance that alters ordinary biological functioning and, in that most psychoactive drugs affect mood, judgement, perception and co-ordination, it seems reasonable to expect them to appear in the complex equations which underlie traffic crashes. However, their role has not yet been proven, the art is difficult, the opportunity fleeting and so a number of authorities have refused to notice the fact that drugs other than alcohol do present a hazard

There can be no question that all drug use has risks and the question is whether the risks are tolerable in view of the benefits gained. Most psychoactive drugs have a continuous logarithmic normal curve for their dose response and thus it is inevitable that the higher the dose and the more other drugs are interacting with the one agent the greater the likelihood of hazards. We are usually working with multiple drug users - heavy drinkers are heavy smokers, more prone to have drugs prescribed and more prone to take drugs to relieve states of anxiety or hangovers. Thus, unravelling the complex etiology of a crash in which such a multiple drug user is involved is difficult, but not impossible. It is because of this dose response curve that not all drug use makes for traffic accidents and one must remember that a given dose of a drug will not only produce different effects in different people, but in the same person from time to time. Serum levels after a particular dose vary enormously.

As scientists we should adhere to two principles:

1. we should select for examination from our overflowing cornucopia of unsolved problems only the most simple and important questions;

2. we must subject our suggested answers to the most stringent and continued criticism.

The real gains which result from clinical science and legislative action have generally depended much more on serendipidity and the use and testing of folk medicines and folk wisdom, than they have on the practice of scientific principles. The examples of this truth, ranging from reserpine to penicillin, from digitalis to phenothiazines, are overwhelming. Clinical experiences and anecdotal histories were the basis of Hippocrates' work (which was not

so bad). No control trials were needed in the early years of World War II to convince us all of the value of penicillin. Similarly it seems to me that if you take a drug which tends to put one to sleep, then it is reasonable to expect the use of this drug to be associated with motor vehicle accidents. Is one to test this by giving it to drivers in the ordinary road using situation? If you are to do this type of scientific research in the United States I think you should look to your medico-legal insurance. Otherwise it is surely reasonable to extrapolate from animal and human laboratory studies, directed by clinical experience and anecdotes, and then go on to epidemiological investigations.

In the laboratory one can use either very simple tests or very complex driving simulators, but one can never reproduce the true casual driving situation and the best one can do is make reasonable predictions on the basis of animal and human laboratory studies. One can extrapolate from clinical experience and laboratory work if the results are consistent over a wide range of species and tests, as is the case for many drugs. My own first research with the driving simulator involved the use of the commonly prescribed antidepressant amitriptyline, given to healthy young subjects in a moderate dosage and testing this drug alone and in combination with sufficient alcohol to bring the Breathalyzer reading to .09%. The drug and alcohol group had four times the error score of the group on alcohol alone. In addition to this two out of twelve subjects in one of the alcohol and drug treatment groups fell unconscious, one for a quarter of an hour and one for three-quarters of an hour. I think it is reasonable to predict that if a person falls asleep at the wheel of a driving simulator, in the stimulating and unusual conditions of the laboratory experiment, others may fall asleep at the wheel of a motor car when under the influence of the same drugs.

One must also consider the other factors that will exaggerate drug effects, especially fatigue, pre-occupation, psychological disturbances and mental illness. For example, studies which involved sitting healthy young subjects at a boring lengthy driving simulator task, show just how potent the effects of a low dose of a drug like diazepam can be if the subjects have been deprived of sleep for only one night. Various techniques of stressing or in other ways making it harder for our subjects to act as contestants in a laboratory game, which they can easily win, must be employed in our research; sleep deprivation is a particularly good technique. After all, sleep difficulties often lead to the prescription of psychotropic drugs which at least in the long term are

rarely effective in relieving these sleep disturbances, producing CNS disturbing effects in themselves.

In Australia, before we introduced our current very tight restrictions on the prescribing and general distribution of amphetamines, there was a considerable problem not only with the illicit use of these drugs by children, but among long-distance trans-continental truck drivers. These drivers were involved in accidents which fell into two main groups: those associated with a toxic confusional state (sometimes related to alcohol use as well as the use of amphetamines) involving very faulty perception, risk-taking driving including driving on the wrong side of the road at excessive speeds and so forth; and another group associated with sudden fatigue when the effects of the stimulant drug wore off unexpectedly in a driver who had been depriving himself of sleep. However, drug users themselves cannot tell you just what effects led up to a particular event such as a motor vehicle accident because the intoxicating effects of drugs which act upon the mind make for false perceptions and faulty judgements. I have done a great deal of work with Police Breathalyzer Squads and there is an amazing consistency in the statements made by intoxicated drivers. They all said that they had had "just two beers." In the State of Victoria, with nearly 1,870,000 drivers, 16,000 people had their driving licenses suspended or cancelled last year after being picked up on a Breathalyzer charge. Their average reading was about .15% so that if this was achieved by drinking just two beers the glasses in which the beer was served must have been extremely large.

It is at this point that I must part from the views of some researchers and assert that drugs other than alcohol do present a real driving hazard which could be noticed and declared as the result of adequate study. It is my view that our epidemiological tools are at present not sharp, fine or strong enough to do the work we would like to ask of them. Yet despite the inadequacies of our techniques of specimen collection, analysis, difficulties of time and personnel and of generally laughably inadequate equipment, most surveys of drugs in accident-involved and sometimes fatally injured drivers show that the drugs occur with what the investigators describe as the "expected frequency for the population as a whole." It then amazes me to see reviewers jump to the conclusion that drugs other than alcohol play no role in motor vehicle accidents, for if one allows for the inadequacies of our methodology then they are obviously overrepresented. Let me remind you that most psychotropic drugs are used in very small dosages, that they tend to be cleared

from the blood, in most cases up to 90% of their quantity in less than an hour, and that the active principles are generally fixed in minute quantities deep in the brain stem or limbic system and are thus unavailable to ordinary investigation. Even in blood and urine, taken in adequate quantities, we are still looking for nanograms and adequately qualified laboratory staff have neither the time nor the equipment to fully identify these drugs or their metabolites.

Common sense is needed in this situation and common sense dictates that drugs by definition must affect the skills related to driving safety and affect them generally in a deleterious fashion. When a new safe "super drug" is advertised on the market we must be as critical as possible, and a single anecdotal warning of a possible new adverse reaction should alert all clinicians and social scientists.

In this context it is probably appropriate to refer to criticisms of statements about the role of alcohol in the road toll - it may be the case that in scientific terms it has been proven that only 10% of accidents are caused by those who are intoxicated. It therefore follows that the other 90% are caused by sober drivers - the obvious answer is to get the sober bastards off the road and leave it safe for the rest of us!

5.0 RESEARCH PROBLEMS

5.1 Faulty Categorization

The trouble with much research is that in order to simplify it we often tend to pigeon-hole complex social problems and try to over-categorize individual people. This pigeon-holing most often stems not from scientific endeavour, but simplistic application of conventional wisdom and accepted prejudices - it is easy, quick and safe from the trouble of original thought. Thus, people using alcoholic beverages are categorized as "light drinkers" or "social drinkers" or as "alcoholics" - treating what is in statistical terms a continuous variable, which can be represented by a smoothly curved figure, as if it were a discrete variable. I suppose the best example one can give of a discrete variable is the pregnant state, a woman can either be pregnant or not pregnant, she cannot just have a touch of it. Continuous variables are much more common. Age, for example - the years merge one into another so that middle age is always at least ten years older than I happen to be at present. Very few modern social or health problems fall into discrete variable patterns of distribution, because of the complexity of our

environment and of our general psychological and physical function. Thus, a woman's reaction to her pregnancy can only be expressed in terms of a continuous variable and this is also true of peoples' use of drugs including alcohol. Most of us are users and to label individuals as "alcoholics," "alkies," "winos," "lushes," "junkies," "addicts," is simply to beg the question and to exacerbate our problems by a false defining-out of society of ordinary people, who merely show an exaggeration of widespread behavioural patterns or at least the obvious results of drug using behaviour.

5.2 Deaths and Injuries

There is an unfortunate tendency for researchers to concentrate on deaths; deaths are most often associated with the high speed head-on traffic crash which most commonly occurs with young and otherwise inexperienced drivers, often with aggressive personality traits and a criminal record and a history of inappropriate use of alcohol. Certainly road deaths now kill five times as many people in Australia as do all the infectious diseases put together (although road deaths have not yet elicited the wide ranging campaign to overcome them that proved so successful with the infectious diseases) and are the biggest identified cause of lost years of working life, a factor of immense economic importance to any nation. However, it may well be that less severe accidents involving minor injuries, property damage, some lost time off work, or at least a great deal of family upset, insurance costs and minor states of chronic disease (such as often stem from whiplash injuries), may be much more important in overall economic and social terms than deaths themselves. But these so-called minor accidents are quite inadequately studied and in my clinical experience are the ones in which a housewife taking an anti-depressant or an anti-anxiety agent, driving children to school at a reasonable speed in a busy rush hour, is most likely to be involved. They need studying. It may be that concentration on a sort of football league or success table of road death statistics has led to our becoming callous; as Joseph Stalin said, "the death of an individual is a matter of great concern, pathos and grief - the death of a million, a mere matter of statistics." (One's mind then leaps to Winston Churchill's opinion of statistics, that they are "a shapeless, meaningless peril, expressed in figures, charts and graphs.")

5.3 Point and Period Prevalence

Another criticism which I must make concerns the powerful reviews which have refused to notice the true habits of

drug use and driving, in that they generally quote drug use surveys which deal with "period prevalence" of drug use in the community and contrast these with "point prevalence" studies of drug use in accident-involved populations. There is a big difference between point and period prevalence, as any researcher who has done Breathalyzer tests at random knows. In the same way, the ordinary member of the public knows that it is possible to drink and drive and not to have a crash. This is a type of Russian Roulette which is generally played with a very large magazine. We have a great deal of work to do and must take the opportunities, rather than deny the possibilities. A drug effect represents a complex interaction between the pharmacological agent, the individual and the environment; we need to study the effects of drugs including alcohol, not just in low, medium and high dosage, but in terms of hangover and withdrawal effects (both of these as yet inadequately studied, even for alcohol).

We need to study effects in healthy and in sick persons, in the young and the old, in skilled and unskilled drivers, in multiple drug use situations, among persons with various personality traits (particularly those involving aggressiveness and risk-taking), we need to study the effects of different moods and patterns of social interaction and so forth. This complex study is still in its infancy, but if we find some answers then these may be applied to other social situations of an equally complex nature, including poverty and criminal behaviour.

6.0 OTHER ISSUES

6.1 Faulty Action

Other difficulties in the alcohol and drug problem field stem not just from excessive or otherwise inappropriate use or from the false categorization of people and their problems, but through faulty judgement leading to faulty action based on an emotional response. When "emotion is in," just as when the wine is in, reason tends to go out of the window. We have seen that a panic reaction to problems of illicit narcotic use may lead to the simplistic distribution of another potent narcotic, methadone, in such a way that methadone deaths tend to outnumber heroin deaths (as is now the case in the United States and becoming the case in the United Kingdom). But many problems do stem from attempts to deal with defined sub-groups such as "problem drinkers," when these do not really exist, merging into other sub-groups you like to name including that thought to be made up of "social drinkers."

There is no disease called "alcoholism" and no creature called an "alcoholic," there are simply people who drink and people who do not drink. Even the teetotallers have their problems through alcohol use in the community, because they can be run over by an intoxicated driver and they pay taxes, some small amount of which is diverted into answering alcohol use problems of various sorts.

6.2 Conflict of Interests?

I suppose one trouble is that so many of us have a vested interest in establishing the role played by alcohol in many human troubles and community costs, that we are disturbed by seeing a possibility of funds and interests being diverted towards other drugs. Unfortunately, multiple drug use, poly-pharmaceutical promiscuity, is a practice increasing each day and so we must consider all the drugs together, just as we must take into account all the complex functions of mind and body, vehicle and traffic systems, if we are to study and combat the causes of motor vehicle accidents. Let us not assume that by simplifying our problems down to the one drug, alcohol, we will win the day. Simple answers do not resolve complex questions.

6.3 Prescribing and Advice

Questionnaire surveys and laboratory testing suggest that 35-50% of drivers will drive after drug use at least once per year and that some 10-15% of drivers involved in motor vehicle accidents are later described as under the influence of a drug (although this is not necessarily related to the crash). As vehicles, alcohol and other drugs are increasingly used in any society, the potential dangers and proven problems associated with this complex behaviour must become more commonplace. Too often this factor is ignored by physicians when they prescribe drugs. A survey of 4,584 patients attending family doctors and psychiatrists showed that 753 were given a prescription for psychotropic drugs which might affect driving safety. Of the men 85% regularly took alcohol, 66% were licensed to drive and 57% were therefore at risk of drinking and driving while taking the drug prescribed. Thus, a doctor when prescribing should take care to issue appropriate warnings or at least inquire into each patient's drinking and driving habits. My own practice is to warn against all use of alcohol for anyone taking a psychotropic drug or another drug which might affect driving safety and to warn against driving at least for the first few days of therapy, until the patients know whether or not they may suffer side effects like fatigue and drowsi-

ness; such advice at least tends to reduce the drug dependency which is becoming more prevalent with agents like Valium® in our society. A study in the 1960's revealed that among 68 drivers who were on chlordiazepoxide (Librium®) over a period of 90 days, these patients suffered ten times the normal traffic accident rate and also were involved in a number of injuries and accidents in the home.

7.0 HIGH RISK DRUG USE

Fundamentally there are four basic factors underlying high risk or heavy drug use. These factors are:

1. availability
2. a high level of peer group usage
3. diminished societal control, and
4. developmental retardation.

Alcohol and other drugs are readily available; advertising and ill-judged pressures to liberalize legislation in terms of so-called civilized drinking and free prescribing will exaggerate this trend. Also many peer groups have characteristically heavy patterns of drug usage, not only among experimenting school children but among politicians and journalists, housewives and researchers. Diazepam and chlordiazepoxide head your list of the fifty most prescribed drugs, the great majority of which fall in the psychotropic drug group anyway. The availability and peer group pressures often combine to escalate drug use; escalation usually involves an individual in having to take the drug in increasingly concentrated forms with increasing frequency. Escalation from beers to wines and spirits has been the experience of many, just as escalation from oral use of drugs to "injectables" has now been established (the old American folklore that escalation did not occur has now been exploded, as common sense predicted). Diminished societal control is obvious world-wide, but increasing family breakdown, unemployment and migration in various forms, contribute to diminished controls, as does the lack of an effective statement and example of ideals from our political leaders.

Developmental retardation means quite simply that the person has failed to reach the milestones expected of him by society or himself, in terms of his functioning. This functioning may relate to subsistence, education, social functioning, sexual functioning, physical abilities and so

forth. In a number of these areas unrealistic goals have been set by the mass media and so many people feel themselves to be developmentally retarded even though in practical social terms they are not.

A sense of developmental retardation and unhappiness with oneself leaves one prone to drug use in order to modify one's functioning or one's perception of function. Many of us are taught to feel inadequate and to need drugs. Fortunately for the United States your controls on new drugs are rather better than in most other nations, so that you have for example been spared the hazards and the dubious benefits of drugs such as nitrazepam (Mogadon®), widely marketed in Australia as a "safe soporific." It is a drug with proven hangover effects and deleterious effects on driving skills for up to 15 hours after a single dose.

8.0 RESPONDING TO A DRUG PROBLEM

If you have finally decided to declare an identified drug use problem (and this is as much political declaration as it is a responsibility of researchers) then there are seven basic societal responses that one must consider in relation to a particular type of drug use. These are:

1. laissez faire
2. take profit
3. measures to curtail or prevent substance use
4. punishment (deterrence, quarantine, retribution)
5. treatment
6. altering the environment (education, alternatives, advertising, etc.), and
7. adopting an attitude of inquiry.

8.1 Laissez Faire and Profit

The "laissez faire" response is very popular with most of us because of previously established priorities (you remember that I have wondered whether many of us may not be adverse to declaring a drug use problem, because we fear it may divert funds from measures to overcome alcohol use problems). The "laissez faire" response is linked with the "take profit" response which is pushed so successfully by

pharmaceutical companies, breweries and vintners. One should also remember the vast income derived by Government from licit drug use. In Australia over $500,000,000 is received by the Federal Government each year as excise tax on beer alone, $385,000,000 from tobacco and so on. The "take profit" response combined with a lack of watchfulness on the part of our medical journals and other people concerned with advertising leads, in my view, to virtually criminal anti-social pressures. Thus, one can see advertisements for antihistamines stating that these are "safe at any speed" for any driver, though when you look at particular drugs you will find that the background research information with respect to them is quite inadequate. Sometimes the research results actually contradict the claims made in the advertisements, as in the case with the product called "Fabahistin®." Regular use of sedatives at night is still a feature of western civilizations and although in Australia our use of barbiturates has gone down from 4 1/2 tonnes to 3 tonnes per year (for a population of only 12 to 13 million) since controls on prescribing were introduced a few years ago, this is matched by the escalation in our use of drugs like diazepam and nitrazepam. In terms of driving safety all of the benzodiazepines have, just as have the barbiturates, been proven to have deleterious effects on driving skills, at least in laboratory experiments. This combination with alcohol tends to result in a potentiation (or at least an additive effect) of adverse effects. It has been shown that even half a litre of beer could potentiate the effects of just one dose of a barbiturate. Drugs like diazepam are being increasingly used in dentistry and we have newly recognised hazards with trace anaesthetics and the commonly used trichloroethylene in industry.

Seventy per cent of drug use stems from over-the-counter preparations, self-medication (usually resulting from a sense of personal inadequacy rather than any real therapeutic need) and even cough syrups (particularly those containing codeine) have been shown to be a hazard for the driver. The various ways in which different groups of drugs including anti-inflammatory drugs and anti-tuberculosis preparations, right through to the narcotics, can affect driving safety, are outlined in my Monograph.

8.2 Prevention and Prohibition

Measures to curtail or prevent substance use are often seen as ineffective, but in practical terms they do work and are essential. The only trouble is that if a single measure is used you will generally get a negative feedback loop

operating. Thus, in the United Kindgom amphetamine ampules were being used illicitly and their production and distribution was stopped by agreement between the pharmaceutical companies and the Government. The young people turned instead to injecting barbiturates with at least as bad a result. However, legislative measures to restrict the availability of drugs have reduced the use of amphetamines in Australia to an entirely insignificant amount and has significantly reduced the use of barbiturates.

Most Americans, I find, are ignorant about the way in which your own "prohibition" worked. The truth is that prohibition was in many ways the single most effective political move of this century, for its principal goal was to destroy the Irish Catholic-American political clubs (in which a fair bit of drinking was done) and it was certainly effective in keeping the Kennedys out of office for many decades. The second goal was to try to reduce alcohol use; deaths from cirrhosis of the liver and similar alcohol-related conditions dropped to a third of their pre-prohibition levels and only reached these levels again in 1971. I suppose the third result of prohibition was to promote private enterprise, which is after all regarded internationally as the Great American Goal. Measures to curtail substance use must be applied with care to see that they are part of a total community response to an identified problem.

8.3 Punishment

Punishment is a popular response and indeed is a responsibility of the judiciary, but its cost-effectiveness has been quite inadequately surveyed. With drinking drivers there is some evidence that the severity of the punishment is unrelated to changes in subsequent driving behaviour. Punishment is linked with prevention, but both should be considered in terms of the other responses, otherwise we get involved in unproductive arguments about so-called legalization of marihuana when we really wish to talk about the controlled use of cannabis (which incidentally is increasingly being identified as a hazard for drivers not only in laboratory experiments but in some epidemiological surveys).

8.4 Treatment

Treatment as a response is necessary and popular and I would like to describe the comprehensive approach involving prevention, education, treatment and rehabilitation which we have in Victoria. This is based on potentially tough legislation providing for compulsory assessment of those for

whom there is evidence that they have an alcohol or other drug use problem. My own service provides not only some 300 beds for in-patient treatment, but extensive out-patient, day hospital and other community oriented programmes for helping people overcome their problems. The four city units are co-ordinated from a central office to provide a specialized back-up service which can co-ordinate, extend and adequately evaluate all community responses from family doctors, through general and psychiatric hospitals, to voluntary and church agency work. Care is taken to identify client and management programme variables and the legislation under which we work ensures an adequate followthrough, so that evaluation can be made of individual and social cost-effectiveness.

8.5 Altering the Environment

A response attractive to many is that of trying to alter the environment, to prevent the inappropriate use of alcohol and other drugs and untoward driving behaviour by means of education, to reduce advertising pressures and to provide valid alternatives to the inappropriate use of drugs. Unfortunately these measures are little understood and indeed many educational campaigns of a simplistic nature tend to be counter productive. A very expensive six-week programme in a part of Scotland aimed at fostering the use of safety belts so disturbed the community that at the end of the six weeks only one third as many people were using safety belts as at the beginning of the campaign. Similarly adult-oriented warnings about hazards of fast driving on a particular stretch of road or under certain circumstances will often alert the risk-taking adventurousness of the maturing youth and precipitate exactly the behaviour which it was hoped to counteract. So-called drug education will also often excite experimentation. Nonetheless we must work towards the principle that education will produce learning, attitude and behavioural changes, on a basis of correct information, and so reduce our social problems.

The "prevention" alternative is a long term and expensive measure, and until it can be effective adequate controls must be kept. It is often claimed that it is easier to modify the system, the design of roads and cars, rather than to improve driver performance, but unfortunately it is driver performance which is far the most important factor underlying the majority of traffic crashes.

8.6 Inquiry

Inquiry - wanting to find out just what is happening - is the most often neglected response to any potential drug use problem, but one that we see concentrated in this Symposium.

Our inquiries in the past have been quite inadequate as regards the range of studies, working with various people of various levels of health and driving ability, various ages, different sexes, taking different doses of drugs alone or in combination with alcohol and other drugs, racial factors, concurrent dietary intake of caffeine, smoking habits and so forth. There is a gross inadequacy of much of our instrumentation and staff availability for laboratory testing for the presence of drugs, even including alcohol.

9.0 ENVOI

Most drinking of alcoholic beverages produces problems; the nature, extent and importance of these depend upon the individual's vulnerability, their amount of use and the environment in which the use takes place. What we are dealing with when we talk about alcohol use and other drug use problems, the road toll, social diseases of many kinds, are total community problems which do not represent any simple pharmacological equation, but which are essentially bio-social-psycho-pharmaco-politico-educo-economo-ecologo-engineering phenomena. We are all involved or guilty and no simple solution can be provided for any phenomenon so wide ranging.

I would like to try to apply the ancient Roman virtue represented by the Goddess Aequitas. She was always shown with a measure in one hand and a balance or scales in the other. We need to truly measure our problems and then balance them in the scales not just of individual, but of social cost-benefit analysis. At the same time we must keep in mind the fact that a drug effect represents a complex interaction between the chemical agent, the individual and the environment and thus avoid erroneous simplistic thinking, which has led some people in the past to deny any possible deleterious effects from so-called low doses of prescribed drugs, alcohol, cannabis, etc. Let us also remember that our environment grows increasingly complex and in a consumer society we often strive to make it even more so, so that the result of any new type of behaviour or behaviour associated with taking a prescribed drug is becoming increasingly hard to predict.

Complex problems cannot be overcome by simple answers - indeed an attempt to apply simplistic answers will generally result in unexpected and bad effects in some other part of the system due to the operation of negative feedback loops. At this stage let me say that I think it is quite wrong to debate any problem unless one is prepared at the same time to talk in terms of recommendations to overcome the problems. We do not have the time or finance to engage in sterile debate.

Let us then think of hazardous driving, often associated with the inappropriate use of alcohol and other drugs (or at least the inappropriate prescribing of other drugs) not as being illnesses, but as social behavioural patterns. They are learned and tend to spread as an infectious disease. When you are dealing with a spreading problem action is essential, but should be based on thorough inquiry. I trust that this Symposium will lead to just that.

DRUG/DRIVING RESEARCH REVIEW

SYMPOSIUM

APRIL 1975

CHAPTER IV

A Report of the
Working Sessions on:

RISK IDENTIFICATION

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1.0 INTRODUCTION

The basic problem in characterizing any situation in which an interaction or interactions occur between a human being, a pharmacologically active substance, and a behavioral performance lies in the complexity of the situation. At the same time, the complexity of the situation (for the interaction of drugs with human motor vehicle operation) is determined by a variety of factors, including those listed in Figure 1. From just a brief glance at this listing, it should be obvious that this work session cannot address itself to a consideration of all of these factors in the limited time available. It should be possible, however, to single out a few for special attention and to place the remainder in at least their proper perspective.

Before examining the individual factors, however, it is necessary to briefly examine the background of the entire situation of drug involvement with the human performance involved in motor vehicle operation. A number of reports have been published from various sources indicating that drugs may be contributing factors to motor vehicle accidents. The story with regard to ethyl alcohol is best-known and is not a required part of this worksession; nonetheless it must be remembered that ethyl alcohol is a specific pharmacological agent and has relevance, not only in its own right, but also as the most common component of polydrug situations. The story with regard to other drugs is less clear. Epidemiological studies have shown the incidence of barbiturates in the blood of subjects involved in crashes to be higher than that in the general population; various questionnaire studies have indicated that as many as 15% of the driving population may be taking drugs (licit or illicit) prior to operating a motor vehicle; numerous studies of blood, tissues, or excreta from drivers in fatality accidents find significant amounts of drugs.

Nevertheless, it is probably impossible to accurately estimate the numerical values associated with the drug-driving population: crash losses in dollars, numbers of drivers actually operating motor vehicles under the adverse influence of drugs, quantitative evaluation of driving impairment by drugs, identification of precise roles of drugs and other factors in accidents. The major reason for being unable to achieve these estimations is a very simple one - a lack of appropriate factual material from which to scientifically draw accurate conclusions! This work session, in attempting to identify some of the risk factors involved in the drug-driving problem, will also be forced to delineate

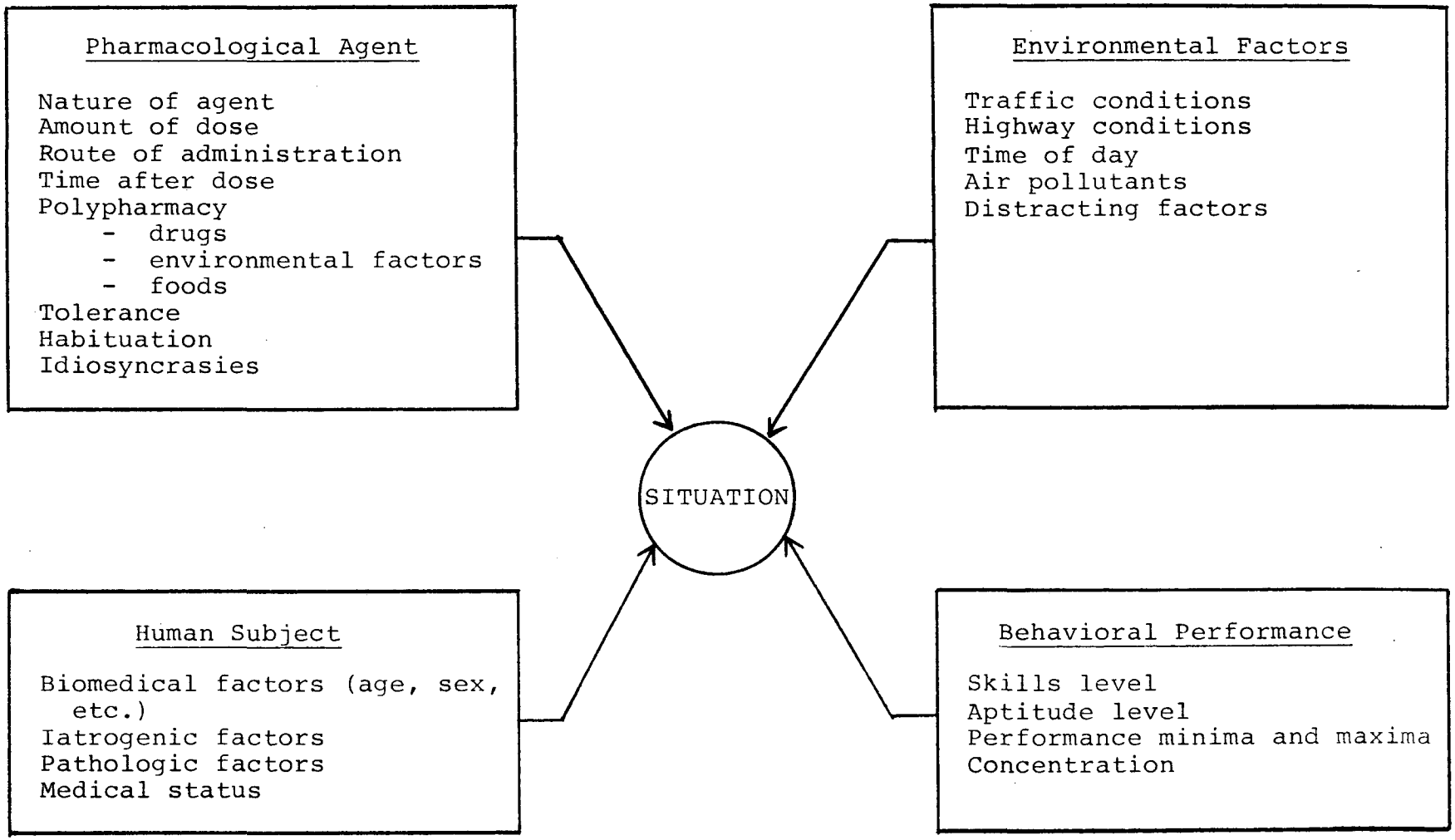
Pharmacological Agent
Nature of agent
Amount of dose
Route of administration
Time after dose
Polypharmacy
- drugs
- environmental factors
- foods
Tolerance
Habituation
Idiosyncrasies
Environmental Factors
Traffic conditions
Highway conditions
Time of day
Air pollutants
Distracting factors
SITUATION
Human Subject
Biomedical factors (age, sex, etc.)
Iatrogenic factors
Pathologic factors
Medical status
Behavioral Performance
Skills level
Aptitude level
Performance minima and maxima
Concentration

FIGURE 1

the characteristics of the problem as it currently exists in terms of this lack of factual material.

2.0 BASIC DEFINITIONS, SEMANTICS AND TERMINOLOGY

Before proceeding any further into a detailed presentation of material, it is essential to characterize the terms and concepts to be utilized, especially since so many of the items involved are erroneously used by the general population and the news media. In particular, it is essential to standardize the terminology to be used when referring to pharmacological classes of drugs and when describing the actions that drugs may have that are especially relevant to motor vehicle operation or to human behavior.

2.1 Drug-Driving Risk

The drug-driving risk may basically be defined as the likelihood that a traffic accident will occur, due to abnormal driver behavior caused by a drug, all other things being equal. In this sense, for example, although a drug may be present in the driver it need not necessarily be a direct causative agent of aberrant driver behavior or of an accident. Factors such as adverse road conditions, poor driver judgment, driver error, fatigue, or vehicle defects may be causative - the mere presence of a drug may be the primary cause, a contributing factor, or no factor at all. Of particular importance in delineating the possible or actual role of a drug in any given accident situation are those aspects concerned with the pharmacological actions of drugs.

2.2 Pharmacological Actions of Drugs

Pharmacological actions of drugs may be defined as those actions of chemical agents that can be clearly attributed to actions of the agents on various body systems. It is a truism that a drug can only exert effects on already existing biological processes, that is, a drug cannot cause the organism to do something that requires the development of a new system. Thus, a drug cannot induce the growth of a new extremity, nor can it enhance or improve intelligence. A drug can, however, increase or decrease blood pressure or heart rate, stimulate or depress respiration, increase alertness, cause drowsiness, or alter muscular tension. In so doing, the drug can have its actions only when an appropriate amount (exceeding the minimal effective level) is present at the site of action.

2.3 Minimal Effective Level of a Drug

The minimal effective level of a drug, sometimes called the threshold level, is that concentration of the active compound that must be reached at the specific site of drug action before the effect(s) of the drug will be observable. In animals, where tissue samples can be readily obtained, this level may be defined as concentration - unit mass of drug per unit mass of a given organ or tissue (micrograms of drug per gram of brain, for example); this level in a tissue can often be correlated with the concommitant level in circulating blood. However, in man, where one is restricted to sampling blood or other body fluids, the minimal effective level is usually considered to be that in the circulating blood (whole blood, serum or plasma); a graphical presentation of effect against the concentration (the dose-response curve) is used to describe the response(s) of the organism to the agent and to determine values such as minimal effective dose.

2.4 Dose-Response Curve

The dose-response curve is defined as the graphical presentation of biological effect (usually plotted in linear scale on the ordinate) against dose or concentration (usually plotted in logarithmic scale on the abscissa). A typical dose-response curve is presented in Figure 2. The sigmoidal is typical; the significant points are labeled and described in the legend. Of particular importance is the fact that doses below the minimal effective dose (M.E.D.) are devoid of pharmacological activity; thus, the mere presence of a drug in the body does not insure that it will have its usual pharmacological effect. A further complication lies in the fact that the dose-response curve holds true only for that point in time at which the drug level meets or exceeds the level required for activity. At other points in time, a changing level may have more or less effect, thus necessitating consideration of time-response factors.

2.5 Time-Response Curve

The time-response curve is defined as the graphical presentation of biological effect (usually plotted in linear scale on the ordinate) against time (usually plotted in linear scale on the abscissa). A typical time-response curve is presented in Figure 3. The significant points are labeled and described in the legend. It is pertinent to remember that the relationship of time, dose, and effect

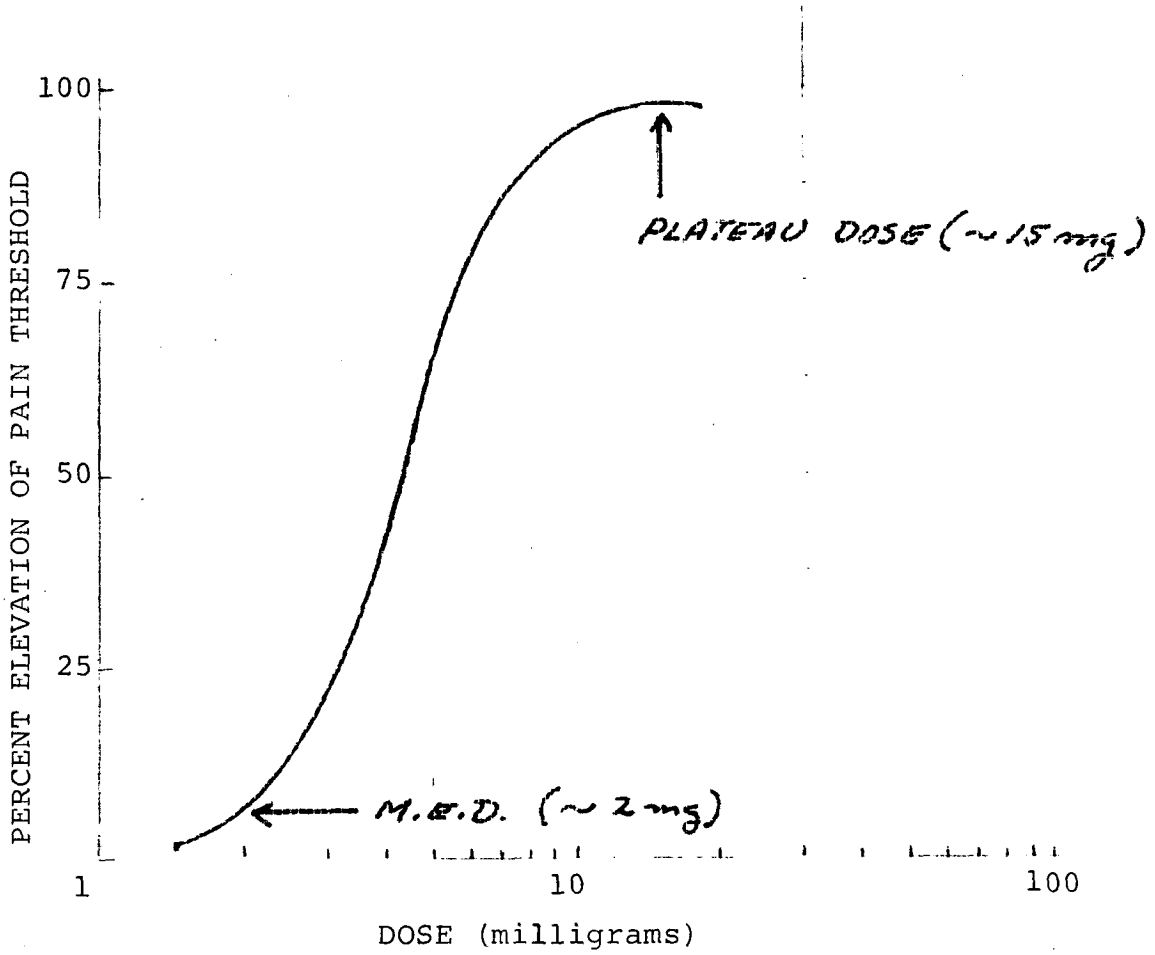

FIGURE 2

Dose-response curve obtained in normal human beings for the analgesic action of morphine. The ordinate shows the analgesic effect as percent elevation of pain threshold; the abscissa indicates the dose administered.

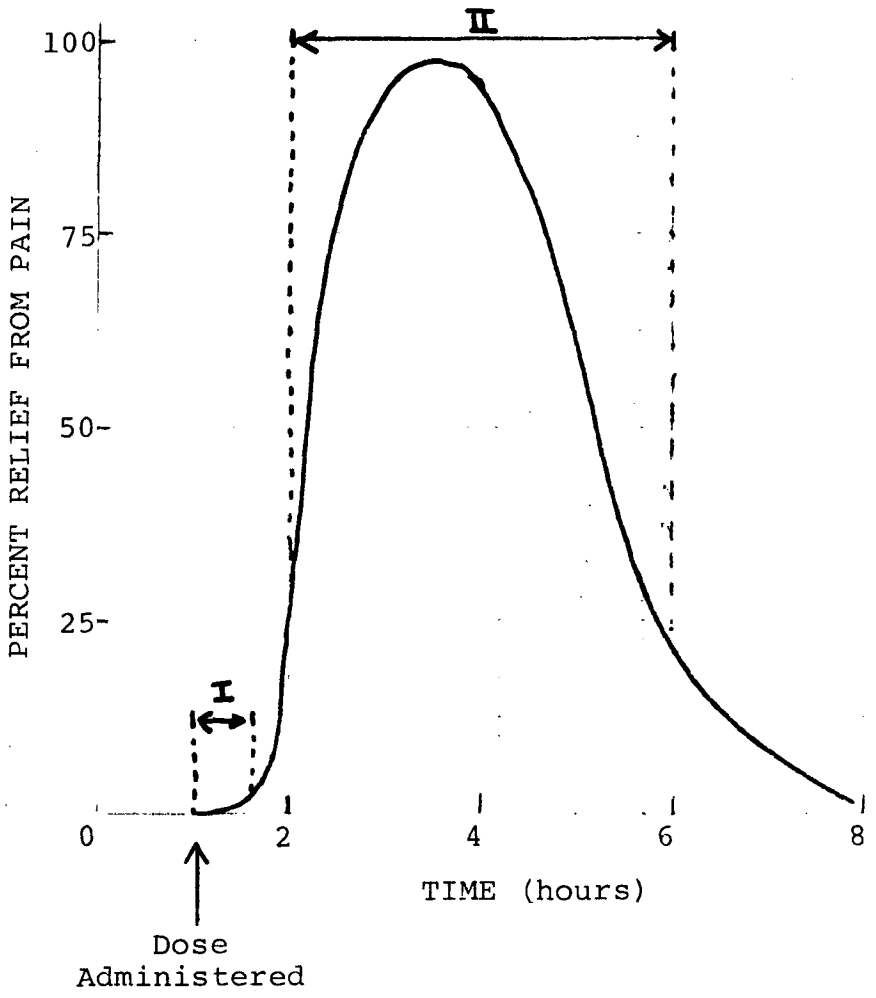

FIGURE 3

A time-response curve for meperidine in humans with post-surgical pain. The ordinate shows the percent relief from pain, the abscissa shows the time (in hours) and indicates the point of administration of a single oral dose of meperidine. The area labeled "I" on the curve represents the lag time due to gastrointestinal absorption. The area labeled "II" represents the time period of effective analgesia.

is due in great measure to the fact that drugs are not retained in the body ad infinitum, but are effectively removed from the body by various excretory processes or are first inactivated by biological processes that chemically convert them, often to pharmacologically inert entities. The "decay" in the concentration of an active agent with time (the plasma decay curve) is the basis of the modern science of pharmacokinetics.

2.6 Plasma Decay Curve

The plasma decay curve is defined as the graphical presentation of the concentration of drug (plotted on the ordinate) against time (usually plotted in linear scale on the abscissa). When the decay of a drug follows zero-order kinetics, i.e., when the rate of decay is constant, a straight line is generated from a linear-linear plot; such a situation is shown in Figure 4. However, most drugs have a multiphasic decay curve and follow first order kinetics where the decay is proportional to concentration. In such situations, linear-linear plots may be used or logarithmic-linear plots may be required; examples of these situations are shown in Figures 5a and 5b. Of particular significance are those situations where multiphasic decay curves exist; the second (beta) phase is often extremely lengthy and may be responsible for "hangover" effects of a drug (Figure 6). Such lengthy drug presence situations may also be responsible for a variety of drug - drug interactions that may complicate behavioral effects.

2.7 Drug-Drug Interactions

Drug-drug interactions may be defined as those situations in which the presence of more than one drug (at the same time) in the body of an individual may seriously alter the drug effects that are seen. A variety of possible situations exist. For example, the effects of two drugs may simply be equivalent to the sum of their individual effects; in this case, as illustrated in Table 1, the overall effect is said to be that of addition, i.e., $1 + 1 = 2$. In contrast, the effects of one drug may reduce those of a second agent by any amount; such a situation, as illustrated in Table 2 is called antagonism, i.e., $1 + 1 < 2$. Finally, the total effects of a drug combination may be greater than merely the sum of the individual effects; such a situation, as illustrated in Table 3, is called potentiation or synergism, i.e., $1 + 1 > 2$. Interactions such as these may occur between drugs that are in the same pharmacological classes or between drugs of different pharmacological classes.

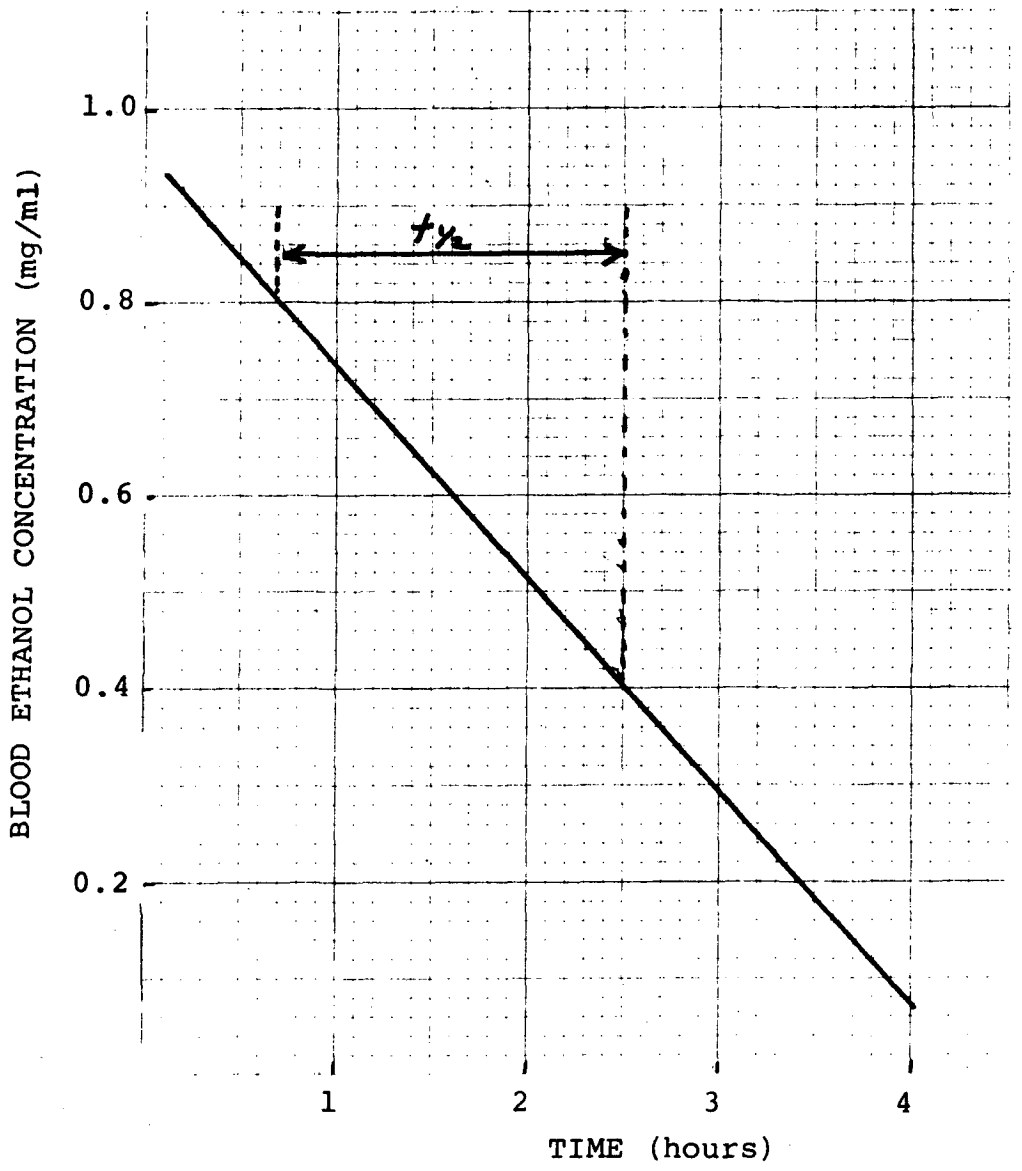

FIGURE 4

Plasma decay curve in normal human subjects for ethanol, a drug that follows zero order kinetics. Values on the ordinate are ethanol concentration in blood (in mg/ml); values on the abscissa are time (in hours). Biologic half-life (t 1/2) is indicated.

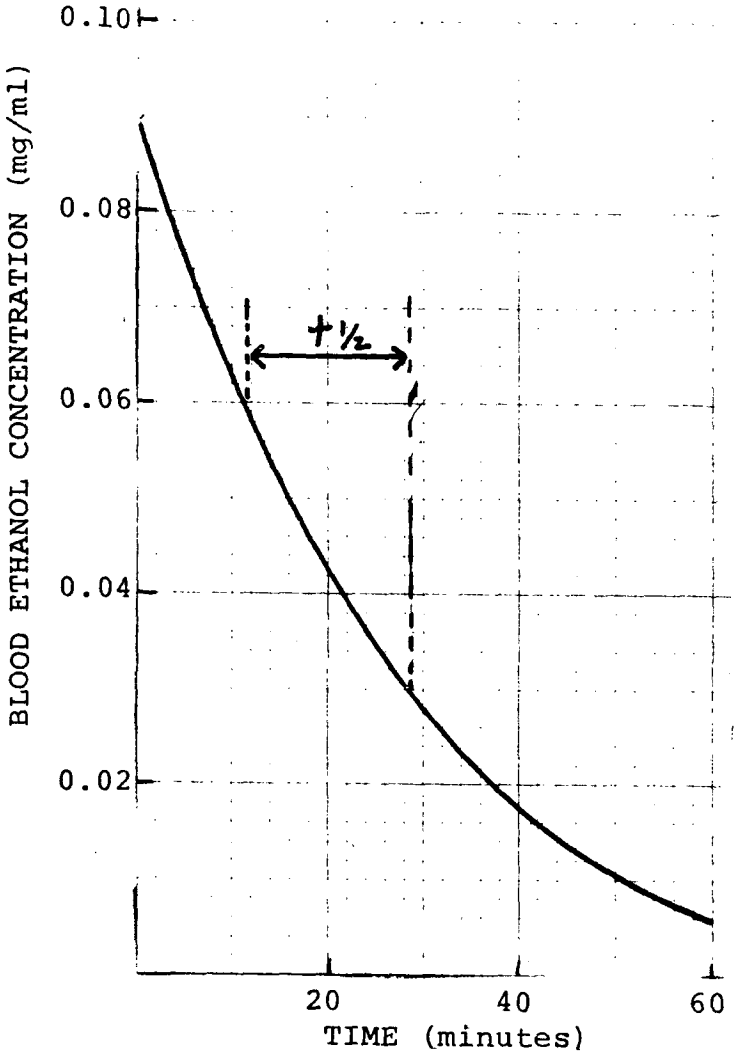

FIGURE 5a

Plasma decay curve in normal human subjects for low levels of ethanol which follows first-order kinetics. Biologic t 1/2 is indicated.

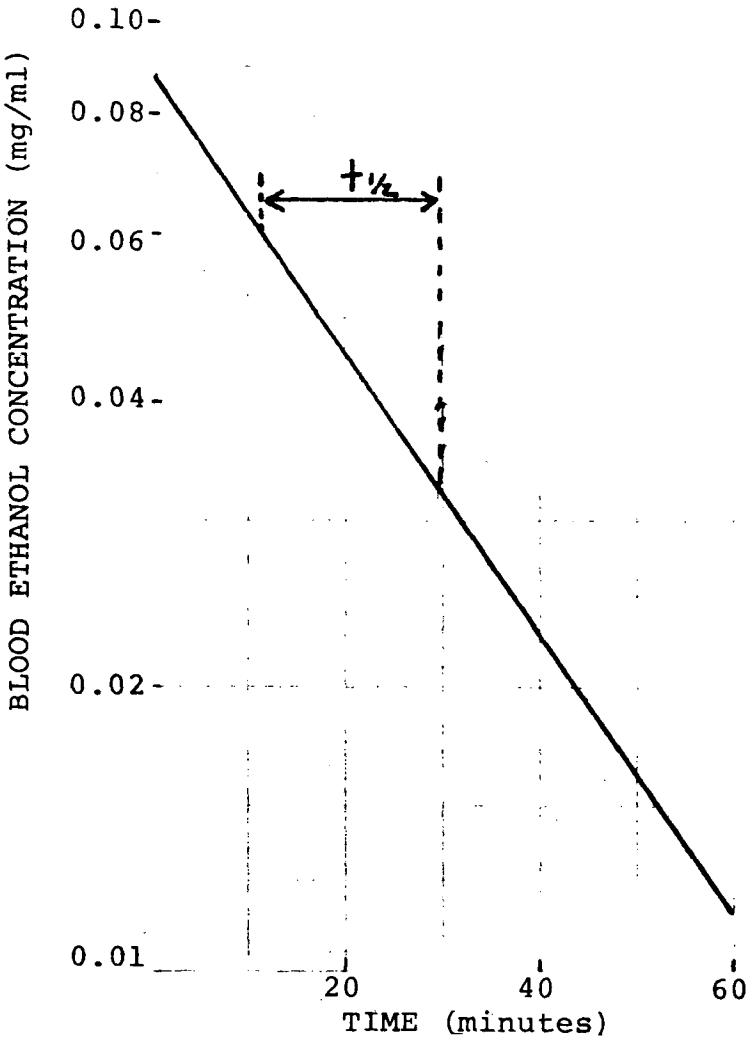

FIGURE 5b

Same data as in Figure 5a, but plotted on linear-logarithmic scale. Note that biologic t 1/2 is the same regardless of plot system used.

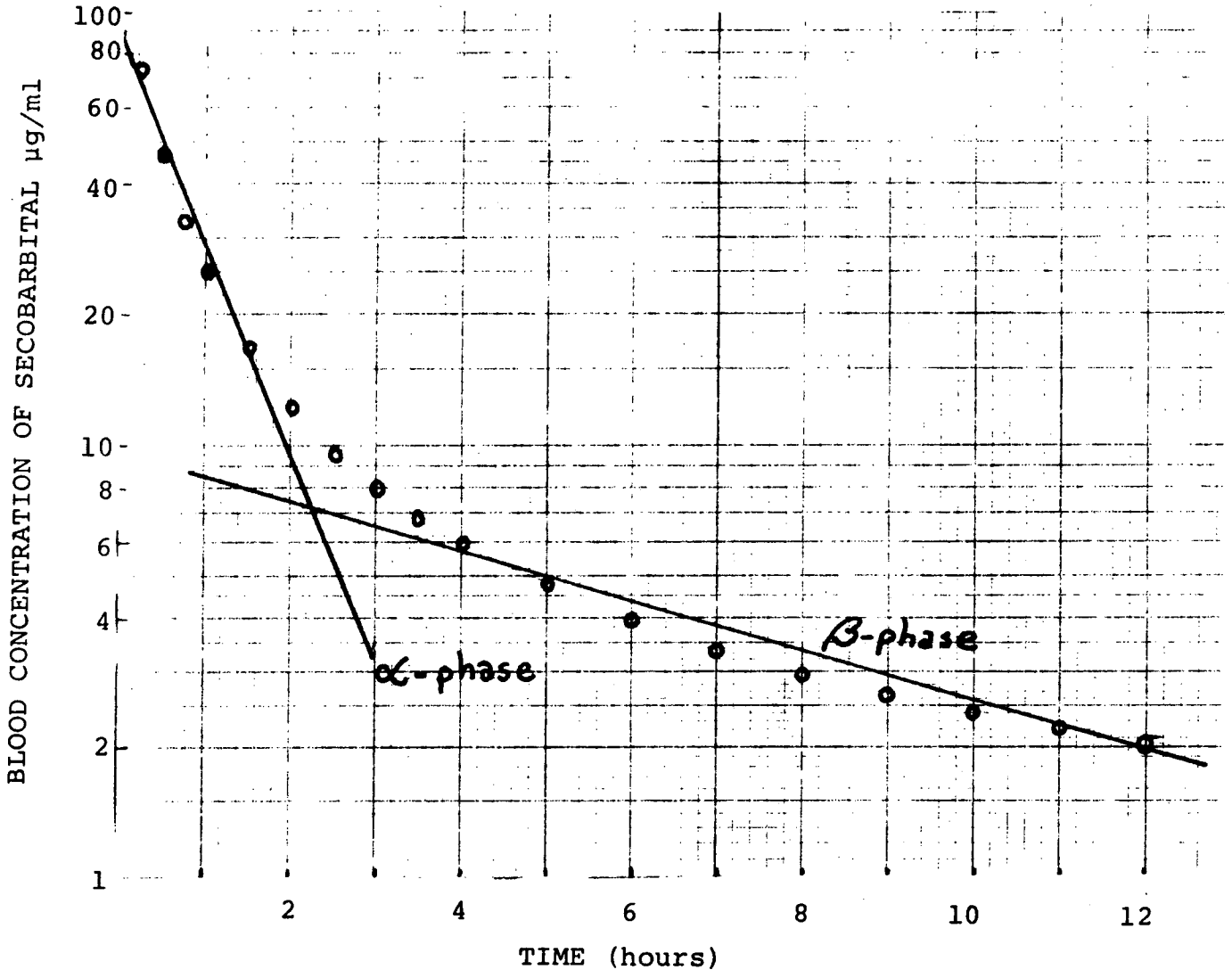

FIGURE 6

Plasma decay curve for a barbiturate such as secobarbital in normal humans. The open circles are actual measurements of blood levels of drug. The lines represent phase decay curves obtained by Feather analysis. The t 1/2 value for the α-phase is approximately 36 minutes, while the t 1/2 for the β-phase is approximately 5.2 hours.

TABLE 1

ADDITIVE EFFECTS OF ANALGESICS IN PAIN RELIEF

Drug(s) Administered	% Elevation of Pain Threshold*
Aspirin (225 mg)	32 ± 4%
Phenacetin (150 mg)	31 ± 7%
Aspirin (225 mg) + Phenacetin (150 mg)	67 ± 5%

*Values are mean ± S.D. for 14 subjects in each single drug group and all 28 subjects in the combined dosage group. Value for combined dosage group is not significantly different from expected sum of single dosage values.

TABLE 2

ANTAGONISTIC EFFECTS OF AGENTS ON BLOOD PRESSURE

Drug(s) Administered	mm Fall in Blood Pressure*
Histamine (µg/kg)	38 ± 6
Diphenhydramine (6.4 mg/kg)	4 ± 2
Histamine (1 µg/kg) + Diphenhydramine (6.4 mg/kg)	8 ± 6

*Values are mean ± S.D. for 8 test animals under each set of conditions. Combined dosage is not significantly different from control but is significantly less than histamine only.

TABLE 3

SYNERGISTIC EFFECTS OF DRUGS ON BLOOD PRESSURE

Drug(s) Administered	mm Rise in Blood Pressure*
Tranylcypromine (10 mg)	10 ± 3
Imipramine (50 mg)	2 ± 1
Tranylypromine (10 mg) + Imipramine (50 mg)	51 ± 6

*Each single dose value is the mean ± S.D. of 10 test animals; combined dosage was tested in 20 animals. Combined dosage is significantly greater than expected sum of single dosage values.

2.8 Pharmacological Classes of Drugs

Pharmacological classes of drugs may be considered as those categorizations of agents having similar effects on the organism. Each class is defined in terms of its predominant therapeutic use and predominant pharmacological action. A tabular listing of pharmacological classes particularly relevant to the drug-driving problem is presented in Table 4. This is not meant to be an exhaustive list of all therapeutic agents; obviously the selection process reflects the scientific expertise (and biases) of the author. It must also be recognized that the classes are defined in terms of the major useful therapeutic actions of the agents included. In this regard, it is essential to realize that no drug has only a single effect. In addition to the primary desired therapeutic effect, every agent has a variety of undesirable actions generally referred to as side effects. While these actions are undesirable, they are also inherently present due to the nature of the agent and its interactions with the diversity of biological systems within any organism.

TABLE 4

PHARMACOLOGICAL CLASSES OF DRUGS WITH THE POTENTIAL FOR IMPAIRMENT OF MOTOR VEHICLE OPERATION

Pharmacological Class	Examples	Type of Effect
Anticonvulsants	diphenylhydantoin phenobarbital phensuximide primidone	Drowsiness, sedation
Antihistamines	chlorpheniramine diphenhydramine promethazine tripelennamine triprolidine	Drowsiness, sedation, lack of attention
Antipsychotic Agents	chlorpromazine haloperidol thioridazine	Drowsiness, ataxia
Anxiolytics	chlordiazepoxide diazepam meprobamate	Drowsiness, muscle weakness
Cannabis	hashish marijuana THC	Disorientation, altered perception, altered timing
Environmental Agents	carbon monoxide trichhoroethylene volatile solvents	Drowsiness
Hallucinogens	DMT LSD mescaline phencyclidine	Distortions of time and space, mental aberrations
Narcotic Analgesics	codeine heroin hydromorphone meperidine morphine propoxyphene	Drowsiness, loss of coordination

TABLE 4 (Continued)

Pharmacological Class	Examples	Type of Effect
Over-the-counter Agents -		Various effects, depending on content
Sedatives/Hypnotics		
Barbiturates	amobarbital pentobarbital secobarbital	Drowsiness, stupor, "hang-over," ataxia
Non-barbiturates	ethchlorvynol flurazepam glutethimide methaqualone	Drowsiness, stupor, "hang-over," ataxia
Skeletal Muscle Relaxants	carisoprodol chlorzoxazone methocarbamal	Muscular weakness, ataxia, loss of coordination
Stimulants		
Amphetamines	amphetamine methamphetamine methylphenidate	Hyperreactivity, rebound fatigue, loss of attention
Non-amphetamines	caffeine	Hyperreactivity, loss of attention

2.9 Side Effects of Drugs

Side effects of drugs may be defined as those actions of pharmacological agents that occur in addition to the desired therapeutic effect. Such actions may range from minor unpleasantness that can be virtually ignored by the subject, through serious discomfort, to major toxicity and even life-threatening or fatal reactions. Some major examples of side effects of drugs that are relevant to the drug-driving problem are presented in Table 5.

TABLE 5

SIDE EFFECTS OF DRUGS THAT MAY HAVE ADVERSE EFFECTS ON MOTOR VEHICLE OPERATION

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 also not meant to be a complete listing, but rather 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.

2.10 Species Differences and Individual Variations

It is truly unfortunate that ethyl alcohol has been the most widely studied drug relative to the problems of motor vehicle operations, since it is one of the most atypical drugs in terms of the way it is handled by the body. The vast majority of drugs must be chemically altered in order for the organism to be able to dispose of them by excretory pathways such as the urine; for most agents, but not for ethyl alcohol, the chemical alterations are carried out by unique catalytic systems called liver drug metabolizing enzymes (LME's). These systems have a considerably different potency in various animal species, as illustrated by the data in Table 6.

TABLE 6

SPECIES DIFFERENCES IN METABOLISM OF HEXOBARBITAL

Species	Biologic t 1/2 (min)	Relative LME Activity
Mouse	19	100
Rabbit	60	32.8
Rat	140	22.4
Dog	260	6.0
Man	360	2.6

Although such species differences tend to make it difficult to extrapolate data from animals to man, other data (as shown in Table 7) indicate that if one ignores dosage differences and considers only effective drug levels in blood, it is possible to extrapolate quite well from animals to man.

TABLE 7

SPECIES SIMILARITY IN EFFECTIVE PLASMA LEVELS

Species	Effective Plasma Level of Carisoprodol µg/ml
Cat	125
Mouse	130
Rabbit	100
Rat	125
Human	105

A further complication exists in the fact that most drugs show a considerable variation in the rate of metabolic destruction, and consequently in their biologic half-life and duration of action in humans. This situation, as illustrated by the data presented in Figure 7, is known as individual variation. It arises from the facts that man is a heterogenous species and that the levels of LME activity are under genetic control. Thus in a given group of individuals, the same dose of drug may produce effects ranging from virtually nothing to almost toxic. Since most laboratory animals come from highly inbred strains, this further complicates the problem of extrapolating data from animals to man. In addition, species differences in the pathways of metabolic conversion of drugs and the related problem of pharmacologically active metabolites add further complexity.

2.11 Pharmacologically Active Metabolites

The vast majority of drugs undergo some sort of chemical change prior to being excreted from the mammalian body (see Section 2.10). These changes are referred to collectively as "drug metabolism;" The new compounds produced in the body are called "metabolites." In many cases, the conversion from drug to metabolite is also a conversion from pharmacologically active to pharmacologically inactive. However, in a significant number of instances, the chemical change leads to the production of an "active metabolite," that is, a substance with pharmacological activy. Indeed, for some drugs, the agent (as ingested by the subject) is pharma-

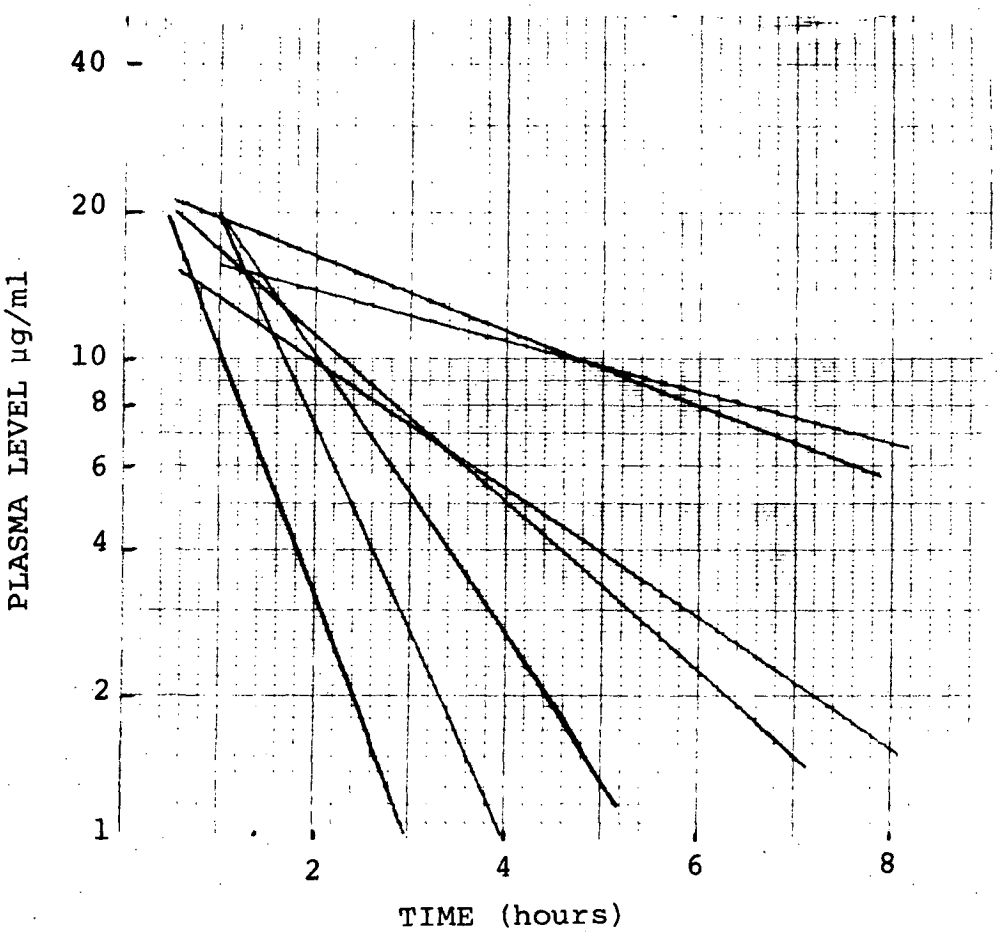

FIGURE 7

Individual variation in plasma decay curves of normal subjects given a single dose of diphenylhydantoin. Each line represents one subject.

cologically inactive and must be chemically changed (by the body) to have pharmacological activity. For others, the active metabolite has an activity different from that of the parent drug. In addition, each metabolite that has any significant pharmacological activity must be considered in terms of its own pharmacokinetic profile (topics discussed in Sections 2.2 to 2.6) and in terms of its interactions with the parent drug or other drugs present in the body. Some examples of drug metabolism are given in Table 8.

3.0 METHODS FOR IDENTIFICATION OF RISK FACTORS IN DRUG-DRIVING INTERACTIONS

At the present time there are three possible ways to evaluate the potential risk(s) involved in drugs being taken by someone who is operating a motor vehicle: predictions from available animal and/or human studies, epidemiological studies of drivers, and planned human studies. For all practical purposes, the latter has been done in a relatively few cases and is a need for future research. The other two procedures also suffer from serious weaknesses; nevertheless it is worthwhile to discuss each of these briefly to adequately describe the problem and set the stage for recommendations for future additional work.

3.1 Predictions of Risk From Available Data

The scientific literature contains a large volume of material relative to the effects of drugs on behavioral phenomena and having a bearing on drug effects on motor vehicle operation. In general, such material can be classified into one of three categories: animal behavioral testing, human behavioral testing, and incidental observations. While no one of these three bears a perfect relationship to the drug-driving situations, the sheer volume of available data permits one to draw some basic, if not quantitatively precise, conclusions.

3.1.1 Animal Behavioral Testing

Animal behavioral testing of many drugs has been carried out as an inherent part of drug development studies or basic research into animal behavior. The types of testing that yield conclusions most relevant to driving skills are being discussed by another working group presentation and will not be considered here. Some indication of the utility and applicability of the results may be seen in these other presentations. For example, animal studies of a drug that show effects such as loss of motor

TABLE 8

EXAMPLES OF DRUG METABOLISM IN HUMANS

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

coordination or muscular weakness to a significant degree should be considered as evidence that the drug should be studied further to determine if it would impair motor vehicle operation. Similarly, animal studies that report clear cut impairment in operant behavior are likely to be indicative of potential adverse effects in humans and suggest the need for additional testing to fully define behavioral effects.

A problem specific to such studies, however, lies in the age-old complication of extrapolation of data from animals to man. Because of the well-known differences between the rates of drug metabolism in animals and man, strict correlation between dosages is rarely, if ever, seen. Correlation can be found, however, in terms of blood levels, time-cause of drug action, and aspects of drug-drug interaction, as these are all phenomena that often transcend specific variation.

Nevertheless, it seems that much useful qualitative information regarding the potential risk for drivers taking certain types of medication can be obtained from animal data readily available from the open literature.

3.1.2 Human Behavioral Testing

Human behavioral testing is a second category of accessible and available material from which one can estimate drug risks in a driving situation. Many published studies report on the effects of drugs on human behavior and performance as determined by a variety of testing procedures. In these situations, several problems can also be identified and cannot be ignored. For example, the fact that a given drug may adversely affect the performance of a test subject in a task such as decision-making is not absolute proof that a similar erroneous reaction will be seen in response to the need for a decision in a highway traffic situation. Similar criticisms may be made with regard to other testing procedures such as coordination skills, response integration, or evoked behavioral responding. Perhaps more relevant tests are measurement of specific performance characteristics such as depth perception, color perception, visual acuity, or response time. As with animal behavior studies, while it may be difficult to estimate quantitative aspects, one should be able to at least find gross relationships that infer the risks to be expected from certain drugs.

In particular, testing of this type can be found in the aeromedical and aerospace literature. The relevance

of drug effects on aircraft piloting performance to effects on motor vehicle operation is clearly quite high. Specific types of testing (such as Link trainer systems) may even permit the evaluation of approximate dose-response curves in terms of performance impairment for complex situations. Of course, the problem still remains of the precise relationship of any sort of laboratory testing to the actual driving situation. A summary of the major problems involved is presented as Table 9.

TABLE 9

PROBLEMS INVOLVED IN RISK PREDICTION FROM AVAILABLE DATA

Problem/Difficulty	In Relation To: 3.1.1	3.1.2	3.1.3
Lack of dose-response data	Rarely	Sometimes	Always
Lack of time-response data	Rarely	Sometimes	Always
Extrapolation from animals required	Always	____	____
Inpatient/laboratory studies only	____	Always	Rarely
Drug blood levels not determined	Sometimes	Sometimes	Always
Questionable precision of measurements	Rarely	Sometimes	Always
Subjective evaluations	Never	Sometimes	Sometimes

3.1.3 Incidental Observations

Incidental observations are those comments that are found in published clinical reports about therapeutic agents, and most-especially, about their side effects. Observations such as patients reporting dizziness, drowsiness, lethargy, muscular weakness, discoordination, tremors, or other "nuisance-type" side effects of drugs, if repeatedly seen for a given compound, may well indicate a real side effect and a potential drug risk for the operator of a motor vehicle. In particular, such incidental observations may

reflect slight differences in drug action (due to irregular dosage, fatigue, nutritional habits, etc.) that are not observed under clinical testing or inpatient conditions, but do become apparent when the drug is taken by an outpatient. This is particularly relevant to the drug-driving situation, since hospitalized patients are not part of the driving population, while outpatients are clearly potential active members of that population. Thus, while incidental observations are not directly quantitative materials, they certainly make a significant pool of information from which drug risks can be qualitatively evaluated.

3.2 Prediction of Risk from Epidemiological Studies of Drivers

A modest number of attempts have been made to estimate the incidence of drug use by drivers involved in motor vehicle accidents. The statistics for the incidence of ethyl alcohol are well-known, although they do suffer from the weakness of not being considered in terms of dose-response statistics. Within the last twenty years, three types of epidemiological studies have been applied to the drug-driving problem: post-fatality studies, post-crash analyses, and questionnaires. The problems of such studies are summarized in Table 10.

TABLE 10

PROBLEMS INVOLVED IN RISK PREDICTION FROM PRIOR EPIDEMIOLOGICAL STUDIES

Problem/Difficulty	In Relation To: 3.2.1	3.2.2	3.2.3
Legal restrictions on subjects	Rarely	Frequently	Rarely
Validity of answers	Rarely	Rarely	Frequently
Limited precision of results	Rarely	Rarely	____
Unreliable methodology	Sometimes	Frequently	Sometimes
Sample handling procedures	Frequently	Frequently	____
Limited scope of examination	Frequently	Frequently	Rarely

3.2.1 Post-Fatality Studies

Post-fatality studies are those in which samples of tissues or fluids are obtained from the bodies of drivers killed in accidents; subsequent analysis of the samples can lead to identification and possibly quantitative estimation of the kind(s) and amount(s) of drug(s) present at approximately the time of death. Such studies, while moderately useful, suffer from a variety of weaknesses. For example, the question of sample handling from time of death to time of analysis is a critical one. It is known that many drugs are not even chemically stable in dead tissues unless frozen; nevertheless, it is a relatively uncommon situation for a sample to be obtained by autopsy in less than 4-6 hours after death in a motor vehicle accident. Similarly, suitable analytical procedures are not readily and widely available to permit accurate and precise analyses of drugs in biological samples. Of particular significance in this regard are polydrug problems, problems involving volatile materials or cannabis, and problems involving active metabolites (see Section 2.11).

In addition to these chemical and pharmacological problems, there are numerous additional difficulties to be considered. For example, biases in sampling procedures are almost always present, beginning with the fact that a sample population limited to fatalities is in itself biased. Other sample population biases include a variety of demographic factors such as those listed in Table 11.

TABLE 11

SAMPLE POPULATION BIASES IN EPIDEMIOLOGICAL STUDIES

Population Density
- urban
- rural

Age

Sex

Characteristics of Community
- college
- industrial

Time of Accident(s)

Location of Accident(s)

Finally, the problems of comparing control and drug use populations must also be considered. This is especially true in the case of fatality cases where little or no pre-information is available, that is, where one doesn't know what drug was taken or at what time. In such cases, the only estimate of agents that is possible comes from the analytical results obtained. In the absence of appropriate dose-response information, the assumption that the mere presence of a drug indicates that it can be considered causative in an accident is unfounded. Similarly, mere demonstration of drug presence in the body of a fatality driver cannot be used in evaluation of a risk of that agent for motor vehicle operation; it must be demonstrated that the level(s) of drug(s) present, at the time of the accident, were in the pharmacologically active range.

3.2.2 Post-Crash Analyses

Post-crash analyses are those in which drivers who are involved in motor vehicle accidents without being killed are subsequently tested for the presence of drugs in their body. This system is well-known, adequately instrumented, and generally legally accepted in the case of ethyl alcohol. However, in the case of other drugs, the system is almost a total failure. Analytical methodology is not readily available (see Section 3.2.1), and legal constraints are severe.

Even if one could carry out such a study, the lack of appropriate dose-response and time-response data for drug effects and the limitations of present methodology would make the results considerably less than completely accurate. The possibilities for misleading or even completely erroneous conclusions being drawn from such results are serious; the potential problems that such conclusions could generate are severe. One striking example may be given. In one such study (performed outside of the United States) approximately 12% of drivers and passengers hospitalized after motor vehicle accidents were found to have barbiturates present in their blood as opposed to only 4% of the population as a whole. Such data tempt one to draw the conclusion that barbiturates are a major risk to the driver. However, the question of whether the drugs were present at pharmacologically active levels remains unanswered and thus even an inferential cause-effect relationship cannot be legitimately derived.

3.2.3 Questionnaire Studies

Questionnaire studies are those in which some form of information collecting system, based on verbal or written

questioning, is used. The sample population may be drawn in a variety of ways, and may be adjusted to suit almost any design situation. Two very major problems exist in terms of the validity of such studies; either of these is sufficient grounds to seriously doubt any conclusions drawn therefrom. First of all, any information obtained is dependent on the accuracy and veracity of the respondents. If they have been involved in an accident, both of these factors may be less than acceptable. Secondly, even if the answers are correct and truthful, the lack of knowledge regarding blood levels of drug and pharmacological activity at the time of the mishap makes satisfactory interpretation difficult, if not impossible.

3.3 Predictions of Risk from Planned Human Studies

This is probably the most accurate and precise means of estimating the risk of drugs to the driving situation. A large number of such studies have been performed by Linnoila and Milner. In addition, a variety of other studies have been done, generally with single drugs based on the interest(s) of the principal investigator. Such studies suffer from a number of weaknesses, some of which may actually lead to a questioning of the validity of the data obtained and the conclusions derived therefrom. Some of these problems have already been mentioned, i.e., blood levels, pharmacological activity, dose-response relationships, and time-response relationships. In addition there are three critical problems, unique to this area, that must be considered.

3.3.1 Driving Simulators

Driving simulators of one variety or another are often used in such studies. There are serious questions as to the relevance of such artificial test systems and the ability to extrapolate the results obtained to the actual highway situation. In view of criticisms of these systems that have been raised by Moskowitz and others, it seems most reasonable to assume that some problems do exist and that the simulators are not to be given a blanket acceptance without question.

3.3.2 Motivation of Subjects

Motivation of subjects is also a critical variable that is currently not completely understood. This variable has great significance in terms of extrapolating any laboratory test system to a real world situation. Of particular pertinence is the fact that many drugs that influence behavioral

performance have effects dependent on psychological variables; thus, the level of motivation may be an extremely critical confounding variable.

3.3.3 Human Subjects Research

Research involving human subjects is subject to legal restrictions. Because of these restrictions, experimental design factors regarding safety must be rigidly enforced. In addition, the restrictions with regard to new, experimental or dangerous drugs are also severe. Thus, any potentially hazardous situation must be handled with appropriate care and in accordance with legal and ethical standards.

4.0 CONCLUSIONS AND RECOMMENDATIONS

The preceding sections presented material relevant to the determination of the risk created by the driver who has ingested a specific pharmacological agent or agents. The problem of determining this risk is fraught with difficulty. No single solution can be proposed. Several suggestions were made during the working sessions that, hopefully, can lead to a better understanding of the problem.

In approaching the determination of the risk posed by the "drugged" driver, it is essential to recognize that analogies between many drugs and alcohol may be totally irrelevant. Thus, approaches that have been used to assess the risk posed by alcohol cannot be simply adopted or translated to examine the risk posed by other drugs.

The following actions are suggested for assessment of the risk posed by drugs and driving:

- Determination of the pharmacological characteristics of a drug that would make one logically expect the agent to interfere with motor vehicle operation.
- Determination of the availability and frequency of use of the drug (both licit and illicit use).
- Characterization of the drug-drug interactions likely to occur with the agent when taken in combination with other agents.
- Evaluation of the type and extent of alterations in human performance produced by the drug use.

- Delineation of other factors that must be considered in terms of the action of drugs on driving, such as personality, environmental factors, social and human characteristics.

- Broad epidemiological studies are not recommended, at this time, because of the severe scientific and legal constraints that make it most probable that such studies would not produce meaningful results. Development of an adequate base of scientific knowledge and establishment of legal privilege should be objectives to support future epidemiological research.

DRUG/DRIVING RESEARCH REVIEW

SYMPOSIUM

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CHAPTER V

Speaker's Paper

DRUGS AND PERFORMANCE AS RELATED TO DRIVING

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Under Contract Number:
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1.0 INTRODUCTION

Any review of the literature on the effects of drugs on performance is a many-faceted endeavor. Thus, for the purposes of this paper, only those studies which are in any way related to driving skills will be discussed. The types of tests generally used for measuring the effects of drugs on performance involve combinations of different components of behavior.

For instance, there are psychomotor components in a vigilance task as well as attentional components; there are learning components in some psychomotor tests. This characteristic of performance measurements is both beneficial and detrimental. For example, Carpenter (1) concludes that the more complicated a task becomes, the more it is affected by alcohol. Therefore, these multicomponent tests may be sensitive to drugs whereas simpler tests are not. Unfortunately, what specific component of behavior is being measured may not be clear.

In terms of assessment of driving skills, there have been no studies done which show correlations between accidents and laboratory tests. No measure which can predict automobile driving activity and performance during stress of driving has been devised. There have been attempts using the so-called driving simulator which are similar to the studies using mock-up airplane cockpits which have proved to be useful to the training of pilots (2). Unfortunately, the motivation factors in driving have proved too difficult to control. If subjects really were motivated to the point that their licenses or livelihoods were in jeopardy then perhaps these tests would be sufficient measures of performance. After all, no one will get killed driving off the road in a simulator.

A classic example of the effects of motivation on drug performance is the study by Hill, et al (3) using ex-addicts in a reaction time experiment to measure the effects of three levels of motivation after intramuscular (i.m.) administration of 250 mg pentobarbital or 15 mg morphine. Under one condition the subjects were paid beforehand with (i.m.) morphine rewards (low incentive). In another instance, they were given (i.m.) morphine after the experiment. The third method involved giving morphine immediately for performing as fast as possible. The rate of response under 250 mg pentobarbital was faster than for the placebo; thus, the subjects were able to overcome the effects of barbiturates given in high doses.

Another important aspect of assessing the effects of drugs on performance is the method of administration. Are the drugs given either in single doses or by chronic administration to normal volunteers versus chronic administration to patients? The greatest number of studies with normals are done using acute single dose administration. Studies have been done measuring the effects of barbiturates (4), amphetamines (5), narcotics (3), cannabis (6), mild tranquilizers (7), antipsychotic agents (8), antidepressants (9), alcohol (1), antihistamines (10), toxic substances (11), and nicotine (12). While some of these drugs have been tested under chronic conditions with patient populations, most have not. For instance, the Early Clinical Drug Evaluation Unit (ECDEU) does not standardly include performance measures in their assessment of drugs to be administered to adults.

Tests vary from purely sensory ones which include sensory thresholds such as visual acuity and hearing, to the most complicated combination of cognitive and learning tasks involving psychomotor components. Although Goldstein (13) demonstrated that no one task correlated well with driving skills, the more complicated tests involving more than one component might have a better correlation. The importance of the complexity of the test is evident from varied measures of performance with cannabis sativa. A test such as that of Moskowitz et al (14) in which the subject is required to count flashes of a central visual stimulus while being distracted by peripheral stimuli is a sensitive test. Its sensitivity is such that the effects of alcohol and cannabis were different; it is a test which parallels some of the behavior involved in driving. A study of hallucinogenic drug abusers (15) attributes the subjects' "flashback" experiences to a prolonged afterimage of distracting headlights. Cannabis similarly affects the perception of autokinetic phenomena experienced when a single light source is viewed in a room bare of any other cues. Doses of 0, 50, 100, and 200 mg Δ^9-THC have increasing dose effects on apparent motion distances. This phenomenon can be related to driving skills especially at night (16).

A problem which has been explored very intensely is the interactive effects of the more commonly used drugs. For example, Lawton and Cahn (17) measured the effects of diazepam and alcohol on psychomotor performance and found detrimental effects of both drugs, but no potentiating effect by diazepam. Landauer et al (18) found no synergistic action between medazapam and alcohol during a variety of tests including driving simulation. These authors cautioned that the subjects used were healthy young men who were highly

motivated to do well, making the results good only for that group. Linnoila and Mattila (19) during driving simulation found no impairment of performance by low (5 and 10 mg) doses of diazepam or by low doses of alcohol. However, when used together, this combination of drugs produced impairment.

It is interesting to note that the subjects' reports did not agree with the performance changes. This anomaly indicates one of the problems associated with driving is that the subjects don't realize that their performance is affected negatively.

Such conditions exist all the time. The "anxious" outpatient is prescribed an anxyiolitic agent or the insomniac is prescribed an hypnotic and both stop off for a drink before going home. One of the hidden problems that exist is that so many people use mild tranquilizers unnecessarily. These individuals present a potential problem in the field. The result is one of potentiation of the hypnotic, or an additive effect with the antianxiety agent.

The procedure usually used in conducting an acute study is to test the subject prior to administering the drug, then at periodic intervals after administration. Sometimes the methodology is varied so that a particular agent which must be "built up" in the system is administered for two or three days prior to the study; then the "testing drug" is administered. Such studies are basically acute studies. In addition, a placebo condition is run even though a pretest is given.

A summary of studies on each class of psychotropic drugs will be presented. This is not intended to be a comprehensive review of the literature, however, examples will be given which are illustrative of the general types of performance changes characteristically brought about by particular agents.

2.0 TESTING AND DRUG EFFECT

2.1 Hypnotics and Depressants

This rubric includes barbiturates as well as nonnarcotic sedatives, all of which are generally depressant in nature. However, the motivation of the subject can alter their effects (3). Tasks requiring concentrated behavior such as the Digit Symbol Substitution Test (DSST), card sorting, Wilkenson Math Test, digit span, nonsense syllables,

delayed auditory memory tasks, feedback, cancellation tests, tapping tests, and serial learning tasks are markedly and adversely affected by hypnotics. Reaction time, pursuit rotor, Continuous Performance Test (CPT), and other tests whose primary action is attention are less affected. Kornetsky and Orzack (20) found, after administration of 200 mg secobarbital to normal subjects, that the greatest effect was on the DSST and little or no effect occurred with the CPT.

Most hypnotics are used by subjects for the purpose of facilitating or inducing sleep. A hangover effect may be present, however, because the patient has waited too long to take the medication. If the effects described above are indicative, the patient could still be impaired by the drug during the hangover period.

A comparison study of two non-narcotic hypnotics (glutethimide, ethchlorvynol) with secobarbital by Kaplan et al (21) using delayed auditory feedback, a stress task, showed that glutethimide was more impairing than the other drugs. Although there were no significant differences between glutethimide and secobarbital after four hours, the trend indicated better performance under secobarbital. Eight hours after administration placebo was generally better than all three. With the pursuit meter, an attention task, glutethimide treatment was more impairing than the other treatments at four hours. After eight the differences disappeared. In addition, the subjects' reports equated the effects of secobarbital and gluthethimide at four hours. The most important of the non-narcotic depressants is alcohol. The impairing effects of alcohol on intellectual behavior, even when the amount is moderate, are striking but are not pertinent to this symposium.

2.2 Antipsychotics

Antipsychotic drugs include phenothiazines (most commonly chlorpromazine), butyrophenones such as haloperidol, rauwolfia (reserpine), and thioxanthenes such as thiothixene. Their effects are considerable when administered to normal subjects. One hundred fifty to 200 mg of chlorpromazine caused normal volunteers to increase omission errors significantly on the CPT, a very simple test of attention (8). Tasks requiring short-term concentration such as reaction time and DSST are not affected, while pursuit rotor task or a track tracer task involving motor coordination were greatly impaired (8). Actually, the more motor components in the task, the greater the detrimental effect, as, for

example, scores on a tapping test which were reduced (22). Steadiness is considerably affected, although manual dexterity is not significantly impaired. Different phenothiazines have slightly different effects, but there is very little drug-to-drug variation at the highest dose levels.

One of the important properties of these drugs is their synergistic action with alcohol. Prior to the recent decision to let the majority of mental patients leave the hospital, this problem was not great but now there are many patients in the community taking phenothiazines and frequently drinking. Since these patients are on medication for legitimate reasons the effect may be beneficial even during driving. However, the interaction effects with alcohol obviously are not beneficial.

2.3 Hallucinogens

Hallucinogens, while illicit, are frequently used. The mildest one but the one which presents the most problems as a driving hazard is marijuana. There have been many studies done on marijuana itself or its main chemical component (Δ^9-THC) which demonstrated effects on coding, DSST (23), learning (24), divided attention (25), pursuit rotor (26), memory and perception (27), and time estimation level tasks (23, 24). A study by Klonoff (28) compared driving in a downtown traffic situation during rush hour with driving on a course in a secluded territory. Both this study and that of Kielholz et al (29) point up that the behavioral changes which occur are intensified in a stress situation. Performance was worse when the subjects were driving in traffic than on the course. The authors point out that rapid decisions and actions as measured by reaction time, were prolonged and more poorly performed. In the Klonoff study such vital skills as brake time were prolonged and poor judgment was used at intersections.

With regard to driver performance it must be remembered that the chronic cannabis user is not nearly as affected by drug administration as is the naive user (23); nevertheless, both may drive. The risk study (30) in which cannabis is said to decrease driving risk has not been replicated. However, the description of driving behavior of the "drugged" subjects who were on high doses of cannabis indicates that they clearly took more "risks" than did those on either low doses or placebo. Whether this behavior was a function of the increased autonomic arousal from the stress situation or the increased arousal as measured by heart rate associated

with cannabis smoking, is unknown (23). It is important that Klonoff (28) did demonstrate that some subjects performed better in the low dose cannabis situation than the placebo, probably because of motivation and compensation.

2.4 Stimulants

The effects on performance of amphetamines, caffeine, methylphenidate, and magnesium pemoline, are variable and depend not only on the nature of the task, but also on the length of the task. One of the necessary conditions for a stimulant to change performance is for the organism to be impaired for some reason (31, 32). The best example of this is demonstrated by the way which d-amphetamine counteracted the effects of 68 hours of sleep deprivation on a short term vigilance task (8). The type of task which is most affected is a dull and boring monitoring task such as devised by Orzack et al (33) where the subject was required to match numbers by pressing the appropriate key when he saw a number flashed as a stimulus. Both 50 mg of magnesium pemoline and 200 mg caffeine were able to counteract the effects of this task over a three hour period. The short term tasks like the DSST and reaction time showed much less change (8). The effects of amphetamine on driving are considerable. The long distance driver uses it to keep awake; it can help under some conditions. However, problems with too high a dose can occur, and if the subject is overstimulated his performance can decline. The concept of overstimulation is one which has been treated hypothetically with the inverted U-curve (34) which hypothesizes that arousal or activation and performance are not monotonically related. The theory holds that less arousal is associated with poor performance, that the median level produces optimal performance and that overarousal is associated with poor performance. The clinical evidence about overstimulation from stimulants is such that there is little doubt that the hypothesized curve will be demonstrated empirically. This author is now conducting a systematic study testing the inverted U-curve hypothesis.

2.5 Antidepressants

Closely associated with stimulants are antidepressant drugs. Behavior after administration is similar but the mode of action is different. In acute studies, imipramine and amitriptyline do not show effects on behavioral skills. Rather, it is only with repeated doses (even in normals) that these effects can be obtained. Patman et al (9) found that dot tracking, pursuit rotors, and simulated driving tasks showed no deterioration after five days of chronic

dosage of amitriptyline amounting to 400 mg. The addition of alcohol altered the performance on the pursuit rotor and the simulated driving tests, but there was no interaction effect between the two agents. The sedative effects of tricyclic antidepressants decrease in the course of therapy after treatment (35). Nevertheless, patients, especially of this type, may freely alter their doses of medication and exchange medications with one another. In addition, such patients should be careful about consuming alcoholic beverages.

2.6 Antihistamines

Hypnotic effects produced by antihistamines have been observed in a double blind study by Hughes and Forney (10). In a comparison of the effects of clemizole, diphenhydramine, and tripelennamine on pursuit rotor and delayed auditory feedback tests they found that no significant impairment occurred but the subjects felt that they had taken a depressant. In combination with alcohol there was significant potentiation of the effects of diphenhydramine, while alcohol alone produced impairment in all tests.

Linnoila (36) compared subjects on different doses (200 and 400 mg) of chlormezanone, diphenhydramine, and meclizine, or a placebo, alone, and in combination with 0.5 g/kg alcohol. He found that neither dose of meclizine was detrimental to performance of a coordinated psychomotor task related to driving and a choice reaction time (RT). Some improvement occurred with RT and has been attributed to a "relaxed" effect. Diphenhydramine caused similar effects and at 90 and 150 minutes psychomotor performance improved. The lower dose of meclizine did not enhance the effects of alcohol; the higher dose had effects at 30 minutes, but after 90 minutes no effect remained. The effect of diphenhydramine did show impairment in combination with alcohol and lasted longer than the meclizine. Chlormezanone improved the short term test result. Again this effect is attributed to "a relaxing effect." At 400 mg no change occurred at all, probably because the "relaxing effect" and the impairment balanced out. Similarly chlormezanone did not potentiate the effects of the alcohol. Linnoila points out that these subjects were highly motivated and that there was great variability in the performances. Hence, he cautions that the effects on some people produced by diphenhydramine and alcohol could be a real hazard in driving (36).

2.7 Anti-anxiety Agents

The anti-anxiety agents or mild tranquilizers which are used so abundantly in modern medicine may present special hazards. Berry and Grubb (37) did a careful study in which they assessed the effects of 10 and 20 mg oxypertine and 10 mg chlordiazepoxide on a driving simulator test (Redifon Autotutor), a spatial coordination task called the "Oops" test, and a pursuit rotor task. After an hour there was a significant improvement in braking time with oxypertine at one hour, but deterioration at two hours occurred with 10 mg. Contrarily, the effect of 10 mg chlordiazepoxide was to cause deterioration on all the tasks for three straight hours, with no initial improvement.

In another study Holmberg and William-Olsson (38) compared 200 mg of benzquimanide, 60 mg of chlordiazepoxide, and a placebo. Benzquimanide decreased critical flicker fusion and auditory span, and increased coordination errors, while chlordiazepoxide increased only standing steadiness. Lawton and Cahn (17) measured the interaction of alcohol and diazepam. The placebo-placebo group was superior to the placebo-diazepam group on a pegboard task and on an addition task. This was a semi-acute study where normal subjects were given diazepam three times a day for three consecutive days and then administration of the test drug on another day. These studies point out the possible hazardous effects of these particular types of drugs which are prescribed so ubiquitously to the general public and are often mixed rather injudiciously with alcohol (35, 39, 40).

2.8 Miscellaneous

Nitrous oxide (laughing gas), carbon monoxide, and nicotine have been studied frequently. Studies of nitrous oxide have shown that its action is similar to that of barbiturates in that it depresses intellectual activity as well as motor activity (41), estimation of duration of time, and on the acquisition of learned tasks (42). This drug is used frequently in dental surgery, but otherwise probably doesn't present a hazard to driving.

Carbon monoxide, however, is always present in the driving situation. McFarland, et al (43) found that a small amount of CO impaired certain measures of vision, such as acuity, critical flicker fusion, and visual perimetry. Exposure to carbon monoxide is comparable to performance at high altitudes, which was characterized by impairment of many intellectual and psychomotor tasks (44, 45). In combination

hypoxia and carbon monoxide are additive; the tests used are often so sensitive that even the increase of carbon monoxide in the blood from smoking a single cigarette was detected in task performance.

Horvath et al (46) measured errors in a visual monitoring task in which a response was required for each stimulus. The results indicated that the number of signals identified correctly decreases as dose increases between 0, 26, and 111 ppm in the blood. Such a decrement has obvious implications for driving.

Nicotine, which is a mild stimulant has been shown to have effects on hand steadiness, skin temperature, and blood pressure. Subjects showed a significant effect from the first cigarette but the subsequent ones created no significant change (12). Reaction time, on the other hand, is improved in cigarette smokers as compared to the non-smoking condition (47).

3.0 CONCLUSION

The problem of mixing one or more psychotropic agents together is of paramount importance. Frequently the effect is more than additive, especially if the second drug is alcohol (39).

The evidence points to the conclusion that a pure and simple predictive measure of drugs on performance cannot be obtained. The literature is extensive on drug effects on performance tasks, but while drug effects can be defined operationally, confounding variables such as motivation, set and setting are modifying influences on the stability of such tests, and may actually obscure the "true" drug effects. In short, while partial indicators may be obtained from the use of performance tests, a measure of driving ability is best obtained in a real life driving situation.

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DRUG/DRIVING RESEARCH REVIEW

SYMPOSIUM

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CHAPTER VI

A Report of the
Working Sessions on:

MEASUREMENT OF DRUG EFFECTS ON BEHAVIOR

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1.0 INTRODUCTION

This paper summarizes the discussions of the working sessions dealing with the measurement of drug effects on human behavior. The participants were concerned with examining current research to identify the state of the knowledge of testing methods that measure the effects of drugs on human behavior parameters that are related to the driving task.

A logical approach for the discussions would have been to establish a framework which identified the human factors involved in the driving task, the behavioral tests which examined such factors, and then examine the literature which described the way in which test subjects were affected by various drugs.

While such an approach is both logical and desirable, the current state of knowledge does not permit the development of such a conceptual framework. The driving task has not been adequately defined, existing testing methods have not been correlated with known components of the driving task, and only limited measurements of drug effects have been made.

The examination of the effects of drugs on driving is a complex multidisciplinary research problem. At least three basic research areas and three different disciplines are involved, although there is significant disciplinary overlap among researchers working on various aspects of the problem. The research areas are not precisely defined in the research literature but may, for convenience, be identified as follows:

- Driver Task Analysis
- Behavioral Test Development
- Analysis of Drug Effects

The first research area has been the subject of concern by Human Factors researchers at least since the first national conference on that topic was called by President Hoover in 1924. The ultimate research goal is the development of an empirical model that defines the parameters of human behavior involved in the driving task and relates those parameters to the probability of accident occurrence. T.W. Forbes (1) has edited a series of readings on "Human Factors in Highway Traffic Safety Research" that describe the area and the status of current knowledge.

Studies of driver behavior and the driving task have been fraught with methodological difficulty reflecting the complexity of the problem. A study by Miller et al (2) comments on the nature of existing research.

> "Individual studies of the relationship between various driver characteristics and measures of driving 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 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 fluctations 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 working group faced an initial problem. The parameters that should be examined to determine if drug use adversely affects driver behavior are not well-established.

An examination of the second research area relating to behavioral test development also posed a problem. Test development has been a concern of experimental psychologists for many years. Tests have been developed to examine human behavior and provide greater insight into mental processes. Tests have been developed by researchers to examine the particular facet of human behavior which was the subject of their research. One finds tests developed to assess specific aspects of human performance without reference to real world activity. For example, cognitive ability may be tested without reference to any particular application. The psychological literature on testing and drugs includes studies that report drug effects observed on tests. Unfortunately, assessment of these results in terms of the real world, rather than the laboratory, is difficult if not impossible. This is because of the artificial nature of the laboratory setting and the lack of established correlation between the testing method and real world applications such as driving. Test results that demonstrate gross impairment, as when the subject falls asleep, strongly suggest potential risks. Other test results that suggest subtle influences defy reliable extrapolation to the driving task.

The psychological literature presents another problem in that an uneven profile appears in the results reported. In many cases the researchers are primarily interested in test development rather than the examination of drug effects. Experiments may be conducted without adequate consideration for dose-response effects. Thus, the results may present less than a complete picture of drug effects. Frequently, the subjects are atypical of the general population and the sample size very small. Typically, only one drug or a few drugs are examined. The literature is tantalizing but far from definitive.

Similar problems exist with the pharmacological literature that reports testing for drug effects. Pharmacologists tend to be concerned with defining pharmacological activity of drugs with primary emphasis on main effects rather than side effects. One finds carefully documented data on a drugs chemical action within the body but only limited information on behavioral effects. Behavioral effects, when noted, are often described in general terms rather than in the more precise measurements that flow from sophisticated behavioral tests.

The field of psychopharmacology has grown rapidly in recent years with the increase in the development of psychotherapeutic agents. Thus, better data are appearing in the literature; however, the pressure for examination of drugs in the context of treatment has limited the scientific resources available for detailed examination of drug effects that are not treatment-related. Some literature exists dealing with measurement of drug effects related to driving behavior. It is very limited and incomplete when one considers the range of drugs that pose potential impairment risks.

Thus, the participants began their discussions with the recognition that there were serious limitations on the quality and scope of existing research dealing with measurement of drug effects.

2.0 MEASUREMENT SYSTEMS

The participants examined the various testing methods known to be used by researchers for the examination of drug effects. The most direct method of testing discussed was the observation of a subject operating a motor vehicle, driving simulators were examined next and then the various psychological tests believed to relate to the driving task. The following sections briefly describe the testing methods and discuss specific issues associated with the various methods.

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 (3) 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 com-

plexity 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 atypical subjects. 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.

2.2 Driving Simulators

Driving simulators are attractive measurement devices as 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 in the previously cited work of Forbes (1). While it is possible that 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 Verkehrssicherheit listed 17 devices in use in 11 locations in the United States and 11 in 9 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.

2.3 Multiple Performance Testing

A multitude of procedures have been devised over the years by psychologists to measure and evaluate human performance. These same procedures or modified versions of them have been utilized in the evaluation of factors believed related to driving performance. While many of these tests may detect effects of a drug or differences between two or more drugs, there is not necessarily any correlation between these effects and motor vehicle accidents. Safe driving is the result of complex integration of perceptual, cognitive and psychomotor skills with personality characteristics as well as prior driving experience. Some tests utilized to evaluate human performance as it may relate to driving are described in the following sections.

2.3.1 Card Sorting

The actual variable measured by this test is decision time. It involves the use of a modified deck of playing cards consisting, for example, of the ace through eight in the traditional suits. The testing involves the time required to sort the cards into two, four and eight equal-sized stacks as compared to the time required to sort them again into two, four, and eight equal stacks, first by color, then by suit and finally by numerical value.

2.3.2 Mathematical Tests

These are complex tests which place a high demand on the central nervous system. They have been used to assess the effects of varying degrees of sleep loss.

2.3.2.1 Mental Arithmetic

In this test, the subject is required to add four one-digit numbers, then add the two digits of the answer, then multiply two of the numbers and finally add the two digits of that answer. Scoring is in terms of the time required to correctly solve a problem, as well as the errors for each problem.

2.3.2.2 Paced Math Test

This test consists of a series of pairs of single digits presentd by tape to the subject at a given rate. The subject adds the paired digits presented and writes the answers on a sheet. The digits may be presented at varied speeds of approximately one every two seconds.

2.3.3 Digit Symbol Substitution Test (DSST)

This test was developed to assess cognitive association aspects of performance and requires the subject to associate a series of ten symbols with their corresponding digits. Performance of this test, which requires the subject to write symbols beneath numbers in accordance with a predetermined code, necessitates sustained attentive performance and attention to a visual display.

2.3.4 Continuous Performance Test (CPT)

This test, like the DSST, is designed to measure a subjects capacity for sustained attention. The subject is required to sit in a darkened room and to watch a screen upon which letters of the alphabet are flashed rapidly and in random order. The subject is to press a button whenever a specified critical letter is presented. Apparently the presence or absence of prior experience with the test has no effect on performance.

2.3.5 Vigilance Testing

This test involves detection procedures. Like the CPT (2.3.4), the subject is required to indicate the presence or absence of some specified change in the environment. A test of vigilance could involve the use of a meter with a line capable of deflecting. The subject's response is to press a lever whenever the line deflects a specified distance from center. The term "vigilance" is based upon the concept of the physiological adaptive efficiency of the central nervous system and has been used to refer to a control process or state of the organism. Simple Reaction Time (RT) is also measured in this way. The time period between presentation of the signal and the subject's response is measured as the RT. Any sensory modality could be used in the vigilance or reaction time tests. The less frequently the stimulus is presented, the longer the RT will be on the vigilance test. Also the probability of detecting a signal declines with the time the subject spends on the task. This decline is usually attributed to loss of alertness due to low task requirement.

2.3.6 Divided Attention Tasks

With divided attention tests, a subject, while performing one task, usually a vigilance test, is required to attend to at least one other relatively simple but attention-demanding task. Differences in perceptual load imposed by one task, while not apparent on that task, sometimes are demonstrated in terms of different levels of response on the secondary task.

2.3.6.1 Choice Reaction Tasks

One example of a divided attention task is the Choice Reaction Test. With one example of this test, the subject must respond to green, yellow, blue or red signals by pressing with the right index finger a button of the corresponding color. In addition, he must respond to a white signal appearing at irregular intervals by pressing a pedal with the right or left foot. Additionally, he must attend to auditory signals of high or low frequency by pulling a right or left hand lever. Stimuli are presented automatically in random order at progressively faster rates.

2.3.6.2 Moskowitz Vigilance and Divided Attention Task

This test was developed by Moskowitz and DePry (5). The vigilance phase consists of detecting the presence of a signal in background white noise. The divided attention task involves repeating a series of digits presented to one ear while vigilance stimuli are presented simultaneously to the other ear.

2.3.7 Time Estimation

This is a complex task which places a high demand on the central nervous system. The test is usually administered in one of two ways: first, the subject is requested to press a button after a specified interval has elapsed, or secondly the subject is requested to keep a button depressed until a specified interval has elapsed and then release it.

2.3.8 Autokinetic Phenomenon

This phenomenon is defined as the apparent motion of a stationary source of light in a darkened environment free of spatial references. Several components of this test can be measured, however, the final displacement of the light source in any given trial is the usually measured end point. Although this test is subject to subjective, social and drug influence, knowledge of the cause of the autokinetic effect is limited.

2.3.9 Critical Flicker Fusion (CFF)

With this test, the subject is allowed to view a flickering light from some selected distance and to adjust the flicker rate until it just appears to be a steady light. This rate is called the critical flicker fusion. The actual

flicker rate is measured electronically. In addition to drugs such as ethanol which affect the CFF, other factors influencing it are age, size of pupil and body temperature.

2.3.10 Delayed Auditory Feedback

This test is used to measure mental performance under conditions of self-induced anxiety. The subject speaks into a microphone and the voice is recorded for delayed playback through headphones. By this method a short delay of a fraction of a second is introduced into the auditory feedback. The subject is presented a variety of tests utilizing reading material or problems such as verbal output, reverse reading, forward or reverse counting, addition or subtraction problems.

2.3.11 Psychomotor Tests

Just as there were psychomotor components in many of the previously mentioned tests which involved performance of a response such as lever pulling or button pushing, there are other components such as learning and vigilance in psychomotor tests.

2.3.11.1 Tapping

This is a relatively simple test in which the subject is requested to tap a morse key as rapidly as possible. The number of taps made in a short period of approximately 10 seconds serves as the score. Results of this test are dependent on age and disability of subjects.

2.3.11.2 Tracking

This is a test in which fatigue is likely to result. In this test, a subject must make continual adjustments as the course he is trying to follow or track changes from moment to moment. It is much like driving a car in traffic on a windy day when the movements of the car are not very predictable. Usually performance on a tracking task will show an improvement over time, as a result of continued learning. However, if the subject is already highly skilled, efficiency will decrease the longer the task is continued as a result of fatigue. The workload of tracking tasks can be increased by requesting the subjects to monitor a flashing light and remember the frequency of flashes. Often this second task is not even scored, but merely introduced to increase the complexity of the tracking task.

2.3.11.2.1 Dot Tracking

This task requires the subject to draw a continuous line between small dots (approximately 5mm apart) arranged in an irregular spiral. This pattern, attached to a slowly rotating turntable, is tracked with a pen through a small aperture cut into the lid of the apparatus. Since dots are tracked from the center to the periphery of the spiral, response speed has to be gradually increased. The test is scored as the total number of dots tracked accurately.

2.3.11.2.2 Pursuit Tracking

One version of this test involves the use of a dual-beam oscilloscope and a steering device which the subject can use to control one of the oscilloscope beams. A pursuit meter is programmed to display patterns of varying complexity with one beam while the subject's task is to track these patterns with the second beam. The difference between both trackings is recorded as the error signal, and calculated as the deviant distance from a perfect score.

In another version of this test, the subject tracks the target with a stylus containing a photoelectric cell at its tip. The track may be a circular or triangular pattern and the target may move at a fixed or variable speed but the subject is instructed to keep the stylus in contact with glass covering the track and target. A timer keeps a record of the total time on target.

2.3.11.2.3 Flow Maze

Like other tracking tests, this test measures gross changes in eye-hand coordination. This test consists of a metal maze through which the subject pushes a metallic stylus, tracing through the maze as quickly as possible with-out touching the sides. The time required to complete the maze as well as number the contacts with the sides is recorded.

2.3.12 Physiological Effects

In addition to behavioral measurements of drug effects, physiological measurements of variables such as heart rate, respiration, pupil diameter, and accomodation should be performed to fully interpret drug action. Electroencephalograph (EEG) tests have also been suggested.

3.0 RESEARCH ISSUES

The discussion of measurement methods and the literature led to identification of a number of problems that must be considered in developing future research directions. The following sections briefly present major issues and comments developed in the working sessions.

3.1 Experimental Design Problems

Several consistent methodological problems surfaced as past studies were discussed. These must be avoided in the future if adequate results are to be obtained. Some of the lapses noted can be traced to a lack of multidisciplinary involvement in the design and execution of research studies.

3.1.1 Subject Selection

Many studies utilized a population of subjects that represented a sample of convenience and were not representative of the general driving population. The use of young college students as subjects may produce results that are significantly biased. Care must be taken to select subject populations that are representative of the general driving population. Specifically included must be a sufficient number of subjects who are representative of the drug-using population.

In some studies personality evaluation tests (e.g., MMPI) have been used as screening tools to eliminate subjects who appear to fall outside of normal limits. Rejection rates as high as 70 percent were reported. This approach may introduce significant bias as it may be the rejectees are representative of a portion of the population that presents an abnormal drug/driving risk.

3.1.2 Drug Characteristics

Only a select few of the drugs that have the potential to affect driving performance have been tested. Many of the study results are difficult to interpret because of the way in which the drug administration was reported.

No single dose of any drug will produce the same result in all subjects. Many factors are known to affect drug action. For example, sex, weight, and health of the subjects, the route of administration of the drug, and pretreatment interval of drug administration are just a few. Another confounding variable to be considered is duration of

treatment. Many drugs are taken under the supervision of a physician for a relatively long period of time. Phenobarbital, for example, is routinely prescribed for epileptics and generally the duration of the treatment is continued indefinitely. With prolonged administration of a drug, the possible development of tolerance must be kept in mind. Tolerance does not necessarily develop to all actions of a drug in all individuals at the same time or to the same degree. Also, withdrawal of a chronically adminstered drug can produce behavioral changes and effects.

Thus, the experimental design must provide for very careful documentation of the mode and quantity of the drug administered and utilize full dose-response schedules.

Most studies of drug effects report the actions of acute dosage and therefore bear little resemblance to the conditions under which many of the drugs are licitly used. In contrast, some studies report the effects of therapeutic dosage levels of drugs that are known to be significant drugs of abuse that are commonly taken by abusers at much higher dosage levels. Such results also bear little resemblance to real world conditions.

A further complication in experimental studies is the short interval between administration and testing that is used in many studies. A significant number of drugs have long half-lives in the body and can continue to exert their effects long after the experiment has been concluded. Good examples of this case are the drugs which produce their action through the metabolite rather than the parent molecule. Only through careful consideration of the pharmacodynamic profile of given drugs can an adequate experimental design be developed. Usually, analytical measurement to verify drug action should accompany tests designed to record behavioral effects.

3.1.3 Test Selection

Some of the studies reported in the literature appeared to utilize tests on the basis of convenience or availability rather than because of any correlation with driving behavior. Care must be taken to examine the characteristics of the drug and the driving task in selecting an appropriate test or battery of tests.

3.2 Experimental Strategies

The present literature tends to reflect the interests

of individual researchers in either a particular drug or a particular test. A more coordinated approach to the examination of drug effects must be undertaken. Available epidemiological data indicating risk associated with particular drugs/drug classes as well as experimental evidence from human and animal studies should be assembled to develop a priority set of drugs for behavioral testing. As correlations are developed between animal impairment and human behavioral effects, a system to monitor animal test results on new and existing drugs should be established to allow early detection of drugs that appear to be potential risks.

3.3 Drug Interactions

Current information on drug use suggests that polydrug use is common and may play a significant role in driver impairment. The most frequent drug interaction is apt to arise when alcohol and drug use occurs. Development of a testing strategy must consider the probabilities of polydrug use and test for these conditions. Interaction of drugs that are medically used for treatment of a chronic condition, with alcohol or with other commonly used or prescribed drugs must be considered.

Particular sensitivity must be given to drug combinations that result in an additive or potentiating effect. Concern must also be given to drug combinations that are likely to produce impairment that will be undetected by a user.

3.4 Other Concerns

Research has tended to concentrate on the human factors associated with driving that are more easily detected and measured. Only limited attention has been paid to personality factors such as aggressiveness and risk-taking. In addition to developing testing programs that can approach assessment of these factors in the non-drug-using driver, concern must be given to the effects of drugs on personality and judgment. This is an extremely complex area but may play a very significant role in the crash problem. It deserves examination.

4.0 CONCLUSIONS AND RECOMMENDATIONS

Conclusions and recommendations were a continuous product of the discussions and have been reported in prior sections of this paper. The following points represent summary suggestions on key issues.

- The driving task must be analyzed to identify the human behavioral parameters which are most susceptible to impairment by drug use.

- Existing behavioral tests should be examined to establish better correlations between test results and behavioral parameters associated with the driving task.

- A coordinated program should be developed to examine a selected set of drugs believed to be involved in the drug/driving problem to identify behavioral effects that may present a highway safety risk.

- Drug interactions appear to represent a significant potential risk and should be examined in any research program concerned with the measurement of drug effects.

- A long range program to systematically investigate the risk posed by drug use should be initiated to include both animal and human studies to allow early detection of risk in new as well as existing drugs.

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DRUG/DRIVING RESEARCH REVIEW

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CHAPTER VII

Speaker's Paper

THE QUANTITATIVE DETERMINATION OF DRUGS IN BIOLOGICAL SAMPLES

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1.0 INTRODUCTION

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 a task for specific investigators. 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 continues to remain a difficulty. Why is this so? To begin with, 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. Some of these aspects are being considered in the presentation by Prof. J. Little; others will be discussed later in this presentation. For the moment, let us turn to the scientific aspects of this problem.

Precisely what is meant by the title of this article? What kinds of techniques are involved in the microassay of drugs in biological samples? Are drugs or biological samples unique in the problems that they generate? Let us first examine some of these questions to see how the answers would determine th procedures to be used and the problems to be faced. First of all, 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 1 µg to 100 mg/kg of body weight - a range of 10^5. 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 metabo-

lized 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.

This low concentration range creates the problem of endogenous interfering substances. Consider, for example, the barbiturates and their structural similarity to endogenous pyrimidines, the similarity of autonomic drugs to endogenous catecholamines, and the look-alike structures of many antimetabolites and pharmaceutical steroids and their edogenous counterparts. Not only are structural similarities a problem, but also most of the endogenous substances are present in relatively constant concentrations so that the ratio of endogenous compound/drug look-alike may vary with time from 10^{-3} to 10^{3} or even greater.

Finally, one cannot ignore the fact that the chemical and physical properties of biological samples run the gamut from watery fluids like saliva or urine, to gaseous samples like expired breath, to viscous liquids like blood, and, in the case of animal studies or autopsy samples to heterogeneous semisolids like body tissues.

2.0 GENERAL REQUIREMENTS

It seems obvious that the overall process for analytical measurement of a drug in a biological sample can be described in terms of the general requirements for any analytical procedure. Schematically, this process may be considered as it is presented in Figure 1.

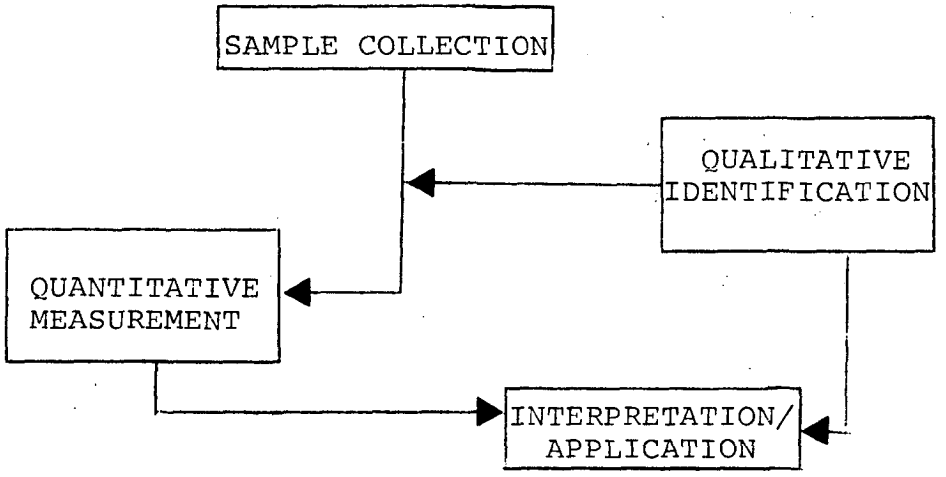

FIGURE 1

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, urine, or possibly, saliva. In the case of a fatality being autopsied, the sample may be blood or urine, or a body tissue, or 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.

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 insure that leakage or evaporative losses do not occur, since such losses may selectively influence the validity of analytical results.

2.1.2 Stability

Stability of the compounds to be analytically determined in the sample must be insured. 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 siutation 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.

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.

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 sort of 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.

2.4 Interpretation/Application

The final step in the overall process is the point at which someone must sit down and assemble 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 to the satisfaction of the analytical lab director 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.

3.0 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? Why does a published procedure work extremely well in one laboratory and fail miserably in another? 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?"

For the purposes of this presentation, let us summarize these characteristics in terms of the concepts presented in Table 1. Each of these can be examined in turn; it is essential to remember that a failure to satisfy any one may lead to a serious practical limitation of the procedure.

TABLE 1

CHARACTERISTICS OF AN ACCEPTABLE ANALYTICAL PROCEDURE

SPECIFICITY
SENSITIVITY
SPEED
SIMPLICITY
RELIABILITY
ECONOMY
SAFETY

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 100 or 1,000 times higher concentration of impurities. There are several common ways to assure the specificy of a

method. The final measurement step may be very specific, as, for example, a fluorescent assay with specific wavelengths of activation and emission. A chemical reaction may be performed 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.

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} M, 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.

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.

3.4 Simplicity

In developing analytical methods over the past 20 years, the author has 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 important to remember, however, that specificity or reliability should not be sacrificed merely to increase the output of results.

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 ±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 ±5% range).

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 consummables of 20¢ per assay would be a savings of $1,040. In a similar manner, 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.

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 $HClO_4$ has been removed by precipitation as $KClO_4$.

From a consideration of all of these factors, it should be obvious that methodology for drug analysis is an area in which special problems abound. Nevertheless, criteria for any given method may be made as rigid - or as flexible - as needed. In this regard, it is necessary to briefly discuss the concepts of minimal detection, minimal measurement, and reasonable limits. The use of appropriate statistical procedures to establish minimal detection limits, minimal quantifiable limits, and even validity of blanks or standards is highly recommended. In fact, one often ignored possibility for input in developing a method is to call on the assistance of a statistician in determining these requirements. For example, it is rather valueless to insist on a method having accuracy to the nearest nanogram when the range of plasma levels to be determined rarely falls below 0.1 µg. Similarly, calculating data to the nth significant figure is inefficient when the means are to be rounded off to the nearest whole number in the 2nd significant figure.

Finally, it should be an essential part of any method to install a set of checks and balances - "indicators" of successful performance, so to speak. When blank values exceed a certain limit, or when standards deviate from the expected value by more than a predetermined value, the analyst should respond almost automatically to question, or even to reject, the data. This is esepcially true since automation and instrumentation have reduced the opportunities of the analyst to observe such possible problems as color, precipitation, particulate matter, and so on, in the analytical sample.

4.0 BASIC CONCEPTS OF SEPARATION AND MEASUREMENT

All assay procedures may be characterized in two parts: separation and measurement. Let us consider each of these in turn, emphasizing the basic ideas involved and looking at general aspects rather than specific points.

4.1 Separation

It is an extremely rare situation when a drug can be measured directly in a sample of biological material without any further treatment. A few techniques such as activation analysis, flame photometry, or atomic absorption spectrometry may be applicable to studies of drugs in biological materials without extensive purification.

For most exogenous compounds such as drugs, some sort of separation procedure must be employed to "isolate" the compund of interest from other substances in the biological material which would interfere with the assay procedure. The most commonly used separation procedures include those listed in Table 2. These procedures may be applied directly

TABLE 2

PROCEDURES FOR SEPARATION OF DRUGS FROM BIOLOGICAL SAMPLES

- PRECIPITATION
- LIQUID-LIQUID EXTRACTION
- CHROMATOGRAPHY
  - Column
  - Paper
  - Thin Layer (TLC)
  - Gas-Liquid (GLC)
  - High Pressure Liquid (HPLC)
- MISCELLANEOUS

to the biological sample, or some chemical reaction may be performed prior to the separation step. The reaction may form a derivative of the desired compound with advantageous solubility characteristics or may eliminate undesirable material by conversion to substances readily separated from the compound of interest. In general, separation procedures depend upon differences in physicochemical characteristics such as solubility, partition coefficient, ionization, or volatility.

4.2 Measurement

Many different techniques can be used to actually quantitate the amount of a specific substance in a sample. The majority of assay procedures, however, depend upon one of the measurement systems listed in Table 3. These pro-

TABLE 3

TECHNIQUES FOR QUANTITATIVE MEASUREMENT OF DRUGS

ABSORPTION SPECTROMETRY
Ultraviolet (UV)
Visible (VIS)
Infrared (IR)
SPECTROPHOTOFLUOROMETRY
RADIOISOTOPIC DERIVATIZATION
GLC DETECTOR SYSTEMS
MASS SPECTROMETRY
PAPER/THIN LAYER CHROMATOGRAPHY
IMMUNOASSAY

cedures, with all their variations and modifications, represent the modern armamentarium of quantitative measuring techniques. When combined with appropriate separation procedures, they yield suitable and effective methods for the microassay of drugs in biological samples.

4.3 Combination of Separation and Measurement

Perhaps the best way to describe the combination of techniques of separation and measurement into an ideal procedure is in terms of a model. Consider a beaker containing a large number of red marbles and a few blue marbles. If we wish to know the percentage of blue marbles, we may make a fairly accurate estimation of this by mere visual inspection. However, if we wish to know precisely the weight of red glass and blue glass, we must separate the marbles mechanically, then measure the weight of each colored batch.

4.4 Qualitative Identification of Drugs

One final aspect to be considered is that of the need for qualitatively identifying the drug being measured. In many cases, the qualitative identification can be made concurrently with the quantitative measurement, since a number of the techniques utilized for identification are inherent components of separation or measurement procedures. A listing of characteristics useful for the qualitative identification of drugs is given in Table 4.

TABLE 4

CHARACTERISTICS FOR QUALITATIVE IDENTIFICATION OF DRUGS

ABSORPTION SPECTROMETRY

Maxima

Minima

SPECTROPHOTOFLUOROMETRY

Activation

Emission

CHROMATOGRAPHY

R_f

R.T.

MASS SPECTROMETRY

Molecular Ion

Fragmentation Pattern

5.0 PRINCIPLES AND PRACTICE OF SEPARATION PROCEDURES

The procedures by which separation of drugs from other components of biological samples may be accomplished are many and varied. In considering methods for the assay of drugs in biological samples, optimal conditions for measurement specificity will be achieved when the final sample contains a maximal amount of the desired substance and minimal quantities of interfering substances. This criterion may be met by application of a single technique, or

it may require the use of several techniques, depending upon the drug, the nature of the biological material and the measurement procedure to be used.

5.1 Sample Preparation

Biological materials exist primarily as fluids, such as plasma, urine, cerebrospinal fluid, saliva, sweat, tears, bile, and amniotic fluid; and semisolids, such as tissues and feces. In addition, there are the respiratory gases which represent special cases. In working with the fluids, drugs are generally present as solutes; adjustment of pH may be the only requirement necessary prior to application of a separation procedures. In the case of semisolid samples such as tissues, the structural integrity of the sample must be destroyed to permit ready separation of the drug. The most common technique utilized to disrupt issues is that of homogenization. In addition, other techniques may be used instead of, or in addition to, homogenization. For example, tissues may be minced or chopped with any sharp-bladed instrument, or they may be subjected to sonic disintegration prior to homogenization, or they may be frozen and pulverized while in the frozen state. The technique of choice will depend largely upon the characteristics of the biological material. For example, brain is very soft and is readily converted to an appropriate consistency by homogenization in an aqueous phase. In contrast, skeletal muscle is tough and resilient and may require extensive prehomogenization treatment to obtain a suitable degree of dispersion.

5.2 Precipitation

In the simplest case, precipitation of unwanted materials (such as proteins or cellular debris) may make the sample amenable to a quantitative measurement procedure. A variety of techniques may be applied to reduce the solubility of proteins and to facilitate their removal from the sample. The two most common procedures are the use of trichloracetic acid (to a final concentration of $\sim$ 5%) or perchloric acid (to a final concentration of $\sim$ 0.4 N). Unfortunately, both of these agents generally interfere with subsequent procedures and must be removed. The protein-free supernatant after centrifugation may be washed several times with cold diethyl ether to remove trichloracetic acid, while perchloric acid may be removed by addition of solid K_2CO_3 to produce the relatively insoluble $KClO_4$. When metaphosphoric acid or the neutral $ZnSO_4$ or $BaSO_4$ procedures are used, there

is generally no need for treatment to remove the residual precipitant substances.

5.3 Liquid-Liquid Extraction

Separation of two similar substances is often accomplished by use of the principles of partition between two dissimilar phases. This basic physicochemical principle is involved in liquid-liquid extraction, as well as in all the variants of chromatography. At this time it seems appropriate to review briefly those aspects pertinent to drug assay procedures, because many applications depend upon successful utilization of partition-related phenomena.

In any given system of two immiscible phases, the Nernst distribution law holds true, and the partition of a given solute can be characterized by $K = f_1/f_2$ and $f_1 + f_2 = 1$; i.e., the sum of the fractions of solute in each phase is equal to the total solute present. This equation is independent of the concentration of solute in each phase, assuming that solubility is not a limiting factor. It is, however, dependent upon the characteristics of the solute and may be influenced by variables such as temperature. The single partitioning of a given drug solute between two immiscible phases forms the basis for liquid-liquid extraction procedures used in many drug assays; repetitive partioning is the basis of countercurrent distribution procedures and many forms of chromatography.

Because many drugs and, unfortunately, their metabolic products have sufficient lipophilic character to possess a partition coefficient favoring their transfer from aqueous to organic phases, techniques of liquid-liquid extraction must be considered to have a primary role in drug assay procedures. The procedures currently in use have varied little from those described by Brodie, Udenfriend, and Baer in 1947 (1). The choice is made of the least polar oganic solvent that will extract from the aqueous phase sample the largest fraction of drug with the least possible quantities of drug metabolites and interfering substances. In this regard, it should be recognized that the relative polarity of solvents can be estimated from a consideration of physicochemical properties such as the dielectric constant as reported by Craig and Craig (2).

5.4 Column Chromatography

This is the oldest chromatographic technique, although its utility has been limited by several factors including

low resolution and long development time. Column packings include substances such as cellulose, alumina, silica gel, or, in a specialized variation, ion-exchange resins. Development is carried out by procedures of frontal displacement or elution analysis (3); the latter is the most popular variation, in which the solvent is allowed to flow continuously through the column, separating the solutes and then washing out (eluting) the separated bands.

The applications of column chromatography to microassay procedures for drugs in biological samples have been rather limited because of the fact that the elution procedures generally result in an excessive dilution of the solute. However, column chromatography serves well as a "cleanup" step for removing interfering substances prior to subjecting the sample to a final separation step and subsequent measurement. An excellent compilation of applications of column chromatographic techniques to drug and drug metabolite analyses may be found in Hirtz (4).

5.5 Paper Chromatography

Although paper chromatography as a routine laboratory technique is barely 30 years old, it has been widely applied to many drug assay procedures. Paper chromatographic separations can be considered analogous to repetitive partitions; development for 20 to 25 cm is the equivalent of thousands of countercurrent distributions. The bound water in the paper sheets represents the aqueous phase; it may be altered by pretreating the paper with buffer or by replacing the bound water with appropriate nonpolar compounds. Theoretical aspects of separation as a function of pH dependent partitions have been presented by Carless and Woodhead (5).

In addition to the use of paper chromatography as a separation technique, it may also be used as a combined separation and measurement procedure by the application of appropriate additional procedures. For example, the desired spot may be eluted prior to or following a derivatizing procedure, or densitometry or reflectance fluorometry may be applied. If a radioactive derivative has been produced prior to chromatographic separation, autoradiography or radiochromatogram scanning may be used for quantitation. The popularity of paper chromatographic procedures has decreased considerably in the past decade because of the generally lengthy time of development required, as compared to other, more rapid, chromatographic procedures (thin-layer, gas-liquid). A development in paper chromatographic technology

that has some unique applications is that of modified cellulose (phosphorylated or DEAE) producing a one-step combination of paper and ion-exchange chromatography; this too suffers from the problem of lengthy development time (6).

5.6 Thin-Layer Chromatography (TLC)

The variations on the theme of a thin-layer of separatory material on a solid support are numerous. Widely used sorbents include cellulose, silica gel, alumina, and polyamides; supports include glass sheets, glass fibers, aluminum, and a variety of polymeric substances. In addition, a host of development chambers and development modes are available, ranging from glass fruit jars to exotic sandwich arrangements to impressive tanks. In general, the presence of water in the adsorptive sites reduces the efficacy of separation. Consequently, an activation process generally involving heating at 100 to 120°C is commonly used, following which the plates are stored in a desiccator. A variety of developing systems are available. Stahl has discussed all the principles and practices of thin-layer chromatography (TLC) in the most recent edition of his excellent book (7).

As a separation technique, TLC is rapid, highly specific, and easily adaptable to a variety of situations. Its applications have been primarily in the area of qualitative procedures; quantitation generally requires that the area of sorbent containing the spot be removed from the plate and the quantitation step performed on an eluate. Some varieities of densitometric techniquies are available, and, of course, autoradiography and radiochromatogram scanners can be used to quantitate isotopically labeled samples. The quality of separation by TLC is quite good, especially if the R_f values of the drug are sufficiently different from those of interfering substances.

Precoated plates have improved the reproducibility of TLC separations because the machine coating procedures lead to better uniformity of coating, homogeneity of sorbent layer, and stability of the finished product. In addition, the precoated plates more readily insure consistency of activation effects because the variability of activation is dependent upon homogeneity and uniformity of the sorbent layer. Newer developments in supporting materials, i.e., the use of flexible sheets of inert polymeric materials, have permitted even greater physical stability to be achieved in the final product. In addition, such plates may be

routinely stored in laboratory notebooks or loose-leaf binders without the weight, thickness, and fragility of glass. Another new variation is the use of a prepackaged mixture of sorbent and developing solvent such as that used in the Kodak Chromat/O/Screen process.

A final innovation is the development of glass fiber sheets that have been impregnated with silica gel or other absorbents. The entire sheet is relatively strong while being light and having development times less than those required for glass plates. Spots may be readily cut out and solutes of interest easily eluted from the excised spot. This technique has recently been applied to a combined forensic and medical procedure for drug identification in a wide variety of sample materials (8). An important aspect of the glass fiber sheets is that both sides of the chromatogram are exposed and easily accessible; thus, two different visualization techniques may be applied to a single chromatogram.

5.7 Gas-liquid Chromatography (GLC)

Another relatively recent addition to separation techniques (developed in the last 25 years) is vapor phase chromatography, so called because the components of a mixture are separated while being carried through a column in a stream of inert gas. The stationary phase may be a solid with an active surface such as molecular sieves, charcoal, or silica gel; in this case, the process is called gas-solid chromatography (GSC). More commonly, the stationary phase is a high-boiling, inert liquid (silicones, polymers, waxes) coated on a solid support such as fire brick, in which case the process is called gas-liquid chromatography (GLC). In general, the carrier gases are inert substances such as nitrogen or helium, carried through the column at a constant rate of flow. For a detailed discussion of all the variables of column packings, carrier gases, and operating conditions, there are several excellent reviews (9,10).

There are many detector systems available for use in GLC techniques. The oldest, and still useful, detector is the thermal conductivity cell. This detector is simple to use, responds to virtually all compounds, has excellent linearity, and is nondestructive. However, its limiting sensitivity, generally 5 to 10 μg, makes its applicability to microassay procedures extremely limited. The flame ionization detector is currently the most popular system because it is easy to operate, has a wide range (both qualitatively and quantitatively) of detection, and will

routinely extend into the nanogram range. From a laboratory safety point of view, this detector does introduce the possible hazard of a tank of hydrogen or a hydrogen generator in the laboratory. Finally, the electron capture detection is used for compounds with a high electron affinity such as halogenated alkyls, nitriles, some conjugated carbonyls, and organometallics. This detector system is sensitive into the picogram range; if the drug per se is not active, treatment to form an appropriate halogenated derivative may easily be employed.

Newer developments in detectors have emphasized the use of techniques specific for a chemical grouping or even a single type of atom within a molecule. For example, the alkali flame detector uses an electrode containing salts of Na^+, Rb^+, or Cs^+. This sytems may be made specific for organic compounds containing phosphorus, nitro groups, or halides with a concurrent increase in sensitivity to below the nanogram range (11). Similarly, a microcoulometric detector may be used that is specifically sensitive to halogens, sulfur, or phosphorus (12).

Finally, one must consider the use of a mass spectrometer as a detector system for GLC. Many variations exist on this theme: the mass spectrometer as a measurement device will be considered in a later section of this review, and the combination system generally referred to as GC/MS will also be examined. Briefly, though, the use of a mass spectrometer as a detector permits even greater confidence to be achieved in the specificity of an analytical procedure. For example, by using a specific mass number, or several specific mass numbers, one can be assured of the identity of a specific GLC peak. This latter procedure has been termed "mass fragmentometry;" the procedure, as first described by Hammar, Holmstedt, and Ryhage (13) has sensitivity well into the picogram range. One inherent problem of MS detectors is that quantitation may prove difficult or require complicated procedures or expensive equipment.

Another new development in GLC should also be considered. In pyrolysis-GLC, the sample is thermally degraded (pyrolyzed) at a high temperature, and the pyrolysis products are swept into a GLC apparatus to produce a "fingerprint" of the compound. This may permit the positive identification of chemically similar compounds such as secobarbital and phenobarbital (14). Comparatively few applications of this process to drug assay problems have been made; the degree of sample purity required may be a severely limiting factor.

5.8 High Pressure Liquid Chromatography (HPLC)

Liquid chromatography is based on the principle that long, narrow-bore columns can achieve separation speed and efficiencies approaching those of gas-liquid chromatography. Columns of 2 to 8 mm internal diameter are commonly used, with sample sizes of 10 μg to 10 mg. High pressures (up to 6,000 lb/in.^{2}) are often needed to force the eluant through the columns, and special instrumentation is required. At the present time, a severe limit to the applicability of this technique is the sensitivity of the detector systems. The most sensitive commonly available system is the ultraviolet detector, which is effective to 100 ng/ml; more sensitive systems are not routinely available because of their prohibitive cost (15).

In the high pressure liquid chromatography, where the stationary phase is nonpolar, i.e., Carbowax 400 on Porasil C, and the mobile phase is also relatively nonpolar, i.e., hexane, reverse phase liquid chromatography uses a nonpolar stationary phase and a polar mobile phase such as water.

5.9 Miscellaneous Separation Techniques

Gel permeation chromatography involves the separation of molecules by virtue of differences in molecular size. The larger molecules in the eluant are retained by the gel, while the smaller ones pass through and are quickly eluted. This technique is somewhat useful for drugs, because compounds of molecular weight less than 1,000 are generally not retained, although aromatic molecules tend to be adsorbed strongly regardless of molecular weight.

The use of ion-exchange resins in column chromatographic procedures has been active ever since the development of the resins. The techniques involved and the applications of these techniques have been reviewed in depth by Edwards (16). A particularly useful application of ion-exchange resins has been the use of Amberlite XAD-2 in the isolation of narcotic drugs and their metabolites from urine (17).

Chromatographic adsorbents such as silica gel or alumina may be used as batch adsorbents rather than in columns or on TLC plates. In the batch procedure, the adsorbent is mixed with the solution in a test tube or centrifuge tube. After centrifugation the solvent is discarded by decantation and the process is repeated with washes, if needed, and finally with an eluant which restores

the drug or metabolite to solution. In a similar manner, activated charcoal may be used as a batch adsorbent; the separation is generally performed by filtration, and the charcoal is washed on the filter paper prior to elution. In fact, some drugs may be selectively removed from solution by precipitation at an appropriate pH where their solubility is limited and they will be carried down (coprecipitated) with an appropriate precipitating agent.

When the drug has finally been separated from other constituents of the biological sample, other procedures may need to be employed to put it into a form suitable for measurement. For example, to facilitate getting the drug from an aqueous phase into an organic phase, it may be necessary to resort to the addition of inorganic salts to the aqueous phase (salting-out). Then, to return the drug from the organic phase to a suitable aqueous phase may require the addition of less polar material to the organic phase (reverse salting-out). Finally, it should be remembered that various combinations of the separation procedures described above may be used, indeed may even be required, to achieve satisfactory separation.

6.0 PRINCIPLES AND PRACTICE OF MEASUREMENT TECHNIQUES

Once a drug or drug metabolite has been separated from the other substances in a biological sample, an appropriate process can be applied to quantitatively measure the amount of drug in the sample. Measurement procedures are many and varied; their sensitivity varies from micrograms to less than picograms in a sample. The sample size required may vary from several milliliters to several microliters. In addition, the usefulness of a given measurement technique may be limited by the linearity or reproducibility of the response or by the magnitude of the residual interfering substances, i.e., the blank. In this regard, a rule-of-thumb relationship may be adopted in which the minimal acceptable quantity of substance to be measured is that which yields a reading equal to that of the blank.

6.1 Sample Preparation

In virtually every measurement procedure, the physical state of the sample is extremely important. For example, spectrophotometric techniques demand that the compound to be measured be in solution; gas chromatographic and mass spectroscopic procedures demand a noninterfering, volatile solvent; bioassy procedures require samples in solution in nonbiotoxic solvents. In addition, the size of the sample

may be limited by the measuring device to be used, and excessive dilution may lower the ultimate sensitivity of the overall procedure. Finally, the presence of varieties of interfering substances may cause extensive difficulties. Thus, suspended particulate matter may cause light-scattering, leading to erroneous higher values in fluorometric or liquid scintillation procedures and erroneous lower values in ultraviolet or visible absorption spectrometry. Light-absorbing material may cause erroneous low values in spectrophotometric, fluorometric, or liquid scintillation procedures by the process commonly known as quenching. The presence of macromolecules such as protein may cause erroneous findings in bioassay or immunoassay because of adsorption or absorption phenomena.

6.2 Ultraviolet (UV) Absorption Spectrometry

Absorption spectrophotometry as a measurement technique is based on the ability of a chemical compound to absorb radiation in the wavelength range of 200 to 30,000 nm. A pattern of absorbance relative to wavelength - the absorption spectrum - is characteristic of the light-absorbing compound and may be used to identify or characterize unknown compounds. More pertinent to this review, the amount of absorbance at a specific wavelength may be proportional to the concentration of the absorbing substance, thus yielding a means for quantitative measurement of the substance.

The basic wavelength limits for routine use of ultravilet (UV) absorption methods are the transmission limit of air (190 nm) and the arbitrary beginning of the visible spectrum (400 nm). Within this region, a large number of organic compounds will have significant absorption peaks suitable for use in quantitative methodology. While quantum mechanics can be used to theoretically relate absorption of light to chemical structures, the complexity of most drug molecules precludes use of the quantum chemistry approach; most relationships have been derived by empirical means. The basic principles of relating structure to UV absorption have been reviewed by Maickel and Bosin (18). In addition to the absorption characteristics inherent in the structure of the molecule, however, the possible impact of environmental influences on the state of the molecule cannot be ignored. In this regard it must be emphasized that UV absorption of a drug molecule is often highly sensitive to the solvent. Moreover, because the solvent or sample containing the drug to be measured may also possess absorbing properties, it is essential that all measurements be made in relation to an appropriate blank.

The applications of UV absorption spectrophotometry to drug assay in biological samples have been many and varied. The basic principles were first proposed by Josephson,

has been reviewed in depth by Scott (20).

6.3 Visible (VIS) Absorption Spectrometry

As one progresses to still longer wavelengths of light, the visible spectrum (400 to 750 nm) is the next segment of the spectrum applicable to the microassay of drugs. However, few drugs contain chromophoric groups absorbing in this region. It becomes necessary to introduce chromophoric groups into the molecule or to alter the state of the molecule in such a way as to produce a chromophore. A simple example would be p-chlorophenol, where merely elevating the pH to produce the phenolate ion introduces significant absorption activities at 420 nm. However, in most cases, actual chemical reactions must be performed on the drug after its separation from biological material. A host of such reactions are known; some of the basic principles have been reviewed by Brodie, et al (1).

6.4 Infrared (IR) Absorption Spectrometry

It is often said that UV and visible absorption spectra are "electronic" spectra because they result from the interaction of light with the electronic configuration of molecules or portions thereof. By contrast, infrared (IR) absorption spectra characterize a molecule by describing its vibrational and rotational energy states. Most IR spectra contain numerous sharp absorption bands considered as "fingerprints" of the molecule. Although IR absorption (wavelengths > 800 nm) has been used as a quantitative technique, it must be emphasized that the primary value of IR absorption lies in identification and structure characterization of organic compounds.

In terms of quantitative microassays for drugs in biological materials, Erley, Blake, and Potts reported on the use of IR absorption as the measurement step after chloroform extraction of drugs from plasma. Several other applications are seen in the book by Kendall (22). However, a recent review chapter by Fales (23), while extolling the praises of IR absorption as a potential quantitative tool, fails to cite a single reference to such applications.

6.5 Spectrophotofluorometry

The basic procedures involved are the activation of a molecule with incident radiation of a discrete wavelength that will be selectively absorbed. The activated molecule, in the process of decaying from the excited state to the lower energy ground state, then emits radiation of a longer wavelength that can be measured and used to quantitatively determine the compound. An excellent discussion of the processes involved may be seen in a recent review by Ackerman and Udenfriend (24) and in a classic book by Udenfriend (25).

Many aspects of fluorescence of organic molecules are still unknown. Indeed, while theoretical grounds can be described for predicting fluorescence or lack thereof in a given molecule, in many instances prediction of the amount of fluorescence from a molecular structure seems more of an art than a science (26). Several aspects of fluorescence procedures, however, must be considered in any method utilizing this type of measurement. The fluorescence yield from a solution containing a fluorescent solute is often proportional to concentration only over a relatively narrow range. At low concentration, the limits of accuracy are often determined by electronic noise in the measuring instrument and by chance contamination, while at higher concentrations quenching by other molecules leads to a significant deviation from linearity. Background fluorescence ("blank") is often a problem because of the high sensitivity of the technique. Reduction of this blank may require the use of specially purified solvents, carefully washed glassware, and elimination of possible trace contaminants. For example, distilled water or buffer solutions may elute fluorescent materials from rubber stoppers or polymeric containers or tubing. Light-scattering of either excitation or emission radiation may also be a problem leading to erroneously higher or lower values. For this reason, colloidal particles must not be present in the sample to be measured. Finally, the process of activation may cause photodecomposition of the solute molecules, especially if the compound is chemically unstable or if oxygen is present in the irradiated solution.

Many compounds possess native fluorescence and can merely be separated from biological materials by procedures as described above, then assayed in an appropriate solution form. The pH of the solution may be critical, as some compounds show markedly different fluorescent characteristics,

depending on the degree of ionization.

Other compounds may be converted to highly fluorescent derivatives by appropriate chemical treatment after separation from biological materials.

Several derivatizing agents capable of producing highly fluorescent products from drugs containing amino groups have been developed. The first of these was dimethyl-aminonaphthalene sulfonyl chloride (dansyl), a compound formerly used to tag terminal amino groups in studies of protein composition and strucutre. A new derivatizing agent, 4-phenylspiro[furan-2(3H),1'-phthalan]-3,3-dione (fluorescamine), has been reported which has sensitivity to less than 1.0 ng/ml (27). This reagent is highly reactive to primary amines and appears to have fewer blank problems.

6.6 Radioisotope Derivatization

A very significant application of radioisotope procedures lies in the application of labeled derivatizing agents. The basic theory behind such applications lies in the principles of semimicro qualitative organic analysis. Thus, a derivatizing agent is used to react with the drug to produce a labeled product which is then isolated and measured by an appropriate technique. Because the specific activity of the derivatizing agent is known, if the characteristics of the reaction are known, it becomes a simple matter to quantitate the amount of drug present in the sample.

A wide variety of reagents are potentially available; such applications may well be in terms of general methods where specificity is conferred by the separation procedures. The basic procedures are simple. The drug to be studied must be separated from possible interfering substances prior to reaction with the radio-labeled derivatizing agent. Alternatively the derivatization step may be carried out on a crude sample, followed by suitable separation procedures. The derivatizing reaction is carried out under conditions that give a stoichiometric reaction; thus, the specific activity of the derivative is directly proportion to the specific activity of the radio-labeled reagent. Quantitative measurement of the radioactivity in the derivative will yield a quantitative estimate of the amount of compound present in the sample. The sensitivity limit will depend upon the specific activity of the radio-labeled reagent and the blank (28).

6.7 GLC Detector Systems

In the discussion of separation techniques, the various types of gas chromatography (GC) have been presented as means of separating compounds from one another and from interfering substances. Such procedures may also be applied to the quantitative determination of drugs, often in a combined, i.e., separation plus measurement, procedure. Compounds may be chromatographed directly, or they may be derivatized to enhance volatility, separation, or sensitivity of detector response. Preliminary separation techniques may or may not be necessary, although it is generally necessary to have the sample in a small volume (1 to 100 µl) of solvent, free from water prior to injection into the GLC system. For details of procedures and scope of applications, the reader should consult reviews such as those of Anders (14).

6.8 Mass Spectrometry

Perhaps no other single development in instrumentation has had such a massive impact on analytical methodology as has the development of mass spectrometry (MS). While the applications of this technique to date have been primarily in the area of qualitative characterization of compounds, quantitative applications are beginning to appear and should become more numerous as instrumentation improvements continue to occur. An excellent review of the applications of MS to pharmacological problems has been made by Guarino and Fales (29).

The use of MS as a quantitative tool is still relatively in its infancy. A recent development has been that of a special computer-MS system which can do both qualitative identification and quantitative assay on the same sample; the first report of this technique was by Green (30). In addition to this technique, the MS system in a specific ion detection mode can be used, together with stable labeled (^{2}H) compounds as internal standards, to quantitate mass fragment (31). The combination of GLC and MS technology, especially in a unitized instrumental mode, is also useful for both qualitative separation and quantitative measurement, as discussed in a recent review by Jenden and Cho (32).

6.9 Paper/Thin Layer Chromatography

As mentioned in the earlier discussion of paper and thin layer chromatography, both of these procedures can be

intimately involved in quantitative measurement, although the actual measurement is done by some other process. Thus, the developed plate may be scanned by a deasitometer (absorption spectrometry, spectrophotofluorometry) or by a radiochromatogram scanner. Alternatively, the spot or band containing the drug can be cut out or scraped off and the drug eluted for measurement.

6.10 Immunoassay

The early work on the development of immunoassay procedures was restricted to large molecules such as polypeptides. Such molecules are dimensionally sufficient in molecular weight to elicit an antibody response in the organism if their configuration or amino acid sequence is "foreign" to the organism (or can be made so by simple chemical or physical treatment). However, Landsteiner (33) showed in 1945 that smaller molecules which are incapable of producing an antibody response by themselves may be coupled with larger molecules to produce an antigenic response. Thus, by attaching a small molecule (hapten) to a larger molecule such as a serum protein, one may readily produce an antigen that will elicit an antibody response. A number of procedures have been used to produce suitable antigens from haptens such as drugs by coupling to readily available structures in proteins.

The basic principles involved in immunoassay procedures, whether fluorescent or radiolabeled, are relatively simple. One needs to produce the specific antibody, then react it with the appropriate hapten and isolate the product. A form of isotope dilution procedure is used. Labeled and unlabeled antigens (or haptens) compete for their specific antibody.

In practice the unlabeled hapten to be determined is mixed with a known amount of labeled hapten and an amount of antibody approximately equivalent to the unlabeled hapten. The competitive nature of the hapten-antibody reaction determines that the amount of labeled hapten that binds to the antibody is inversely proportional to the amount of unlabeled hapten present in the sample. Conversely, the amount of labeled hapten remaining unbound is directly proportional to the concentration of unlabeled hapten. The system is allowed to reach equilibrium, following which the free and/or bound labeled hapten can be removed and quantitatively estimated, thus yielding the concentration of the unknown hapten. The procedures must, of course, be implemented with appropriate controls and generally require

considerable attention to details such as concentration.

7.0 COMPARISON OF OVERALL METHODS

An attempt to produce a side-by-side presentation of analytical methodology for drugs in biological samples led to the development of Table 5. In this case, the final

TABLE 5

Analytical Process	Pre-Work Required		Specificity	Limit of Sensitivity	Reliability	Expertise Required	Time Per Assay	Cost to set-up Lab	Cost Pe Assay
	Man Hrs.	Complexity					Man Hrs.		
UV Absorption Spectrometry	1.0	Moderate	Fair	10^{-6}g	Excellent	B.S.	0.25	$ 3,000	$20
VIS Absorption Spectrometry	1.0	Moderate	Fair	10^{-6}g	Excellent	B.S.	0.25	$ 3,000	$20
IR Absorption Spectrometry	2.0	Considerable	Good	10^{-5}g	Good	M.S.	0.5	$ 5,000	$40
Spectrophoto-fluorometry	1.0	Moderate	Excellent	10^{-9}g	Excellent	M.S.	0.5	$ 8,000	$30
Radioisotopic Derivatization	2.0	Considerable	Good	10^{-12}g	Good	M.S.	2.0	$15,000	$60
GLC Detector Systems	1.0	Moderate	Excellent	10^{-10}g	Good	M.S.	1.0	$ 6,000	$20
Mass Spectro-metry	2.0	Considerable	Excellent	10^{-10}g	Good	Ph.D.	1.0	$35,000	$60
Paper/Thin Layer Chromatography	1.0	Moderate	Good	10^{-7}g	Good	B.S.	3.0	$ 500	$40
Immunoassay	3.0	Considerable	Good	10^{-12}g	Good	M.S.	4.0	$10,000	$70

measurement technique was used as the characterization for each procedure. In preparing the comparison, several assumptions were made in trying to maintain legitimacy. For example, the laboratory was considered to have a certain standard amount of equipment; the procedures were considered to all be utilizing blood as the biological sample; and the level of expense was estimated as that of calendar year 1974. The characteristics compared for the methodologies used were chosen by this author; the estimated values represent personal evaluations as well as a modicum of input from colleagues in the field. The various column headings may be explained briefly.

7.1 Pre-Work Required

This is an estimate of the minimum amount of time and degree of complexity necessary to convert the biological sample into a format suitable for measurement.

7.2 Specificity

This is an estimate of the specificity of the measurement technique as discussed in sections 6.1 - 6.10.

7.3 Limit of Sensitivity

This is an estimate of the smallest amount of drug that can be measured accurately in a single sample as discussed in section 3.2.

7.4 Reliability

This is an estimate of the reliability of the overall process as discussed in section 3.5.

7.5 Expertise Required

This is an estimate of the level of expertise that would be required to carry out the assay without supervision.

7.6 Time Per Assay

This is an estimate of the time it will actually take to run the measurement procedure.

7.7 Cost-to Set Up Laboratory

This is an estimate of the cost of specialized equip-

ment/facilities required for the measurement technique oriented analytical process being considered.

7.8 Cost Per Assay

This is an estimate of the cost in labor and consummables to run a single assay.

8.0 SUMMARY AND OVERVIEW

It should be obvious, even from this relatively brief exposition, that the problem of analytical methodology for the determination of drugs in biological samples, especially as it applies to the drug/driving area, is a most formidable one. There is no single analytical procedure that can be applied to all drugs. There are not simple analytical procedures that can be used for most drugs. Perhaps of most significance, the available methodology has never really been challenged in terms of applicability to a problem such as drugs and driving.

On the basis of these considerations, there are a number of aspects that should be addressed as major points of attack for future research, i.e., as research and development needs. While some may disagree with the order in which they are presented, there is no doubt that the total content is reasonable and accurate.

8.1 The Development of an "Overall Approach" to the Problem that is Realistic, Practical, and Organized

It is not practical to assume that all procedures must use a $100,000 instrument, or demand a Ph.D. level of expertise, or require 4-6 hours to complete a single assay. Coordination of methodological development must go hand-in-hand with development of sample handling and other logistical procedures. Simultaneously, there must be definition and standardization of requirements based on accurate estimations of drug levels needed.

8.2 An Evaluation of Drugs and Drug Metabolites to Be Included in Any Testing Approach

Obviously, one cannot assume that only drugs should be included in any one testing approach. For example, in the case of some drugs, metabolites are the active agents; in such a case, blood levels of the parent compound would be meaningless. In other cases, both parent drug and metabolite have significant activity; meaningful measurements must quantify both agents.

8.3 A Determination of What Sort of Sample Will Be Satisfactory

This problem poses legal, analytical, and pharmacological questions. The question of validity of measurement and significance of quantity may be serious if only a single sample is utilized. Multiple sampling will both simplify and complicate the pharmacological interpretations and will probably complicate the legal issues.

In summary, then, the present status of analytical methodology for the measurement of drugs in biological samples, especially as related to the problem of drugs and driving, is - at best - unsatisfactory. Considerable organized effort will be needed to develop better methodology, to pursue its application to the real-life drugs/driving situation, and to permit an adequate evaluation of the relationship of pharmacological agents to motor vehicle operation.

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DRUG/DRIVING RESEARCH REVIEW

SYMPOSIUM

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CHAPTER VIII

A Report of the
Working Sessions on:

MEASUREMENT OF DRUGS IN BIOLOGICAL SAMPLES

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1.0 INTRODUCTION

As part of this symposium, working sessions were convened for the consideration of drug measurement methodology as it relates to highway traffic safety; the sessions drew together representatives of various areas of the analytical sciences involved with the measurement of chemical substances in biological materials.

The need for a strong body of knowledge and expertise in the areas of drug measurement methodology is multifaceted and has been previously discussed (1). Among these needs, the most pertinent to this symposium seemed to be:

- to help in assessing the scope and incidence of drug use with respect to highway traffic safety,
- to serve as scientific criteria in relating drug use to impairment of driving skills, and
- to serve as a legal standard for the development of countermeasures for the drugs and driving problem.

From these three needs, much of the initial discussion focused on defining the goals and requirements of any analytical methodology to be used in connection with the drugs and driving problem. Among the many questions raised, three key points recurred as a central theme:

- To how many drugs must the analytical methods be applicable and what are these drugs?
- What are the lower limits of detection required of the methods, and to what degree are these limits a function of the drug in question?
- How much information is required to ascertain the correctness of the chemical specificity of the method, and how is this information to be obtained?

In addition to these three key points to be considered, there were strong feelings expressed throughout the discussion about two issues which could not be fully addressed.

The first of these concerns itself with the phrase "under the influence of . . . ." All participants wished to make it clear that there is a great disparity between showing the analytical presence of a drug and showing that a driver

is "under the influence of" that drug, given the present state of knowledge of these relationships.

As a second point, the participants believed that no laboratory could approach the problem of identifying and measuring all exogenous chemical substances in a biological sample, even though ideally, this could be foreseen as some ultimate goal. There were several specific reasons expressed as to why all drugs constitute too wide a field of consideration.

For example, the question of carbon monoxide drew a mixed response. The majority believed that this was not an issue for this symposium; there was, however, a strong feeling that investigation of carbon monoxide as a traffic safety problem would and should involve the same resources as the drugs and driving problem. For this reason, the opinion was expressed that carbon monoxide measurement stands as a legitimate scientific problem for NHTSA and that efforts should be coupled in some efficient way with the drugs and driving problem.

Another important issue raised dealt with those drugs whose presence might not be directly associated with impairment of behavior or driving skills, yet might give an indication of an altered state of health. As an example, it was noted that in the investigation of air crashes, the FAA assays for aspirin levels in all crew members, as possible indicators of headache or hangover. As in the case of carbon monoxide, most participants felt that to include this problem would excessively broaden the scope of the discussion, and make goals rather unrealistic.

Finally, it was asked if the methods should be sufficiently elaborate to detect and measure new drugs (both licit and illicit) which might appear in the future; thus, this could provide an early-warning system for upcoming drug-driver problems. It was even indicated that indeed, with systems of gas chromatography/mass fragmentography, such sophistication was not exceedingly unrealistic. Nevertheless, it was believed that to include extra sophistication for this purpose alone is probably not an efficient use of resources. There are better ways to obtain information about the emergence of new drugs and thus, alter the methodological approach as necessary.

From all of the preliminary discussion emerged one of the most fundamental themes of these sessions, and thus the first of the recommendations to NHTSA. Any approach

towards advancing drug measurement methodology must deal with both sides of the coin: service and research. It was particularly useful during these sessions to have drawn our participants fairly equally from these two halves of the analytical world. Regardless of the drug in question, the setting of its use, or the method applied, it must be remembered that questions of methodology must be attacked from two standpoints. As a research issue, methodology must be examined at maximum intensity with all available and appropriate resources. Yet as a service issue, we must be concerned with obtaining the most useful information with only the optimal resources; furthermore, one must consider validation of the methods, training, and quality control. This "service and research" theme will reappear in further discussions; still, it is a stated initial premise. The dual nature of all drug measurement problems must be recognized, so that both aspects of this important area can grow to maximum utility.

2.0 THE CURRENT "STATE OF THE ART"

From the discussion on the dual nature of methodological problems, discussion turned to assessing the current state of the art in drug analyses. It was reiterated that it was unrealistic to consider the identification and measurement of all drugs; some of the reasons for this have been listed above. A need was strongly expressed for a listing of problem drugs in order of priority with respect to highway traffic safety. Such a listing would, of course, have to be established in conjunction with groups providing input on risk identification. Still, it was fully realized that the ordering of priorities could not be completed without input based on analytical considerations.

A major factor in any such input is that the available methodology varies greatly according to the drug or class of drugs. This was quite apparent from the lengthy discussion on advantages and disadvantages of the many methods presently in use. This discussion encompassed nearly all major classes of drugs which could be expected to alter behavior or driving skills, but it will suffice here to present the conclusions on three classes of drugs: barbiturates, cannabinoids, and antihistamines. These three classes were chosen for two reasons; it was felt that all three are very likely to have significant involvement in traffic safety problems, and they are representative of drugs in three distinctly different stages of methodological development.

2.1 Barbiturates

The barbiturates typify a small class of drugs for which a large number of analytical methods exist; some of these are very well established and documented, others are much newer and still require some "test of time." Because of the existence of such a large body of analytical information, the thrust of current needs should probably best be directed towards evaluation, validation, and characterization of known methods rather than initiation and development of new procedures. It was generally agreed that there are certain characteristics found in all methods which could be enumerated.

All of the more reliable, established methods are biphasic in nature; that is, half of the analysis is directed towards a positive chemical identification of the drug, and the other half serves to accurately measure the amount of drug. In some instances, one method could provide both types of information, though this generally brought 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 immunological reactivities, as in 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. The more empirical chromatographic procedures (GC, GC-D, TLC, and HPLC) have, for the most part, been developed and characterized so well that the problems of false identification have been overcome. The specificity of immunological methods is still being developed, and thus, is not fully known. 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 may be very easily compared by choosing the appropriate parameter to measure.

There were at least seven methods applicable to barbiturate measurement which arose from these discussions: 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 cases, 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. This dependence has led to concentration of efforts on certain optimum combinations of the two phases of analysis. Problems of unreliability or technical difficulties may contraindicate other potential pairs. Table 1 shows the coupling of these two kinds of determinations.

Table 1

Compatibility of Quantitative and Qualitative Analytical Methods for Barbiturates*

	UV/VIS	FLUOR	TC	FID	EC	MS	LS
GC	+	0	+	+	+	+	-
GC-D	+	+	+	+	+	+	0
TLC	+	+	-	-	-	-	-
HPLC	+	+	-	-	-	0	-
IR	-	-	+	+	+	-	-
MS	0	0	+	+	+	+	-
RIA	0	0	-	-	-	0	+

*+ established; 0 possible, unexplored; - incompatible

While this matrix shows many usable combinations, there are but six which are highly developed for use on barbiturates. These are: UV/GC, UV/TLC, GC and GC-D/FID, GC/MS, RIA/LS, and TLC/GC.

2.2 Cannabinoids

The cannabinoids are representative of a large number of drugs for which much analytical knowledge has been and is being accumulated; yet no one method has been amply tested and evaluated. The area is neither unexplored nor

fully explored. Thus, where existing reports are available, there is a need for greater investigation of strengths and weaknesses, and 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 marihuana in humans. Four methods have thus far exhibited the greatest promise: GC/MS, MS alone, HPLC-FLUOR, and RIA.

2.3 Antihistamines

The third category of drugs may well be the largest, and is exemplified by the various antihistamines. 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 apply not only to antihistamines but also 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 many 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 strongly to a need for the initiation of exploratory research into finding usable methods. Returning to the dual concept of methodological needs, the analytical problems associated with the host of drugs in this category belong strictly in the realm of research. Application to a widespread service role will have to wait until a much later date.

3.0 THE NEED FOR COORDINATED INFORMATION STORAGE AND RETRIEVAL

One problem noted in the state-of-the-art discussions 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 call was made by several participants for a comprehensive literature search for the preparation of an annotated review of existing drug measurement methodology. Initially, some participants expressed objection on the grounds that previous projects had been outmoded and rather ineffective. There was general agreement that such a review could be extremely useful, but it would require a careful delineation of goals and objectives to achieve maximum utility. These goals were 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. An outline was drafted to subdivide and better define each of these. It appears as follows:

I. SCIENTIFIC RELIABILITY

A. Qualitative Reliability

1. Sufficient specificity; the ability to discern appropriate drugs and metabolites from inappropriate ones
2. Sufficient generality; the ability to detect all appropriate drugs and metabolites

B. Quantitative Reliability

1. Limits of detection
2. Accuracy
3. Precision

II. SERVICE PRACTICALITY

A. Facilities Requirements
B. Personnel Requirements
C. Cost Requirements
D. Safety

In addition to providing a vehicle for efficient evaluation of existing data, it was stressed that such a review could serve to encourage and establish these criteria for more effective reporting of emerging data. A very worthwhile suggestion was made that NHTSA could and should encourage an expansion and redefinition of the Toxicological Information Program (TIP) of the National Library of Medicine

to assist in the collection, tabulation, and dissemination of this information.

4.0 THE NEED FOR PHARMACOKINETIC KNOWLEDGE

The discussion returned to expand and reiterate the position that many of the limitations for drug measurement methods are due to insufficient knowledge of the metabolism and pharmacokinetics of many behavior-modifying drugs. Several examples of this were offered. As previously mentioned, analytical methods for determining the use or effects of marihuana 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 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. To combat this shortcoming and effectively improve standards of drug measurement methodology, NHTSA should encourage and support investigations of the pharmacokinetics and metabolism of the many drugs.

5.0 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. NHTSA could serve a very useful administrative capacity by helping scientists obtain any or all of the following materials:

1) Drugs and metabolites of known purity

2) Drugs and metabolites, stable - labelled (^{2}H, ^{13}C)

3) Drugs and metabolites, radio - labelled (^{3}H, ^{14}C)

4) Standard reference materials (calibration substances) as supplied in other areas by NIH to maintain high levels of accuracy and precision for quality control of methods

5) Controlled substances

6) A clearinghouse or source of information with respect to how and where these substances are available.

6.0 PROBLEMS IN THE REAL WORLD OF PHARMACOLOGY

An additional limitation to effective development of analytical methods is the scarce and diffuse nature of data concerning typical blood levels of drugs of interest to the drug/driving problem. Scientists with an analytical chemistry background may not have the pharmacological or medical training to be familiar with the broad ranges of drug concentrations in biological materials. As a result, the development of new analytical methods is hindered in progress or usefulness by the great confusion surrounding the appropriate levels of detection. Three very striking instances of this arose during discussion.

First, drug concentration levels in blood vary widely from drug to drug. As an example, typical pharmacologically active levels of four drugs in blood are given in table 2.

Table 2

Typical pharmacologically active blood levels of four commonly encountered drugs (2)

Drug	Typical blood level (mcg%)
Lysergic acid diethylamide (LSD)	0.1 - 0.4
Propoxyphene (Darvon®)	5 - 20
Diazepam (Valium®)	50 - 250
Acetylsalicylic acid (Aspirin)	2,000 - 10,000

Second, drug levels for a single given drug may vary widely from report to report or under different conditions. Table 3 shows a wide range of drug concentrations for a single drug.

Table 3

Variation of blood levels of chlordiazepoxide (Librium®) under different physiological states

Sample	Physiological State	Drug Level (mcg/ml)	Reference
serum	sedated	2.5 - 8.0	(3)
serum	sedated	1.0 - 3.0	(2)
plasma	sedated	0.5 - 1.6	(4)
serum	comatose	20.0 - 50.0	(3)
serum	comatose	5.5	(2)
serum	lethal	20.0	(2)
serum	comatose	8.0 - 20.0	(4)

Third, within a single report on a single drug there may be several values listed due to variations in the specificity of the method or in time of sampling. These variations may be quite confusing unless there is detailed accurate information relating to the methodological variations. Table 4 shows varying levels of the same drug, chlordiazepoxide, as a function of metabolite specificity and time of sampling.

Table 4

Variation of chlordiazepoxide (Librium®) levels in a single comatose patient due to metabolite specificity and time of sampling (4).

Method Specificity	Drug Level: 6 hours	21 hours	51 hours
Unchanged drug	20 mcg/ml	8 mcg/ml	3 mcg/ml
N-desmethyl drug	8 mcg/ml	12 mcg/ml	7 mcg/ml
Lactam	2 mcg/ml	5 mcg/ml	9 mcg/ml

All of these reasons are substantial indications for two steps that should be undertaken to assist in the collection and expansion of drug level data.

There should be support for a literature search to collect and collate existing data on drug levels; for each report, there should be made available as much of the following information as possible.

1) Pharmacological activity - therapeutic, toxic, lethal?

2) Physiological status of subject

3) Amount of drug administered

4) Route of administration

5) Time of sampling

6) Source of sample

7) Specificity of analytical methods

8) Number of subjects, range of values

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

In anticipation of legal and practical constraints, a variety of methods for obtaining an analyzable human sample should be investigated. The discussion recognized that at least five sources of human specimens could have potential for providing an adequate analytical sample for the identification and measurement of drugs. These sources are: blood, urine, breath, saliva, and skin emanations.

Blood is, in most respects, the sample of choice for almost all analytical drug measurement methods in current use; typically, a specimen consists of 5-20 ml. venous blood obtained by venipuncture. There should be further development of existing venous blood procedures such that they can be applied to the much smaller (0.01-0.1 ml) capillary blood samples obtained by finger prick. Analytical methods which currently employ urine samples are not in great need of further methodological development, but do merit further investigation as to the usefulness of the data

obtained. It was generally agreed that positive drug levels in urine provide little or no meaningful information regarding the true physiological state of the individual, yet negative, or absent, drug levels could be of great utility to avoid costly and difficult procedures when screening large populations. The last three samples, breath, saliva, and skin emanations are in need of much research to develop their potential as samples for drug analysis. Research should be encouraged and supported in any of the following areas:

1) Methods of collecting sample

2) Methods of preserving sample

3) Further development of existing methods to greater numbers of drugs

4) Correlation of sample levels to blood levels.

Near the end of these sessions, focus was turned away from a search for new programs and towards a consideration of existing NHTSA programs. Specifically the participants wished to recognize and consider the study "The Incidence of Drugs in Fatally Injured Drivers" by E.J. Woodhouse, of Midwest Research Institute. This contract already provides for a critique of the MRI study (and other similar studies) to evaluate methods and findings based on a critical analysis of the published report. It was highly recommended that such a critique could be strongly supplemented in value by providing for a laboratory critique of methods and findings based upon critical trials and duplications of the methods as published. In addition to such a duplicative laboratory critique, this project should be continued and expanded to include other laboratories and other methods to investigate the possibilities of dependence of the findings upon the methodology employed.

7.0 THE NEED FOR A SPECIALIZED CENTER

Throughout all of the discussion, there were suggestions that whatever action was to be taken in approaching the drug/driving problem, there needed to be a high level of centralization and organization to any such effort. The culmination of these suggestions was the unanimous expression of a need to establish a national development and training center to promote advances in drug measurement methodology. The rationale for such a center rests on several very substantial contentions.

1) There are a very large number of directions for expansions of the existing body of knowledge and expertise in drug measurement methodology.

2) Many of these needs and goals will not be fulfilled spontaneously as a result of invited research.

3) Many of these needs require a multidisciplinary approach.

4) The resources required for many of these needs will be of value in investigating a host of other public and environmental problems.

5) The realization of many of these goals could be most profitably and efficiently achieved by multi-agency support and funding.

A development and training center of this type might serve a variety of functions, characterized principally by three themes in this discussion: consultation, education, and research.

The consultation roles of such a center could include several different functions. It would be used as a service facility in handling analytical needs which are beyond the scope of smaller, more localized facilities. It could also serve as a liaison between widespread, established and newer, less-established methods, particularly in regard to the continual expansion of methods which had been readied for wider, more public use.

As an education facility, this center would serve a very vital need in this area. In conjunction with an aforementioned need, it could serve as a clearinghouse or center for information on existing and emerging methods, facilities and programs. It could also naturally expand into the development of educational workshops, training programs, and possibly even certification programs.

As a research facility, this center might play its greatest role. There would be major facilities for active research in any or all of the problem areas previously described in this report. It should assist in coordination and resource allocation of extramural research complementary to the drug/driving problem. Finally, it would assist in the coordination and most efficient use of information obtained in connection with other agency objectives, such as those of FDA, NIDA, and others.

8.0 LEGISLATIVE ASPECTS

Some peripheral discussion led to an addendum of two very important points concerning legislative actions, which lay somewhat outside the scope of the group's topic area. Nevertheless, these feelings were so strong concerning potential legal limitations on drug methods, that the participants felt compelled to make two recommendations to be taken under consideration by the appropriate groups.

There should be implied consent legislation to make it possible to obtain a biological sample - it should be abundantly clear that the first and foremost limitation of any analytical method is that there must be a sample! The scientific community cannot afford to involve itself in fighting legal constraints against obtaining a sample. Thus, if society wants and is to profit from this analytical data, there must be assistance from the legal community in obtaining the requisite samples.

There should be elimination of the "under the influence" concept with substitution of the "analytical presence per se" concept. This has already been done for alcohol and should be retained as a standard concept for other drugs. It is not the concern of this group whether or not criminal law is to be used as a countermeasure in the drug/driving problem. However, if it is to be used, then scientific analytical data should be used as the standards in determining the quantum of proof.

9.0 CONCLUSIONS AND RECOMMENDATIONS

The participants reached a number of conclusions that led to recommendations. The group believed the recommendations should be implemented but recognized that some of their suggestions require efforts that are beyond the scope of NHTSA responsibilities. Other governmental agencies will necessarily be involved. Adequate response to the drug/driving problem will require action on these recommendations. Accordingly, the participants urge NHTSA to join in cooperative efforts with other agencies to achieve these goals. NHTSA can play a crucial, catalytic role in the development of drug measurement methods.

The major conclusions and recommendations are as follows:

1. Recognition must be given to the dual nature

of present and future needs and the requirement for both research and service efforts.

2. A small list of drugs (or drug classes) which are of highest priority to NHTSA must be established. Analytical methods for these drugs must be thoroughly validated, drug characteristics defined, and research needs established.

3. Pharmacokinetic and drug metabolism studies on the drugs identified in recommendation two above must be undertaken.

4. Existing analytical methods must be critically reviewed. The TIP (Toxicological Information Service) of the National Library of Medicine should be expanded and its mission redefined to more fully support highway safety needs.

5. The federal government should ensure that research and service laboratories can obtain standard reference drugs, stable-labled drugs, and drug metabolites.

6. A central reference point for the collection of data on drug metabolism should be established. The quality of the information on blood levels of drugs following administration of therapeutic doses should be critically evaluated on a continuous basis by a peer review process.

7. Non-invasive sampling techniques should be explored. Critical review of the sensitivity and validity of the techniques must be a part of this examination.

8. The establishment of a national center for consultation, research, and education on analytical methods for drug measurement is recommended. Such a center should be multidisciplinary in nature and draw on the resources of all federal agencies and the research community.

9. NHTSA-sponsored research studies that use analytical methods (such as the MRI study) should be subject to continuous peer review to ensure that appropriate methodologies are used. Further, separate laboratory studies using different analytical methods should be

undertaken to check the validity of the results obtained in the base studies.

10. The passage of legislation, such as the "implied consent" laws, to ensure that biological samples can be obtained from drivers is recommended.

11. Laws prohibiting driving while impaired by drugs should establish drug presence at a defined level as proof of impairment. This approach is now used for alcohol by some states in the "per se" laws.

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DRUG/DRIVING RESEARCH REVIEW

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CHAPTER IX

Speaker's Paper

AN OVERVIEW OF THE LEGAL ASPECTS OF HUMAN EXPERIMENTATION AND RESEARCH

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1.0 INTRODUCTION

The early months of 1975 have seen more alarm created within the community of professional persons who involve themselves in healing human beings or in conducting research involving human subjects than ever before. The notorious Boston abortion case (1) and the current flap over medical malpractice insurance rates (2) are merely illustrative. Throughout the whole realm of activity that may be generically described as research and experimentation on human subjects this controversy ramifies with consequences yet unknown. The purpose of this paper is to provide an overview of the legal aspects of research and experimentation on human subjects, directed somewhat toward behavioral research and particularly behavioral research in non-laboratory settings.

Examining the legal literature in this field leaves two impressions with the reader. One is that the whole subject is deeply tinged with moralistic connotations, stemming from hard to define notions of privacy and human dignity, and the other is that the crux of the issue is something known as informed consent. While I harbor very strong concerns about the need for human beings to be secure in their privacy even when in public places, I find that the writings in this field are not very helpful. Most people either agree or disagree on the merits and the writings themselves add little to resolving the legal problems. In a similar vein, while the writings on informed consent are valuable to legal technicians, they seldom if ever open up the entire field for examination by non-lawyers.

Attempting to avoid either the too general or too specific approaches, this paper will examine the underlying issues from the perspective of basic legal precepts. Such an approach will have its own shortcomings in that very specific questions will go unanswered. In partial remedy of that, some particular attention will be given to current problems of informed consent in field observations of human behavior.

The place of law in society is to regulate human behavior. In most situations where criminal or civil sanctions are to be imposed the regulations are narrowly drawn to truncate extreme modes of behavior perceived by the law makers as socially undesirable enough to be outlawed in one way or the other. The main spectrum of behavior goes undisturbed by the law. Accordingly, when I speak of behavior to be controlled, I mean those modes or extremes

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of human behavior that society has thought unwanted enough to visit legal sanctions upon. The remainder of the paper is organized in five general sections as follows: a discussion of the behavior sought to be controlled by holding researchers liable, and available means of control; elements of various theories of civil liability and defenses to civil liability; special difficulties for field researchers of human behavior; possible solutions; and final thoughts.

2.0 BEHAVIOR TO BE CONTROLLED

So far as imposing liability is concerned, the law generally is attempting to prevent behavior that causes harm to human beings. Historically, the most obvious sorts of harm guarded against were injuries to the body and direct damage to property. Hence, a typical sort of behavior that leads to liability is an automobile crash that injures people and destroys automobiles. More recent forms of injury that have been given recognition in the law are injury to a person's emotions or psychic well-being in the absence of any direct injury to the physical body, and damage to a person's pecuniary interests in the absence of either bodily or psychic injury or damage to tangible property.

In large part the present unsettled legal status of the human experimentation field is given rise to by the newer sources of liability. Certainly, both healers and researchers have long been aware of the potential of liability for bodily injuries suffered by human subjects. The whole well developed subject of informed consent recognizes that fact. Hence, it is mainly the new fields of liability that now define the behavior to be controlled. As shall be seen, the emerging law is insisting that human beings be not unnecessarily and unreasonably exposed to forces that will cause them serious emotional or psychic stress even in the absence of any bodily harm. And the law is beginning to insist that similar exposure to pecuniary damage be avoided even in the absence of damage to tangible property. These are the behaviors to be controlled and to the extent that human experimentation causes the unwanted consequences it falls within the ambit of controlled behavior.

Societies have numerous means of showing disapprobation of unwanted behavior. Most of them fall far short of legal sanctions. As examples, bad boys are spanked and bad men are not made deacons in their churches. Economic sanctions are often used too, as boycotts of products of non-union growers of lettuce and grapes and boycotts of high priced meats have recently demonstrated. Complete social

ostracism is rare in our own culture, but may still be prevalent in others. For professional people, such as participants in human research and experimentation are likely to be, the professions themselves have instituted sanctioning systems. Many professions have in a sense created monopolies for persons accreditted by them. Behavior seriously deviating from accepted norms of the profession leads to disaccreditation and expulsion from the field. Notable recent illustrations are the disbarments of Dean, Erhlichman, Mitchell and others of Watergate notoriety. Hence, to the professional person removal from the field is a formidable source of control. Furthermore, as opposed to practitioners, researchers rarely if ever create the kinds of products that regularly and immediately bring the income needed to support their research activities. Most often, some other entity, usually governmental, must be persuaded to bankroll current endeavors in anticipation of receiving prospective benefits that are not presently saleable on any open market. The threat of losing these sources of support can be as great a control mechanism as any other.

While all of the foregoing sources of control are effective against researchers in some degree, none directly involves the law in either of its two basic modes. One mode is the criminal law that punishes forbidden behavior with jail sentences or fines. Because of the extremely unsavory connotations of criminal convictions, at least for people in professions, subsidiary social ramifications may be equally as dreaded as the criminal sanctions themselves. Nevertheless, owing to the fact that criminal charges are likely to be made only in instances of most egregious behavior, no further consideration will be given to them here (3).

The second basic mode of the law is the civil law. Of direct application is the law of civil wrongs, known as the law of torts in legal parlance. Ordinarily, the sanction of the law of torts is forced recompense in money for harm done. The usual goal is to restore the injured party to status quo, but in extreme cases exemplary damages are levied against a wrongdoer. Although exemplary damages primarily serve a punitive purpose, they are paid to the injured victim and not to the state and do not in other ways carry the extreme stigma of criminal sanctions.

This background discussion can best be ended by observing that the nature of the various sanctions is shaped by several factors. Two are the odiousness and harmfulness of the controlled behavior. Extremes in either characteristic are likely to be visited with extreme sanctions. The third

is the extent that the controlled behavior is not characteristic of the population that makes the rules. The last point can best be illustrated by observing that alcohol drinking offenses are punished little whereas marihuana use offenses are punished much.

3.0 ELEMENTS OF VARIOUS TORTS

The remainder of this paper is essentially devoted to the potential tort liability of researchers engaged in experimentation with and observations of human beings (4) and how it might be avoided. Basically, three kinds of injury-producing behavior are recognized in the law with distinctions among them depending principally upon the mental state of the offender. Intentional torts are wrongs produced by acts intentionally done. Moreover, it is the doing of the act that is intentional and not the causing of harm. Hence, if a researcher intentionally touches a subject's body with no intention to cause harm, but harm in fact ensues as a consequence of the touching, then an intentional tort has occurred. By contrast, negligent torts are wrongs produced by careless acts in situations where ordinary prudence called for more care than was exercised. Finally, strict liability torts comprise the third classification. These are wrongs done by behavior that is so dangerous under the circumstances or so reprehensible that the law holds the actor accountable without respect to whether the behavior was intentional, careless or entirely innocent. Notwithstanding the fact that human experimentation would seem to fit this category, historically it has been reserved for activities connected with the use of land, such as blasting or mining, and actually has little applicability to the subject at hand, except in respect to privacy issues to be discussed.

3.1 Intentional Torts

Researchers who directly touch or manipulate the human body in any way need be concerned about liability for intentional torts. Very brief descriptions of the several most applicable torts will be given along with specific illustrations.

A battery is an unprivileged and an unconsented to harmful or offensive touching of another person (5). Not only does battery give rise to an action for damages actually caused, but owing to its intentional classification, it can also give rise to punitive damages as well. Perhaps more threatening to researchers is the possibility of damages for emotional injury or mental distress caused parasitically

by the physical touching. Examples of batteries would be an insertion of a hypodermic needle into a person's body against his will, and administration of a substance to a subject against his will (or administration with permission if the subject was deceived about the true nature or effects of the substance). Clearly, both healers and researchers must be concerned about the prospects of battery liability.

An assault is an intentional setting in motion of forces that create within another person an apprehension of an imminent battery (6). Hence, assault makes possible compensation of injuries that stem solely from fright or other emotional distress when there has been no actual harmful and offensive touching. An example of assault would be to approach a person with a hypodermic under circumstances that created the apprehension that an injection was to be made against the will and without the consent of the assaulted person. Assault cases usually rise in more mundane circumstances, however, such as in heated arguments when contestants begin to threaten one another.

False imprisonment is an unprivileged and unconsented to deprivation of the liberty of motion of another person (7). Common examples of false imprisonment are the unjustified retention of a patron in a store under accusations of shoplifting, or the locking of another person in a room or house as a coercive measure. Researchers of human behavior must concern themselves with this tort when they engage in projects that require confinement of subjects.

Intentional infliction of mental distress is a rather new and fast developing tort. This tort imposes liability for mental distress caused by intentional and outrageous behavior (8). It differs from assault primarily in that the injured person need not have been put in apprehension of an imminent battery. An example of the cases finding liability for intentional infliction of mental distress is one in which a person sought to punish his mistress emotionally by cutting his own throat in her kitchen (9). This example highlights the outrageous component of the tort. More recent cases have enlarged the scope of outrageous behavior to less extreme situations such as unusual and extreme methods used to collect debts (10). While most situations involving researchers would involve either assault or battery and not this tort, nevertheless methods used in field experimentation could conceivably give rise to liability under this theory. An illustration would be an intended unobtrusive observation of human behavior that was detected, creating fear or apprehension in the observed person.

To these intentional torts the law has recognized certain defenses. The defense of privilege is based upon the recognition that certain relationships require relaxation of the severe restrictions upon human mobility and interchange that would be imposed by an unbending application of the intentional torts. For example, being jostled on a crowded sidewalk can be an offensive touching. To avoid countless battery actions stemming from such situations the law recognizes a privilege that extends to the usual joustings that are inherently part of daily life. Privileges also extend to spanking of children by parents and to good faith arrests by policemen and to many other commonplace activities that are not ordinarily harmful but could be construed as offensive. Anytime the offensive behavior becomes more extreme and shades over into harmful behavior, the actor stands the risk of exceeding the privilege and putting himself in the range of tort liability.

Research behavior is not yet recognized as one of the usual risks of normal human intercourse. Consequently, no rule of law requires that researchers' behavior be tolerated by all who choose to engage in the routine affairs of daily life. Consequently, with possible rare exceptions in healing situations, researchers would not be able to claim privilege as a defense to intentional torts stemming from research activities. Nevertheless, the law does not require that researchers proceed at their peril in the absence of a privilege. Fully consistent with the view that human beings ought to be free of unprivileged intentional torts is the law's acknowledgment that people can consent to what would otherwise be harmful or offensive touching and other torts. Hence, the defense of consent protects surgeons when they operate and can protect researchers when they experiment.

As was pointed out in the introductory remarks, much of the legal literature in the human experimentation field is given to informed consent (11). The addition of the word "informed" reflects the fact that courts have not erected a shield against liability on every pretext of consent. The cases clearly indicate that consent obtained through fraud, coercion and undue influence is no consent at all. Similarly, consent resting upon less than full disclosure of the risks involved is not informed consent. Needless to say, most of the litigation to date has been concerned with procedures performed by medical practitioners, but the theory is fully applicable to research endeavors.

3.2 Strict Liability Torts

Apart from defamation and invasion of privacy, traditional strict liability torts have little applicability to the topic under consideration (12). Defamation is a false statement that damages the reputation of the defamed person. In that absence of truth is an indispensable element of the tort, defamation carries its own best defense as part of its definition. Rarely should the tort arise in research situations.

By contrast invasion of privacy could pose a threat to researchers. This relatively new tort acknowledges that the revelation of private matters, even in the absence of falsehood, can be damaging and ought to be deterred under some circumstances. While the body of cases is somewhat amorphous in form, four major subdivisions have been discerned by courts and scholars.

Owing to its analogy to copyright and patent infringement matters, appropriation is perhaps the most uniformly accepted theory of invasion of privacy. Under this theory the unauthorized use of the likeness of a private person can sustain a cause of action for damages. Ordinarily, this tort applies when an advertiser has used a picture in an advertisement without the consent of the subject (13).

False light is an invasion of privacy in which true facts are used to cast untrue aspersion upon the character of another person. In one example, a young child was struck down and badly injured by a carelessly driven automobile. The picture was published as a news item shortly thereafter with impunity. Freedom of the press to publish news outweighed any privacy considerations at that point. Several months later, however, the picture was used as a frontispiece for a magazine article entitled "They Ask To Be Killed." This was found to be an invasion of privacy in that the child was falsely held in a bad light (14). To the extent that the tort damages reputation, it is closely related to defamation.

Intrusion has been used to control what are at the same time the most outrageous and the least public invasions of privacy. In the prototypic case (15) a motel operator bugged a room occupied by newly weds so as to regale himself with the sounds emanating therefrom. The defendant was held liable for damages for intrusion notwithstanding the fact that he had not made public whatever information he had obtained.

Public revelation of private facts is a mode of invasion of privacy that has been used when quite truthful but secret facts are made public for no good reason. This tort seems on first glance to be complementary to defamation in that defamation brings liability for damages to reputation caused by false statements, whereas revelation of private facts brings liability for publication of damaging true statements. Revelation of private facts has been used very sparingly, however, and only where extreme damage has occurred under circumstances that could easily have been avoided (16). In sum, it clearly falls drastically short of doing for true damaging statements what defamation does for false damaging statements.

With the exercise of appropriate care, researchers should ordinarily not be concerned about liability under any of the strict liability torts. Appropriate care would include obtaining consent in connection with studies that might otherwise involve intrusions or public revelation of private facts. Perhaps the most genuine concern would be potential liability for public revelation of private facts when research data were disclosed after a promise of confidentiality had been given. This possibility will be made more evident in later sections examining testimonial privileges.

3.3 Negligent Torts

As observed earlier, a negligent tort is injury produced by a permitted act done carelessly. For example, surgery without consent would be a battery even if done with maximum care. On the other hand, consented to surgery would not be a battery, but if done carelessly would be a negligent tort. Hence, consent of itself is not a defense to a negligent tort and overriding any theory of defense is the potential of liability for causing harm carelessly. By far most of the law in this area has been generated by medical malpractice litigation.

4.0 DIFFICULTIES FOR FIELD RESEARCHERS

The present status of the law presents different problems for different kinds of research activities. Classical clinical research under laboratory conditions poses no special legal problems so long as genuine informed consent of the research subjects is received and so long as the procedures are prepared and conducted with reasonable care. Problems arise, however, when an experimental design requires that some subjects be unaware of what is actually being done to

them as, for example, when placebos are administered to a control group and an active agent to a test group. A more specific and perhaps more difficult example has arisen in certain field research programs. Studies of the relationship between drug use and traffic crashes can be used to illustrate the difficulty. Sometimes, for example, such a study will require that data obtained in crash situations be augmented with more extensive background information about drug use practices of people involved, including, perhaps, any specific use preceding the crash in question. Obtaining such information from most people would require an absolute pledge of confidentiality if even that would be sufficient (17). In most states, however, the researcher cannot be sure that information so obtained can be withheld in court should a subpoena for its production issue. This may then mean that genuine informed consent requires that the subject be told of this risk. It seems certain that such a disclosure would promptly end the cooperativeness of the subject and undermine the experiment. While there appear to be no cases dealing with pecuniary or penal damages suffered by inadequately informed subjects, researchers clearly would be risking suit if they chose to proceed without informing their subjects of potential risks and the subjects' revelations were later damagingly disclosed in court. In addition, the most recent guidelines on informed consent issued by the Department of Health, Education and Welfare fully comprehend that complete disclosure of such risks be made to research subjects in experiments of this sort (18).

Clearly, the potential for liability in research situations represents an extension of the basic concepts of liability discussed earlier. Nevertheless, in times of enhanced desire to protect the integrity of human privacy and increased alarm about insidious and pervasive governmental invasions of it (note that much if not most research is either funded or conducted by government), it is not unduly timid to give great weight to the potential risks faced by researchers if they ignore the fullest requirements of informed consent.

5.0 RESEARCH PRIVILEGE AS A POSSIBLE SOLUTION

Clearly, the existing law poses a researcher's enigma. Genuine informed consent will invalidate experimental design whereas failure to inform poses liability, non-funding and other hazards for the researcher (19). Any solution would seem to require a state of affairs that would not punish researchers for being silent about the possibility that data

might be used against the subject in court, or that would allow the researcher to say unequivocally and accurately that the data could never be so used. Either position would require a legal basis for excluding the researcher's data from the reach of courts' subpoena powers.

Presently, courts very strongly resist measures that inhibit the "search for truth" in the courtroom. In our legal culture there is a deep-seated policy that every person has a duty to come to court, bearing his evidence and testimony. This duty is compellable by the subpoena power of the courts with refusals punishable by contempt, fines and jail. Therefore, under the law in most states researchers can be compelled to disclose relevant data obtained in experimentation. Whether or not the data are relevant and admissible under the complex rules of evidence are separate issues that will not be examined here.

The historical evolution of the duty to testify reveals its present strength. United States law stems from the common law of England, and in the very early common law witnesses not only could not be compelled to testify but were actually unwelcome in the courts (20). Such people were seen as fomenters of litigation or meddlers in other people's affairs. Times changed, however, and in 1562 a statute of Elizabeth was enacted for the purpose of permitting witnesses to testify (21). Rather quickly, the nature of the adversary system changed so that by the 1600's the duty to testify had become well established in English and American colonial courts (22). When the American revolution came and the Constitution was adopted, the right to compel testimony was acknowledged as an element of fair trials. Consequently, one can argue that the right to compel testimony is a fundamental constitutional right (23) of litigating parties guaranteed by the Sixth and Seventh amendments to the United States Constitution for criminal and civil trials respectively.

Notwithstanding the sanctity of the right to have testimony produced, no right, including constitutional rights, is absolutely inviolable. Acknowledging that the right to compel testimony is sometimes overbalanced by competing values. the courts have recognized exceptions to it in some circumstances. These deviations from the duty to testify are carefully couched in exemptions known in the law as privileges. (Note that the term privilege is used both to describe the exemption from the duty to produce evidence and also to describe a defense to intentional torts. Hence, the earlier use of the term must be distinguished from the present use, which is markedly different.) So far as the common law

is concerned, the lawyer-client relationship constitutes the only universally recognized privilege. In the historical mind of the judges, it is a better policy on balance to enable persons to disclose fully their situations to their lawyers without fear that the lawyer will later be required to disgorge that information under court order than it is to produce every grain of evidence every time. Applying the same kind of policy balance, legislatures in some states have created a doctor-patient privilege, a penitent-priest privilege, and more rarely news reporter-news source (24) and even researcher-subject (25) privileges. In each instance, a decision has been made that society at large is better off if the confidentiality of given relationships can be absolutely secured against the compelling powers of the state than if it cannot.

These decisions are made primarily by judges, lawyers and legislators, but it cannot be gainsaid that their judgments largely reflect intuitions and instincts seeping in from the social body at large. In passing, it is worth noting that the scope of the influential community is growing broader and tending toward greater coincidence with the entire community. In many respects, there is no more noblesse oblige, as the general revulsion at the Watergate mentality demonstrates. In a sense, the times are tending toward everyman's day and, therefore, it is everyman's sensibilities that will determine whether or not the researcher-subject relationship deserves protecting.

In recent years both newsmen and social researchers have sought to establish testimonial privileges based upon the freedoms of speech, press and association guaranteed by the First Amendment to the United States Constitution (26). Under this theory compelled testimony in court represents governmental interference with guaranteed liberties to speak, to publish and to associate with others absolutely free from governmental infringement. Balanced against this argument is the historically steeped duty to appear in court and testify notwithstanding the source of the information or the relationship that gave rise to it.

In a series of recent cases federal courts have balanced the relative weights of these competing interests in the context of some rather important public issues. Caldwell v. United States (27) involved a contempt citation entered against a black New York Times reporter who refused to honor a subpoena to appear and testify before a grand jury investigating alleged criminal Black Panther activities. Caldwell defended on the basis that his unique position of trust and

confidence had gained the public an important news link to the Black Panthers and that such a relationship was protected by the First Amendment. Agreeing with Caldwell's claim of First Amendment freedoms, a federal circuit court of appeals held that Caldwell could not be compelled to testify unless the state showed a compelling state interest outweighing the public's right to be informed (28). Not wanting to announce a sweeping reporter's privilege, the court noted as special facts the sensitivity of the news source and the unique position of trust and confidence that had been achieved by Caldwell. What the court did in effect was to recognize a conditional privilege that could be outweighed if other considerations were given more weight.

Although Caldwell lined up with the policy stance approved by some legal scholars (29), it was not given a warm reception by the United States Supreme Court. Weighing the balance differently in Branzburg v. Hayes (30), the Supreme Court held that no reporter-source privilege existed in respect to information about sources of criminal conduct that the reporter had either seen (31) or been told about (32) or in respect to criminal conduct of other persons (33). Furthermore, the court suggested that even if a conditional privilege did exist, which it had already denied, then the state clearly could establish a compelling need to obtain information necessary to prosecute illegal behavior (34). Dashing the hopes for a reporters' privilege as it did, the Supreme Court left little room for gaining such a privilege for researchers on First Amendment grounds (35). Instead, the Court urged that proponents of privileges lay their arguments before legislatures who are, according to the Court, better able to balance correlative factors and delimit any privilege that they might see fit to grant (36).

Other writers have reviewed the status of the law in various states as it pertains to privilege for researchers (37) and that information will not be repeated here. Instead, attention will be given to illustrating the nature of the protection that can be given the researcher-subject relationship if a legislative body is persuaded to do it. In recent years national alarm has arisen concerning the increase in the use of illicit drugs and the federal government has responded by sponsoring research for preventing drug abuse and rehabilitating offenders. In enacting the comprehensive Drug Abuse Prevention and Control Act of 1970 (38) Congress recognized that this research would be greatly hampered if the research subjects' identities and data about them could be produced in court. Accordingly the 1970 Act empowered the secretary of the Department of Health, Education and Welfare

to authorize a researcher-subject privilege to protect the individuals involved in "research on the use and effect of drugs" (39). This drug research privilege is absolute in that it has no exceptions. Moreover, it excludes use of the privileged information in actions of all kinds, administrative as well as judicial and criminal as well as civil (40).

In the 1970 Act Congress also authorized the Attorney General of the United States "to carry out educational and research programs directly related to enforcement of the laws of his jurisdiction concerning drugs" (41) and empowered him to grant identical researcher-subject privileges (42) to those available to HEW as needed to meet the requirements of the act. Congress later extended a conditional privilege to the doctor-patient relationship in treatments of drug users made available under the Drug Abuse Office and Treatment Act of 1972 (43). Under the Drug Treatment Act records of the "identity, diagnosis, prognosis, or treatment of any patient" are confidential, subject to disclosure under only narrowly prescribed circumstances (44). For example, a court may balance the need for disclosure against "the injury to the patient, to the physician-patient relationship, and to the treatment services" and find the gains of disclosure the more important value under the circumstances. The fact that the court has discretion to select between confidentiality and disclosure is what makes the drug treatment privilege a conditional privilege as opposed to the absolute drug research privilege that is beyond the exercise of discretion by the courts (45).

Many other examples of either absolute or conditional privileges could be given, but these two sufficiently demonstrate the two modes for the purposes of this paper. It should be observed that these Congressionally created privileges have universal application in that they prevail throughout the geographic jurisdiction of the United States and in both state and federal courts as well as in administrative proceedings. If the privileges are indeed effective in keeping the protected information confidential, then their only shortcoming is in the limited scope of the types of research included. This brings up the question of how binding legislatively-created privileges will be upon the courts.

People v. Newman, (46) a recent case decided by the highest court in the state of New York, well illustrates how each of these privileges may be expected to function. Newman was the director of the New York City Methodone Treatment

Program, a drug research and treatment project that automatically fell under a conditional doctor-patient privilege because of its funding under the 1972 Treatment Act. Moreover, both the Secretary of HEW and the Attorney General had designated Newman's project for the absolute researcher-subject privilege under the 1970 Drug Abuse Research Act. Newman's troubles began when a female patient of his clinic witnessed a shooting on a New York City street and recognized the killer as a black male patient of the methodone treatment program. Upon receiving that information, the district attorney subpoenaed photographs and identifying data concerning all black males between ages 21 and 35 who were patients in Newman's clinic. Newman refused to produce the material and was held in contempt by the trial court. On appeal Newman's defense centered primarily (47) upon the application of the absolute privilege of the 1970 act and particularly upon whether the conditional privilege of the 1972 act had the effect of repealing the earlier absolute privilege. The Court of Appeals did not express its views on how effective the qualified privilege would have been had it been the sole privilege available to Newman. Nevertheless, the posture of the arguments raised to the court strongly suggest that the lower courts and even the Court of Appeals itself believed that the need for disclosure in this murder investigation outweighed the possible damages that disclosure might cause to the physician-patient relationship and the treatment program. Hence, this kind of egregious situation appears to establish a line beyond which courts are not likely to go in honoring a conditional privilege of the kind embodied in the 1972 act as they balance competing interests case by case.

The Court of Appeals rejected the contention that the 1972 act repealed the earlier law and held that the absolute privilege properly applied to Newman's situation. Once having so decided, the court without further comment vacated the contempt order and invalidated the subpoena issued to obtain Newman's records. This result firmly demonstrates the effectiveness of an absolute privilege: if it applies, it applies notwithstanding the egregiousness of the behavior that is being shielded or the merits of the case that is being shunned. In essence, the legislature's value judgment that a given area is deserving of unconditional privilege rules out any exercise of judicial discretion on a case by case basis.

6.0 FINAL THOUGHTS

In a general way this article has examined the various theories of liability that researchers engaged in experimentation with and observation of human subjects need be aware

of in designing their projects. It also examines protective defenses including privilege, informed consent and ordinary care.

Highlighted is the special dilemma posed by the seemingly irreconcilable duties to assure subjects of complete confidentiality as an element of informed consent on the one hand and to produce all one's testimony and evidence in court on the other. As has been seen, the dilemma can be resolved by granting a researcher-subject testimonial privilege. While some courts appear to be searching for a rationale to reexamine the issue, the United States Supreme Court refused to acknowledge that the United States Constitution required such a privilege in the closely related news reporter-news source relationship.

Further relief, if it is to be forthcoming, appears to be up to legislatures. While state legislatures can and have created researcher-subject privileges for certain purposes, these privileges apply with certainty only in state courts and only within the jurisdiction of a given state. These limitations alone do not negate the value of state privileges in promoting research objectives, of course, especially in respect to aspects of human behavior that are totally unrelated to locale. Nevertheless, universal privileges such as those created by Congress in the 1970 Drug Research and the 1972 Drug Treatment Acts have greater advantage, particularly in respect to research undertaken in the interest of national goals. It follows that researchers in making their pleas for testimonial privileges must carefully evaluate the factors that legislatures are responsive to. So far as Congress is concerned, nationwide interest is one factor. Intense interest is another. A belief that research documentation is needed badly enough to justify withholding research data from the prosecution of a few crimes or the litigation of a few claims is another.

The recent past shows that drug abuse research qualifies under all counts. Whether or not other research areas will be afforded equivalent treatment may turn largely on the temper of the times. For researchers involved in the special field of the effect of drug and alcohol use on highway safety, it would appear that a strong case could be made based upon the national interest both in controlling drug use and in preventing highway losses.

REFERENCES

1. The 1975 manslaughter abortion conviction of Boston physician Kenneth C. Edelin has created quite a stir in the legal world whose ramifications are just beginning to appear. While the case has yet to receive scholarly treatment in print, it has not failed to produce scholars' comments. See, e.g., "Faculty Voices Mixed Reaction to Edelin Trial," 60 Harv.L. Record 1 (1975).

2. The joint issues of increasing numbers of medical malpractice actions, skyrocketing judgments and escalating malpractice insurance rates have gained quick prominence in the winter and spring of 1975. Volume 11 (May/June 1975) of TRIAL magazine has been devoted to the topic.

3. For additional discussion of criminal liability, see Ladimer, "Ethical and Legal Aspects of Medical Research on Human Beings," 3 J. of Public L. 482, 499-502 (1955).

4. For additional discussion of tort liability, see, e.g., Ladimer, "Ethical and Legal Aspects of Medical Research on Human Beings," 3 J. of Public L. 481, 503-507 (1955); Freund, "Is the Law Ready for Human Experimentation," 22 Amer. Psychologist 394 (1967).

5. All of the definitions of torts used herein are well within the general scope of the law. The reader must be mindful that cases are rarely decided on general statements but upon the nuances and exceptions so typical of the law. For a standard treatment of the tort of battery, see Restatement (Second) of Torts §13 (1965).

6. See, Restatement (Second) of Torts, §21 (1965).

7. See, Restatement (Second) of Torts, §35 (1965).

8. See, Restatement (Second) of Torts, §46 (1965).

9. Blakeley v. Shortal's Estate, 236 Iowa 787, 20 N.W. 2d 28 (1945).

10. See, e.g., Delta Finance Co. v. Ganakas, 93 Ga. App. 297, 91 S.E. 2d 383 (1956).

11. To say the least, legal literature concerning informed consent is voluminous. See, e.g., Fletcher, "Human Experimentation Ethics in the Consent Situation," 32 Law & Contemp. Prob. 620 (1967), and McCoid, "A Reappraisal of Liability for Unauthorized Medical Treatment," 41 Minn.L.Rev. 389; Plant, "An Analysis of 'Informed Consent'", 36 Ford.L.Rev. 639 (1968); Waltz and Scheuneman, "Informed Consent to Therapy," 64 N.W. 2d L.Rev. 628 (1969).

12. Very recent developments in the law of defamation and invasion of privacy cast substantial doubt on whether or not these torts may be any longer uniformly treated as strict liability torts. See, Gertz v. Robert Welch, Inc., 94 S.Ct. 2997 (1974). Further examination of this matter is well beyond the scope of the present paper.

13. See, e.g., Flake v. Greensboro News Co., 212 N.C. 780, 195 S.E. 55 (1938).

14. Leverton v. Curtis Pub. Co., 192 F.2d 974 (3rd Cir. 1951).

15. Hamberger v. Eastman, 106 N.H. 107, 206 A.2d 239 (1964).

16. The prototypical case of public revelation of private facts is Melvin v. Reid, 112 Cal. App. 285, 297 p.91 (1931). In that case the lurid past of a reformed prostitute was made into a motion picture. While her true identity could easily have been hidden, the subject's real name was used, causing her great embarrassment within the community where she had established a new life.

17. Another illustration could involve interviews of surviving drivers in fatal automobile crashes. The researcher might ask for a blood sample, fully disclosing the medical procedure and risks, but failing to disclose the risk that the chemical test results might be used against the subject in either civil or criminal litigation. Failure to inform of this risk may be held to vitiate the consent.

18. The HEW guidelines for protection of human subjects and informed consent are perhaps the most important present source of authority in the area because so much public funding is tied directly to their satisfaction. It's becoming increasingly evident that all sources of

federal research funds are beginning to demand adherence to HEW guidelines even though they are specifically applicable only to funds provided under the Public Health Service Act as amended by the National Research Act, Pub.L. 93-348, §212(a). As defined in recently promulgated HEW guidelines, informed consent has the following meaning:

> "(c) "Informed consent" means the knowing consent of an individual or his legally authorized representative, so situated as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress, or other form of constraint or coercion. The basic elements of information necessary to such consent include:
>
> (1) A fair explanation of the procedures to be followed, and their purposes, including identification of any procedures which are experimental;
> (2) a description of any attendant discomforts and risks reasonably to be expected;
> (3) a description of any benefits reasonably to be expected;
> (4) a disclosure of any appropriate alternative procedures that might be advantageous for the subject;
> (5) an offer to answer any inquiries concerning the procedures; and
> (6) an instruction that the person is free to withdraw his consent and to discontinue participation in the project or activity at any time without prejudice to the subject. 45 C.F.R. §46.3(c); 40 Fed. Reg. 11851 (1975).

19. One of the most spontaneous reactions to unconsented to behavioral research somewhat fittingly involved lawyers as researchers. In the Chicago jury project a research plan was devised to study the deliberations of juries in the secrecy of the jury room. Consent was received from the judges and all lawyers involved in every case to listen in to the deliberations, but the jurors themselves were not informed. Notwithstanding the fact that important learning derived from the studies, many people were shocked at the unconsented to intrusion into the privacy of the individuals involved. Legislatures acted quickly to control such research behavior. New York created a special crime

of "eavesdropping" as it relates to juries (N.Y. Pen. Law §738, replaced by N.Y. Sess.Laws 1965, ch. 1030, §250.05) and Congress outlawed knowingly and willfully recording or attempting to record or listen to or observe the proceedings of United States juries of which the person so acting is not a member. 18 U.S.C.A. §1508 (1964). While the Chicago jury studies themselves were funded by the Ford Foundaton and not by the federal government, it should go without saying that non-funding is somewhat milder than the action taken in this instance.

20. See, e.g., 8 Wigmore on Evidence §2190 (McNaughton 1961), for a complete history and theory of testimonial privileges.

21. St.Eliz.c. 9, §12, cited in 8 Wigmore on Evidence §2190, n.17 (McNaughton 1961).

22. See, e.g., 8 Wigmore on Evidence §2190 (McNaughton 1961).

23. See, 8 Wigmore Evidence §2191 (McNaughton 1961).

24. A Kentucky statute is illustrative: "No person shall be compelled to disclose in any court, or before any grand or petit jury, or before the presiding officer of any tribunal, or his agent or agents, or before the General Assembly, or any committee thereof, or before any city or county legislative body, or any committee thereof, or elsewhere, the source of any information procured or obtained by him, and published in a newspaper or by a radio or television broadcasting station by which he is engaged or employed, or with which he is connected." Ky. Rev. Stat. §421.100. For a listing of other statutes granting news reporter privileges, see Branzburg v. Hayes, 92 S.Ct. 2646, at 2660, n. 27. As to the effectiveness of state statutes in preventing the compulsion of testimony in federal courts, one court has said that they are not "conclusive" but gave them weight in determining the issue on policy grounds. Baker v. F.& F. Investment, 470 F.2d 778, 782 (2d Cir. 1972). Another has said, "Federal courts exercising diversity jurisdiction generally recognize state-created privileges." Karp v. Cooley, 493 F.2d 408 (5th Cir. 1974).

25. See statutes cited in "The Researcher - Subject Relationship: The Need for Protection and a Model Statute," 62 Geo. L.J. 243, 245, 250 (1973).

26. "Congress shall make no law* * * abridging the freedom of speech, or of the press; or the right of the people peaceably to assemble * * *." Amendment 1, United States Constitution.

27. Caldwell v. United States, 434 F.2d 1081 (9th Cir., 1970).

28. Note the subtle distinction between the public's right to be informed and a reporter's right to find out. The court's exact holding was: "In light of these considerations we hold that where it has been shown that the public's First Amendment right to be informed would be jeopardized by requiring a journalist to submit to secret Grand Jury interrogation, the Government must respond by demonstrating a compelling need for the witness' process before judicial process properly can issue to acquire attendance." 434 F.2d at p. 89.

29. See, e.g., Comment, "The Public Scholar and the First Amendment: A Compelling Need for Compelling Testimony," 40 Geo. Wash. Rev. 995. See, also, "The Researcher - Subject Relationship: The Need for Protection and A Model Statute;" 62 Geo L.J. 243 (1973) and Nejelski and Lerman, "Research - Subject Testimonial Privilege," 1971 Wisc. L. Rev. 1085.

30. Branzburg v. Hayes, 408 U.S. 665, 92 S.Ct. 2646, 33 L.Ed. 2d 626 (1972).

31. 92 S.Ct. at 2662.

32. 92 S.Ct. at 2662.

33. "It is apparent * * * from our history and that of England, that concealment of crime and agreements to do so are not looked upon with favor. Such conduct deserves no encomium, and we decline now to afford it First Amendment protection by denigrating the duty of a citizen, whether reporter or informer, to respond to grand jury subpoena and answer relevant questions put to him." 92 S.Ct. at 2664.

34. 92 S.Ct. at 2666. In Baker v. F.& F. Investment. 470 F.2d 788 (2nd Cir. 1972), cert. denied, 411 U.S. 966, 36 L.Ed. 2d 686, 92 S.Ct. 2147 (1975), a federal circuit court of appeals referred to Branzburg v. Hayes as a limited case and recognized a conditional reportorial privilege on the facts of the case before it. In that case plaintiffs in a civil action sought

to compel divulgance by a reporter of his sources of information for an article about racial "block busting" that had appeared in the Saturday Evening Post years earlier. Refusing to compel testimony, the court commented that"* * *(T)though a journalist's right to protect confidential sources may not take precedence over that rare overriding and compelling interest, we are of the view that there are circumstances, at the very least in civil cases, in which the public interest in non-disclosure of a journalist's confidential sources outweighs the public and private interest in compelling testimony. The case before us is one in which the First Amendment protection does not yield." 470 F.2d at 783. While the court's opinion seems to be at odds with Branzburg v. Hayes, its own protestations to the contrary notwithstanding, several factors mentioned by the court may distinguish the two: (1) Baker involved civil rights questions, a very sensitive area; (2) Baker was a civil as opposed to a criminal action; (3) the reporter was not a party to the main action; (4) other sources of information had not been exhausted; and (5) the information was not essential to the cause of action.

35. United States v. Doe, 460 F.2d 328 (1st Cir. 1972) explicitly rejected the contention that the First Amendment required such a privilege. In that case a Harvard social scientist was held in civil contempt for refusing to answer grand jury questions in the course of investigation of criminal conduct surrounding the unauthorized release of the "Pentagon Papers." The researcher was questioned about his sources for various scholarly articles he had written about the Viet Nam war. In a limited holding, the court held that no privileges existed in respect to conversations between scholars. 460 F.2d at 334. It was not necessary for the court to delve into the more general question as to whether the relationship between the scholar and primary data source would be protected by the First Amendment. Presumably, Branzburg v. Hayes, 408 U.S. 665, answers that negatively. The researcher case did afford some slight relief for the researcher in upholding his right to refuse to give his "opinion" about general matters related to his studies. 460 F.2d at 335. The Supreme Court refused to review the case. cert.denied, sub, nom., Pokin v. United States, 411 U.S. 909, 93 S.Ct. 1527, 36 L.Ed. 2d 199 (1973).

36. 92 S.Ct. at 2669. Wigmore set forth the most widely recognized criteria to be met in recognizing privileges. They are:
"1. The communications must originate in a confidence that they will not be disclosed.
2. The element of confidentiality must be essential to the relation between the parties.
3. The relation must be one which in the opinion of the community ought to be assiduously fostered.
4. The injury that would injure to the relation by the disclosure of the communication must be greater than the benefit gained by its contribution to the disposition of the litigation." 8 Wigmore on Evidence §2185 (McNaughton 1961).

37. See, e.g., "The Researcher - Subject Relationship: The Need for Protection and a Model Statute," 62 Geo. L.J. 243 (1973); "The Public Scholar and the First Amendment: A Compelling Need for Compelling Testimony," 40 Geo. Wash. L.Rev. 995 (1972); and, "Social Research and Privileged Data," 4 Valparaiso L.Rev. 368.

38. Pub. L. 91-513; 84 Stat. 1236.

39. "The Secretary may authorize persons engaged in research on the use and effect of drugs to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals." 42 U.S.C.A. §242a(a)(2), as amended by Pub. L. 91-513, Tit. I, §3.

40. Id.

41. Publ L. 91-513, Tit. II, §502(a).

42. Publ L. 91-513, Tit. II, §502(c).

43. Pub. L. 92-555.

44. In full, the qualified privilege is stated as follows:
"(a) Records of the identity, diagnosis, prognosis, or treatment of any patient which are maintained in connection with the performance of any drug abuse prevention function authorized or assisted under any

provision of this shall be confidential and may be disclosed only for the purpose and under the circumstances expressly authorized under subsection (b) of this section.
(b)(1) If the patient, with respect to whom any given record referred to in subsection (a) of this section is maintained, gives his written consent, the content of such record may be disclosed

(A) to medical personnel for the purpose of diagnosis or treatment of the patient, and

(B) to governmental personnel for the purpose of obtaining benefits to which the patient is entitled.

(2) If the patient, with respect to whom any given record referred to in subsection (a) of this section is maintained, does not give his written consent, the content of such record may be disclosed as follows:

(A) To medical personnel to the extent necessary to meet a bona fide medical emergency.

(B) To qualified personnel for the purpose of conducting scientific research, management or financial audits, or program evaluation, but such personnel may not identify, directly or indirectly, any individual patient in any report of such research, audit, or evaluation, or otherwise disclose patient identities in any manner.

(C) If authorized by an appropriate order of a court of competent jurisdiction granted after application showing good cause the court shall weigh the public interest and the need for disclosure against the injury to the patient, to the physician-patient relationship, and to the treatment services. Upon the granting of such order, the court, in determining the extent to which any disclosure of all or any part of any record is necessary, shall impose appropriate safeguards against unauthorized disclosure." Pub.L. 92-555, §408; 21 U.S.C.A. §1175. An identical qualified privilege has been provided by the Comprehensive Alcohol Abuse and Alcoholism Prevention, Treatment, Rehabilitation Act Amendments of 1974 for programs conducted under its aegis. Pub.L. 93-282, §122; 88 Stat. 125.

45. In essence, the legislatively created drug treatment privilege is very closely akin to the researcher-subject privilege that the courts were asked to acknowledge in the series of cases leading up to Branzburg v. Hayes,

408 U.S. 665, 92 S.Ct. 2646, 33 L.Ed. 2d 626 (1972). For a follow up on Branzburg see, Nejelski and Finsterbusch, "The Prosecutor and the Researcher: Present and Prospective Variations on the Supreme Court's Branzburg Decision," 21 Social Problems 3 (1973).

46. People v. Newman, 298 N.E. 2d 65, 32 N.Y. 2d 379 (1973), cert.denied, 414 U.S. 1163, 94 S.Ct. 2d 61 (1973).

47. Application of the New York physician-patient privilege was a subsidiary issue in the case. The Court of Appeals ruled against privilege on grounds that the evidence sought was obtained as an administrative part of the project and not in the confidential physician-patient relationship. 298 N.E. 2d at 653, 654.

DRUG/DRIVING RESEARCH REVIEW

SYMPOSIUM

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CHAPTER X

A Report of the
Working Sessions on:

LEGAL AND PRACTICAL CONSTRAINTS ON DRUG/DRIVING RESEARCH

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1.0 INTRODUCTION

This paper summarizes the discussions of the working group on legal and practical constraints on research in the field of drugs and driving.

The discussions ranged broadly, examining different types of research projects and the legal issues they posed. The basic legal issues flow from the body of law that deals with the protection of human subjects, that is, individuals who are the subject of or who participate in research activity.

The participants were concerned with identifying the practical constraints on research that result from law and regulations, and suggesting solutions that would facilitate research in the future.

Other practical considerations, such as the problems of obtaining an appropriate biological sample for drug measurement and the selection of appropriate tests for measurement of behavioral impairment, were discussed in other working groups.

This report has been developed as a summary of the working group discussion. It has been organized to facilitate presentation and does not follow the chronological order of the discussions. Supplemental material, referenced in the discussions, has been set forth to provide continuity for the reader. The following sections discuss the general legal issues, the issues and problems associated with specific research activities, and present some conclusions.

2.0 PROTECTION OF HUMAN SUBJECTS

The body of law that deals with the protection of human subjects is not neat nor well-defined. The principles have been set forth in numerous ethical codes. Some of these codes have their roots in the reaction of society to painful and brutal experiments such as those conducted in Nazi concentration camps. The famous Nuremberg Trials led to the promulgation of a code of ethics for the use of human subjects in research. The Nuremberg Code (1) places heavy emphasis on the principle of informed consent. Anyone who participates in a research effort should be a true volunteer. Further, the decision to volunteer should be reached only after the subject has been fully informed of all risks and benefits that might be incurred.

The basic principle of informed consent has been restated in the ethical codes of most of the research professions. The medical profession and the associated disciplines of the medical sciences and psychology are particularly sensitive to the concept. This reflects a traditional recognition of risk associated with treatment of physiological conditions or states.

In addition to the ethical codes, a limited body of case law exists to help define the law in this area. The cases are generally civil actions for negligent treatment or malpractice. The courts have tended to adopt the principle of informed consent as representing a standard or usual and customary practice within a profession, and to hold those in that profession to that standard.

A 1965 Canadian case involving drug research illustrates this point. The plaintiff, a college student, volunteered to undergo anesthetic tests for the purposes of medical research. He signed a consent to the test after being advised "that it was a safe test and there was nothing to worry about." He received a $50 renumeration for participation. He was not told that the test involved a new drug of which the defendant doctors had no previous knowledge. He was not advised of the way in which the experiment would be conducted nor the methods that would be used.

As a consequence of the test the plaintiff suffered a heart stoppage and was unconscious for four days and hospitalized for ten days. Plaintiff sued for damages and was awarded judgment for $22,500.

The judgment was upheld on appeal with the court stating that "the test performed by the doctors constituted an actionable trespass unless done with the consent and for consent to be effective it must be an informed consent, freely given. It was the duty of the doctors to give a fair and reasonable explanation of the proposed treatment including its probable effect and any special or unusual risks" (2).

The case illustrates the adoption of the principle of informed consent by a court even though no specific statute or regulation existed or formed the basis for the action. Similar cases may be found in jurisdictions in the United States.

In addition to civil actions for damages, professionals may face action by the administrative boards regulating the practice of their profession.

In July 1963, three doctors, following a protocol that had been approved by the director of medicine of the Jewish Chronic Disease Hospital in Brooklyn, New York, injected live cancer cells under the skin of 22 chronically ill patients. The doctors did not inform the patients that live cancer cells were being used nor that the test was not related to their normal course of treatment.

The experiment led to controversy among the medical staff and an investigation by the grievance committee and board of directors of the hospital. Various forms of litigation resulted. Ultimately, the Attorney General of the State of New York filed charges against two of the doctors involved, with the Board of Regents of the University of the State of New York, the licensing body for physicians in the State of New York. The board imposed the sanction of license suspension on each of the physicians for a period of one year and then stayed the suspension and placed the physicians on probation (3).

Thus, a research professional faces the possibility of professional censure as well as civil liability if the rights of human subjects are not protected in the course of research.

The rights of a subject and the duties of the researcher may be traced to the ethical codes and the specific cases decided by the courts. Unfortunately, the codes are often broad statements that are difficult to translate into operational rules for specific situations. The cases, while more specific, are very limited in number and deal with fact situations that are often extreme. It is probable that other cases exist but are not reported, as disputes may have been resolved without litigation through a settlement process. Such cases are seldom widely publicized, as the professionals involved do not wish to further damage their reputations. If insurance companies are involved they do not wish to encourage other claims of a like nature. Unfortunately, this lack of dissemination may result in a lack of sensitivity by other professionals to potential problems.

The Congress of the United States has required the Secretary of Health Education and Welfare (HEW) to promulgate regulations to require institutions and individuals engaged in HEW-sponsored research to protect the rights of human subjects (4). HEW provided guidelines to researchers on the use of human subjects for some time prior to this act. Thus, the recent Congressional action may be viewed as a broad recognition of the need for protection of human subjects and a general mandate to the Secretary of HEW to establish such policies and guidelines as may be appropriate.

Technically, such regulations are applicable only to HEW-funded projects. Researchers should give these regulations broader interpretation for several reasons.

First, the statutory language that required the Secretary to promulgate the regulations may be viewed as a statement of public policy by the Congress. Courts examining fact situations for rights and duties of parties are sensitive to formal language establishing broad public policy.

Second, the guidelines constitute a statement of policy and a set of standards that establish usual and customary practices within a profession. The guidelines draw upon prior ethical codes and practices. They represent a summarization and codification of "common law" related to the protection of human subjects. It is highly probable that a court examining a fact situation would regard the HEW guidelines as a statement of substantive law establishing a standard of care to be met by research professionals. The regulations also contain certain procedural requirements. The applicability of such procedural requirements is likely to be less general. If a researcher could establish that his protocol met the substantive standards although the exact procedures were not followed, it is likely that a court would conclude that the duty owed the subject was met.

While exact compliance with the procedures contained in the HEW guidelines may not be required to avoid civil liability, a simple aspect of research administration is likely to make compliance necessary.

The guidelines require each institution receiving HEW grants and contracts to establish an institutional committee to review protocols of proposed projects and to monitor ongoing projects which involve the use of human subjects. As a result of this requirement almost all academic and major research entities have established committees which review all research projects which involve the use of human subjects, regardless of the source of funding. These committees are cognizant of the HEW standards and, as a practical matter, tend to apply them uniformly to all proposed research. The committees do not recognize one set of standards for HEW grants and another standard of care for projects funded from other sources. Thus, researchers in academic or research institutions are likely to be required to follow the HEW guidelines in a substantive and procedural sense.

The regulations are codified (5) and HEW has periodically issued a pamphlet providing additional interpretation of the provisions of the regulations. Certain portions of the regulations are directly relevant to this discussion and are set forth in the following paragraphs.

The institutional committee or review board is charged with an examination of each project to determine whether subjects will be placed at risk, and if risk is involved, whether:

1. The risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant a decision to allow the subject to accept these risks;

2. the rights and welfare of any such subjects will be adequately protected;

3. legally effective informed consent will be obtained by adequate and appropriate methods in accordance with the provisions of this part; and

4. the conduct of the activity will be reviewed at timely intervals.

Definitions

a. "Institution" means any public or private institution or agency (including Federal, State, and local governmental agencies).

b. "Subject at risk" means any individual who may be exposed to the possibility of injury, including physical, psychological, or social injury, as a consequence of participation as a subject in any research, development, or related activity which departs from the application of those established and accepted methods necessary to meet his needs, or which increases the ordinary risks of daily life, including the recognized risks inherent in a chosen occupation or field of service.

c. "Informed Consent" means the knowing consent of an individual or his legally authorized repre-

sentative, so situated as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress, or other form of constraint or coercion. The basic elements of information necessary to such consent include:

1. A fair explanation of the procedures to be followed and their purposes, including identification of any procedures which are experimental;

2. a description of any attendant discomforts and risks reasonably to be expected;

3. a description of any benefits reasonably to be expected;

4. a disclosure of any appropriate alternative procedures that might be advantageous for the subject;

5. an offer to answer any inquiries concerning the procedures; and

6. an instruction that the person is free to withdraw his consent and to discontinue participation in the project or activity at any time without prejudice to the subject.

Perhaps the most difficult problem for a researcher or lawyer charged with interpretation of these regulations is the determination of when a subject is "at risk." The classic cases involving medical treatment and the selection among alternative treatments pose problems but those issues are usually definable. Damages normally relate to physical or psychological injury. The definition of social injury is much more complex and burdensome.

Paul Reynolds (6) has set forth six basic categories of "damage" that may result from social science research.

1. Actual changes in the characteristics of an individual (i.e., attitudes, personality, self-concept, physical health, etc.).

2. An experience that creates tension or anxiety.

3. The collection of "private" information which, if made public, might embarrass research participants or actually make them liable to legal action.

4. Deception of the individual, the act of being deceived being considered as "damaging."

5. Providing participants with unpleasant, though true, information about themselves which they might not otherwise have to confront.

6. The "invasion of privacy," the mere act of collecting certain types of information being considered as "damaging," regardless of the consequences for the individual.

His categories 1 and 2 include elements that may be included within the physical and psychological injury classes of the HEW regulations, as well as being potential problems under the social injury class. His categories 3 through 6 appear to fall within the social injury concept. They also appear relevant to our concerns about research related to drugs and driving.

The problems of privacy are of particular concern. The right to privacy has been the subject of litigation and legislation for many years. Congress has acted recently, and perhaps definitively, in enacting the Privacy Act of 1974 (7) which states in part that: "The Right to Privacy is a personal and fundamental right protected by the Constitution of the United States."

Thus, researchers must be concerned with the right of privacy of subjects in the development of any research protocol. If information is to be collected, the disclosure of which would damage a subject, the researcher must be prepared to protect such information from disclosure. If the information cannot be protected from disclosure, the subject must be advised of this risk before the information is collected, in accordance with the law regarding the protection of human subjects.

While the law recognizes a right of privacy in an individual and provides protection for the individual (who may not be required to testify against himself) such a privilege is not generally extended to the researcher who has obtained information from a subject, even if the information was obtained under a promise to treat the information as confidential. There are limited exceptions. Medical

personnel who receive information in the course of treatment, lawyers who receive information in conjunction with legal representation and in some states psychologists and clergy are afforded some legal privilege to safeguard confidential information.

A general privilege to safeguard information collected for research purposes does not exist. Researchers may be compelled by appropriate legal process to produce records, files, and to testify as to their personal knowledge of facts obtained in the course of research (8).

This general lack of privilege has been compounded by the Freedom of Information Act and the Right of Privacy Act which require increased disclosure by federal agencies. It is common for contractual language in federally sponsored research efforts to vest title to the data in the agency sponsoring the research. Thus, a researcher may find that the data collected through his efforts are subject to disclosure by rules beyond his control.

The problem for the researcher conducting research on the problems of drugs and driving for the National Highway Traffic Safety Administration is increased because of specific language contained in the Highway Safety Act of 1966 (9). Section 106 of that act set forth special requirements for public disclosure.

> Section 106. All facts contained in any report of any Federal department or agency or any officer, employee, or agent thereof, relating to any highway traffic accident or the investigation thereof conducted pursuant to chapter 4 of title 23 of the United States Code shall be available for use in any civil, criminal, or other judicial proceeding arising out of such accident and any such officer, employee, or agent may be required to testify in such proceedings as to the facts developed in such investigations. Any such report shall be made available to the public in a manner that does not identify individuals. All completed reports on research projects, demonstration projects, and other related activities, conducted under section 307 and 403 of title 23, United States Code, shall be made available to the public in a manner which does not identify individuals.

While the language requiring that the reports that are to be made public not identify any individual is comforting,

the companion language that requires an employee or agent to testify as to information developed in the course of an accident investigation poses significant problems. Given this language, it appears that an NHTSA-sponsored researcher could be compelled to testify as to information collected in the course of an accident investigation.

NHTSA has sponsored accident investigation teams for over five years. In recent months at least one team has been compelled to testify in civil litigation arising out of a traffic crash.

Several states have passed legislation designed to protect the information collected by such teams and to grant privilege to the team members so that their testimony cannot be compelled in a judicial proceeding. While such legislation may protect the researcher from testifying in a state court, if the information collected is the property of NHTSA, it is possible that a litigant could reach the information by proceeding directly against NHTSA to compel production of the information under Section 106 and the Freedom of Information Act.

Until this issue is clearly settled, researchers must obtain legal guidance to develop research protocols and must provide affirmative notice to subjects of the possibility of disclosure of information if such a possibility exists.

One bright spot in an otherwise depressing picture of the researcher-subject privilege lies in recent Congressional action which authorized the Attorney General and the Secretary of HEW to grant privilege to researchers engaged in drug-related research. The statutes appear to apply only to research sponsored by the Department of Justice and HEW respectively, but possibly may have broader impact. The privilege provisions contained in the Drug Abuse Prevention and Control Act of 1970 (10) provide that the Attorney General or Secretary of HEW may authorize persons engaged in research on the use and effects of drugs to protect the privacy of research subjects by withholding their names or other identifying characteristics from anyone not connected with the research program. Persons so authorized may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify the research subjects.

This statute withstood a strong test in the New York Courts. A homicide occurred. A witness stated that she

had previously seen the killer in the waiting room of a methadone maintenance clinic. A subpoena was served on the director of the clinic ordering him to produce photographs of all patients who fit the general description of the killer. The director, through counsel, moved to quash the subpoena on the basis of the federal statute as the clinic was participating in a HEW research program. Specific authorization granting the statutory privilege had been received from the Secretary of HEW. The Court of Appeals in New York (highest appellate court in the state) upheld the privilege and ordered the subpoena quashed (11). The U.S. Supreme Court refused to review the decision, thus affirming the decision of the state court (12).

From a researcher's viewpoint it would be desirable to have similar legislation covering drug/driving research or to develop administrative procedures that could utilize the existing statutory authority of the Attorney General and Secretary of HEW.

This section has discussed some of the legal issues related to research on the problem of drugs and driving. These issues arise from the body of law dealing with the protection of human subjects. A researcher is required to obtain informed consent from any individual who is to be the subject of research. Such consent may be considered truly voluntary only after the subject has had a full explanation of all risks and benefits associated with the proposed research activity.

The risks may be physical, psychological or social injury. The nature of physical or psychological injury is better established than is the nature of social injury. The invasion of privacy or the release of private information obtained from a subject in the course of research activity are potential sources of social injury.

The general lack of a privilege that would allow a researcher to safeguard information was noted. Some specific exceptions were cited but these exceptions do not appear to apply, at present, to research sponsored by the U.S. Department of Transportation.

The following sections discuss research areas and specific legal and practical constraints associated with such research efforts.

3.0 RESEARCH PROBLEM

The discussants attempted to identify basic research issues that will have to be addressed in conjunction with the drug/driving problem.

The first major research area discussed was that of problem or risk identification. Further action by society will be dependent upon an accurate determination of the effects of drugs on driving behavior and the resultant crash loss. Past research approaches suggest that it will be necessary to examine drivers involved in crashes and drivers representative of the general driving population to determine drug presence and effects.

Accurate methods for determination of drug presence and correlation of such findings with driver impairment will also be required.

If it is assumed that drugs do adversely affect driving behavior, it follows that countermeasures must be developed to reduce the risk of loss. Research on countermeasure development and evaluation of countermeasures will then be required. Such research is likely to require the collection of information from individuals who are participants in countermeasure programs. Other countermeasures may limit the availability of drugs which are shown to impair driver behavior through manufacturing or dispensing restrictions. Imposition of such restrictions will require clear evidence of drug effects developed through a testing program.

As the necessary research was discussed, two basic research categories were identified that served as a useful vehicle for communication. These categories were:

- Risk Identification - research undertaken to define the nature and extent of the drug/driving problem.
- Countermeasure Development and Evaluation - research undertaken to develop response to an identified problem and to measure the effectiveness of the responses.

In turn, two classes of research activities were identified that would be necessary to meet the needs of the research categories. These were:

Class I: Those research efforts which involve giving a subject a drug and measuring the effects. The measurements may be focused on identification and quantification of drug presence or of behavioral effects. This class of research includes the traditional laboratory experiments.

Class II: Those research efforts which involve the examination of a subject who has (or may have) taken a drug before coming in contact with the researcher. The research may involve the collection of a biological sample for drug identification and quantification, the measurement of behavior, or the collection of information from or about the subject relevant to drug use and driver behavior. This class of research includes the traditional field research efforts such as roadside surveys and accident investigation. It would also include evaluative research involving collection of human information.

The research needs of each major category will require research efforts in each of the classes. For example, research dealing with the examination of crashes will require field studies (Class II) but will be dependent upon analytical methods and information about behavioral correlations with drug presence developed through laboratory studies (Class I). Evaluation of countermeasure programs, such as court based treatment efforts, may rely on screening tests to determine if drug use is continuing, or on psychologically oriented personal evaluations based on prior Class I studies. Thus, the research needs must be met through related research efforts. Each class of research activity poses different legal problems which, in turn, create different practical issues and constraints.

The following sections present the major problems and constraints identified in the discussions. The discussions are summarized by research activity class to facilitate presentation.

3.1 Class I Legal Issues and Constraints

The basic structure of a Class I study involves the use of a human subject who is given a known quantity of a known drug. The object may be to measure the behavioral

effects of the drug or to simply develop methods for quantification and identification. (It was noted by the discussants in this working group and others that mere presence does not allow prediction of behavioral impairment for all drugs. Thus, research that correlates measurements of drug presence with driver behavior impairment is required.)

The primary legal issue is posed by the requirements for the protection of human subjects, previously discussed. The potential for other civil liability also exists if standard clinical practices are not followed. (The problems of the non-sterile needle or improper dosage are general negligence problems and are not considered here.)

A researcher who wishes to administer a drug to a subject must ensure that an adequate assessment of the risk to the subject has been made. Adequate knowledge about the drug to be used must exist. In almost all cases this dictates that prior animal studies be completed so that basic dose response and toxicity levels have been established.

Such information is usually available for drugs legally available on a regular prescription or over-the-counter basis. Drugs in an investigational status obviously pose additional issues. Illicit drugs pose even a more serious problem.

The research issues are compounded because early information indicates that multi-drug use, in particular, drug/alcohol interactions, are creating drug/driving problems. Additional risks created by drug interactions must be explicitly examined in assessing the risks for the subject. Again, animal studies of multi-drug use and drug interactions may be required before human subjects may be used.

After the risk of the drug(s) has been carefully examined, the risks of the remainder of the experimental protocol must be examined as well. Risks to the subject or to others must be considered. The potential for physical harm, and psychological or social injury must be examined.

Laboratory scientists are usually very sensitive to physical or psychological harm. Concern must also be directed to the potential for social injury. The breach of confidence or invasion of the right of privacy through disclosure is an area that must be considered.

It is common for a medical history to be taken of a subject. Specific questions usually deal with prior or concurrent drug usage. This information is essential for

assessment of risk and protection of the subject. Such information may be potentially damaging to the subject if disclosed, as for example, if the subject reveals a continuing pattern of illegal drug use. Or disclosure may be simply an invasion of privacy as in the case where a subject may take a sustaining medication for a state or condition that is not generally known and the disclosure would cause the subject embarrassment or other adverse consequences. Researchers must establish protocols that safeguard such information as well as determining the extent to which they can be forced to disclose information.

After fully examining all risks inherent in the research procedure and determining that the benefits outweigh the risks (and after appropriate approvals have been obtained), the researcher must fully inform the subject and proceed only after full voluntary consent has been obtained. The process of informing the subject must include a disclosure of all risks: physical, psychological and social.

Many of the potential experiments identified by the discussants were typical of those routinely done in drug investigations and posed no special legal issues other than those previously discussed.

One type of quasi-laboratory experiment appeared to raise a number of issues. This was the case where a subject is given a drug and then allowed to operate a motor vehicle. The closed track case (where the vehicle is operated in a field laboratory or track free of other vehicles or if other vehicles are present they are under the direction and control of the researcher as part of the experiment) requires care and adequate assessment of risk but does not raise instant concern. In contrast, the experiment in which a "drugged" subject is allowed to operate a vehicle on the open highway or on roadways where other people who have no knowledge of the experiment are present is a much different case. Such drivers, passengers, and pedestrians cannot be said to have given their informed consent to participate in the research.

If the experimental subject is impaired, a crime is being committed in most jurisdictions within the United States. Not only the driver but potentially the researcher could be the subject of criminal prosecution. It is highly probable that if a crash or other event resulted from such an experiment the researcher and/or his institution would be held civilly, if not criminally, liable.

The nature of this type of experiment causes a lawyer automatic concern, and a conservative response to a request for an opinion as to the legal propriety of such experiment is likely to be a recommendation to forget it. Such a response is likely to flow from an understanding of society and legal dynamics rather than an analysis of the actual risks inherent in the experiment.

If such research is proposed, carefully documented evidence must be developed to demonstrate the nature and extent of risk involved to the research subjects and to the public. While it is not practicable to obtain the consent of every person who might be "at risk" in the experiment, it would seem necessary to obtain the concurrence of public officials who might be deemed to give consent upon the part of the public. At a minimum the proposed activity should be reviewed with law enforcement and prosecutorial agencies to resolve any issues of criminal liability in advance. Hopefully, an adequate explanation of risks and benefits would produce cooperation and immunity from prosecution. Absent such approval, the exposure of a subject to prosecution or potential civil liability seems unconscionable and completely inconsistent with existing law.

Assuming adequate permission to engage in the activity could be obtained, the high probability of civil liability in the event of a crash or other damaging event is such that special precautions should be taken through insurance or other indemnity to protect the subject, the researcher, the institutions and the public.

With the exception of the open road driving case discussed above, most Class I studies fall within the patterns of traditional drug investigations. The legal issues are reasonably defined and guidance for the researcher is available from the institutional human subjects committee. The law and procedure applicable to Class I studies are more clearly understood and thus a researcher is less likely to slip into difficulty unknowingly.

Another practical problem is that institutional committees responsible for project review are becoming more cautious and may limit inquiry in the future.

The nature of the drug/driving problem suggests that it may be the abusive use of drugs that is the problem in some cases. In those cases drug dosages significantly above the therapeutic level are taken. It may be impossible to gain approval for research protocols that propose to use

similar drug levels in test subjects. The refusal is likely to be based on the potential risk to the subject. A similar problem may be encountered when testing of drug interactions or illicit drug effects is proposed.

A companion issue has been suggested. It is hypothesized that some drivers who habitually use a drug may be impaired when its use is discontinued. Approval of projects which propose the withdrawal of a therapeutic drug may be denied unless it can be shown that the risk to the subject is low.

In summary, the Class I issues turn on the legal problems of assessment of risk and informed consent by human subjects. Researchers must consider not only physical and psychological consequences but social injury as well. Social injury is most likely to result from disclosure of confidential information obtained in conjunction with the research effort.

Concern for the risk of human subjects may cause practical problems by limiting dose levels or multi-drug experimentation.

Laboratory experimentation that extends to the open highway and exposes individuals to risk who have not consented to participate in the experiment poses critical legal and social issues that require clear resolution before the experiment is undertaken.

3.2 Class II Legal Issues and Constraints

The basic structure of a Class II study involves the examination of a human subject who has (or may have) taken a drug before coming in contact with the researcher.

We do not suggest by such wording that a researcher may avoid the legal issues suggested in the Class I discussion by inviting subjects to take drugs at their own risk and then present themselves for examination or testing. Such an approach would be quickly disposed of in the courts as a sham and the full standards applicable to Class I research would be applied.

What is suggested is the typical field study where individuals selected from a particular population are examined to determine their state or condition at a particular point in time. The two most common examples of this type of highway safety research are (1) the investigation of

traffic crashes to determine drug presence and effects, and (2) the random examination of the general driving population to assess the presence of drugs in the population at risk.

The two above-cited examples may be undertaken to determine the nature and extent of the drug/driving problem or such studies may be conducted over a lengthy period of time to measure changes in the problem possibly attributable to countermeasure programs. In the latter case, the studies may be regarded as evaluative research.

Class II also includes other evaluative research activity dealing with human subjects. Present countermeasure programs developed to deal with alcohol involve a treatment-based response as a part of legal system action or in a diversionary program. Evaluation of the effectiveness of such efforts requires the collection of information about subjects and may in some cases involve physiological and psychological testing.

The same basic constraints that flow from the law dealing with the protection of human subjects apply to Class II studies just as they apply to Class I studies.

While the application of the law is the same in principle, in practice it is considerably more complex. First, the risk of physical or psychological injury in Class II studies is relatively low. Possible civil issues (associated with the collection of biological samples for drug testing) can be foreseen, but these are not substantially different from the risks associated with standard medical tests; they are generally regarded as a low risk activity when performed in accordance with medical standards.

Potential civil liability can result from any activity on the highway. Thus, some risk is associated with accident investigation and roadside surveys. The interference with traffic flow could result in additional crashes or injury. The past history of success in these areas suggests that these investigations will be allowed if due care is exercised.

Second, the risks associated with social injury are not well-defined nor are many researchers presently engaged in Class II studies particularly sensitive to potential risks and the need for protection of human subjects. In fact, many researchers do not think of the individuals from whom they collect information as "human subjects" in the same sense that the clinical researcher engaged in a Class I study approaches his subjects.

Examination of the characteristics of Class II studies in light of the legal constraints suggests that major legal issues are most likely to arise in conjunction with information obtained in the course of the research. The action that is likely to precipitate maximum difficulty will be the disclosure of information about an individual by the researcher (or his agent, or from records) that is damaging to or invades the privacy of the individual.

While this problem is one that is common to all studies of risk in the accident population, it is particularly critical in drug/driving research. In a crash investigation it is critical to ascertain if the driver(s) had used a drug(s) and to what extent that contributed to the crash. Statements of the driver and witnesses are minimum requirements and a biological sample for quantitative examination is desirable.

Given the information requirements, what legal issues are posed? First, it must be recognized that the information is sought as part of a research effort. It is not sought for the benefit of the driver-subject and the collection of information is not a part of the subject's normal activity. The collection process represents a deviation from the subject's normal activity and is solely for the benefit of the researcher.

In this instance, the driver is clearly a "subject at risk" in the language of the law relating to the protection of human subjects. The researcher is obligated to disclose any potential risk and obtain informed consent before proceeding with the collection of information.

The risk that is posed, in most cases, is the risk of disclosure of information that the subject does not wish disclosed. In a simple case this may be seemingly trivial information such as the fact that a marital dispute immediately preceded the accident. Although trivial in some eyes, it is not for the subject. A more difficult case emerges where the information established that the subject was at fault and may as a result be subject to civil or criminal liability. In a drug case, precise information on drug presence and quantity might be sufficient to establish criminal liability or at a minimum civil responsibility.

Unless the researcher can ensure that the information collected in conjunction with the research project will not be disclosed, an obligation exists to affirmatively advise the subject of the potential of disclosure in clear terms so that true informed consent may be given.

From the discussion and experience of the working group participants, it appeared that very few researchers engaged in the collection of information from drivers or pedestrians involved in crashes are giving affirmative warnings of the risk of potential disclosure to subjects involved in the research.

In some cases it appeared that the research projects have not been construed as involving human subjects by either the researchers, the parent institution or the sponsor. Thus, no examination of the research protocol had been made from the viewpoint of the protection of human subjects.

In other cases the issue had been considered and a determination made that the data handling procedure provided sufficient safeguards to preclude disclosure. Such protocols appeared to rely on the separation of files and the storage of information in jurisdictions other than the location where the event occurred.

In some states (New Mexico, New York, Massachusetts, Virginia) limited privilege statutes have been enacted and researchers are relying on such protection.

From the discussion it appeared that this sensitive subject had not been given adequate consideration by the research community engaged in highway safety research.

As previously noted, no general privilege for a researcher to treat information obtained in the course of research as confidential exists. This is true even if the information was obtained under a promise to treat the information as confidential. Precedent exists establishing that NHTSA accident investigation teams can be subpoenaed and forced to disclose information in legal proceedings arising from the crash investigation.

Reliance upon state statutes that establish privilege is at best a risk because of the lack of cases interpreting the law. The situation is complicated for DOT-sponsored research because of the explicit language of Section 106 requiring disclosure in legal proceedings.

Recent guidance by the NHTSA Counsel's office to one investigation team directed the release of information upon order of a court. In another case, during litigation, counsel for a party was permitted to examine the case file and raw data at NHTSA headquarters in Washington. Thus, it appears that NHTSA will follow the spirit of the Freedom

of Information Act and the requirements of Section 106. Accordingly, researchers funded by NHTSA must recognize the potential for disclosure and act responsively in dealing with human subjects.

Reliance on a file system that precludes linking of the basic information with a particular subject was discussed at length, as a means for protecting information from disclosure.

The difficulty of developing such a file for accident cases was noted. While accidents are frequent events, they are relatively unique. In order to construct a file that would preclude tracing information to a particular accident and driver, so much information would have to be deleted that the value of the file for research purposes would be seriously impaired.

The development of a file system that successfully conceals the identity of parties is more probable when projects like roadside surveys are considered. The research value is again reduced because the ability to compare the collected data with other data files is eliminated.

The logical argument for the creation of "safe" files that cannot be linked to an individual, as constituting sufficient grounds for not providing a warning to the subject of the risks of disclosure, has a fatal flaw in many cases. The information to be placed in the file must be collected by someone.

While some projects may provide a sufficient division of labor to preclude anyone from linking critical data with a person, it is not likely. It is more probable that human information will be collected by an interviewer who will be privy to sensitive information although this may not include all data such as analytical test results. The recollection of the interviewer, if subpoenaed, represents a potential for disclosure that cannot be ignored. Suggestions have been made that researchers could have convenient lapses of memory when called to testify.

A lengthy discussion of the ethics of basing a research protocol on the premise that researchers or their subordinates would either suffer from memory lapses or commit perjury does not seem necessary.

From a practical standpoint it is often the unusual case, the horrible example, that reaches trial. This type

of case is most likely to have associated with it the unusual features that remain in the memory of the researcher. While recollection may have faded, it is unlikely to have been extinguished. Thus, the potential for disclosure continues to exist, regardless of the file structure.

This potential for disclosure may possibly be eliminated through mechanisms which preclude any member of the research staff who might be subject to subpoena, from having any knowledge that would link a subject with data. In the working group discussions several projects were anecdotally mentioned where this was attempted. Typically, the information was collected in one state while the files and linking information were stored and analyzed in another. Unfortunately, this is not likely to provide adequate protection as U.S. legal procedures provide for compelling the production of information even though it is located in a state other than the one in which the legal action is initiated. This may be accomplished through pre-trial discovery proceedings.

While the procedures for interstate discovery are well established, international procedures are not. Thus, files located in a foreign country may well be protected from discovery. Such files would have to be beyond the control of an individual within the United States or a court could simply order the individual to have the files brought into the United States.

A possible research strategy was discussed that would involve the collection of information from a subject through a self-reporting form. The form could then be mailed by the subject to a cooperating research entity in a foreign country. Data reduction and correlative analyses could be performed in the foreign country and only mass data made available for use in the United States. Obvious variations on this theme exist. A subject might be interviewed and asked to record responses on a form that the subject would later mail. Regardless of the approach, the objective is to ensure that members of the research staff do not have personal knowledge of sensitive information linked to a particular subject.

Adequate protection would appear to be provided if (1) no member of the project staff had personal information, and (2) the data files were beyond the jurisdiction of U.S. courts.

The discussion to this point has dealt primarily with the fact situations that arise from accident investigations

and to a limited degree from field surveys focused on the general driving population. A similar problem exists in evaluative research that focuses on subjects involved in rehabilitation and treatment programs.

The object of evaluative research is to determine the effectiveness of the program under examination. Given a program designed to reduce the risk of drug-impaired driving, the obvious concern is to determine the effect of the program on the individuals involved. A common evaluation design provides for independent confidential interviews of program participants to determine drug use and driving patterns. Examining only the legal problems associated with such a design, one notes that the information "confidentially" collected probably is not confidential.

Assume that a subject in such a program is involved in a traffic crash or other event that creates civil or criminal liability. An astute prosecutor or attorney would seek relevant and material information from all sources. Research information, unprotected by any privilege statute, directly relevant to substantive issues such as drug use would be a prime target of such inquiry. Disclosure would most likely be required by a court, and the disclosure of information harmful to the individual would be considered by most people a social injury.

The previous paragraphs have examined three basic types of Class II research studies: accident investigations, driver surveys, and evaluative research. In each case accurate information is needed from individuals on drug use, impairment and driving behavior. In some cases such information would reflect adversely on the individual if disclosed and would produce social injury.

The present state of the law has been discussed, with emphasis on the requirement to notify the subject of the potential of disclosure, if it exists. Various methods of precluding disclosure were also discussed. While the law is not clearly settled, it appears that absent specific statutory protection, a researcher privilege does not exist and the potential for disclosure exists in all basic research areas in Class II. This essentially creates a requirement for each researcher to affirmatively warn each subject of the disclosure potential.

Such a requirement and warning is believed most likely to significantly reduce the level of cooperation and to impair the quality of data. Thus, research would suffer.

The participants took note of the language of the Drug Abuse and Control Act authorizing the Attorney General and the Secretary of HEW to grant privilege to researchers engaged in drug research.

The significance of the problem of drugs and driving and the complexity of the research issues suggest the imperative need for similar protection for those examining the drug/driving problem.

The participants also expressed concern over the limited recognition of the significant legal, practical and social issues accompanying Class II research studies. A concise summary of the issues should be circulated among those engaged in such studies and the personnel of Federal, State and local agencies sponsoring research efforts.

4.0 CONCLUSIONS AND RECOMMENDATIONS

The participants of the working group on legal and practical constraints on drug/driving research reached the following conclusions:

- Drug/driving research intimately involves experimentation with human subjects and requires full adherence to the spirit and letter of the law dealing with the protection of human subjects.

- Attention must be given to the protection of subjects from social injury. The disclosure of information that would adversely affect the subject presents the greatest potential for social injury.

- Congressional action to establish a researcher-subject privilege is a critical requirement for valid examination of the drug/driving problem.

- Pending Congressional action, NHTSA should determine if existing privilege statutes authorizing the Attorney General and the Secretary of HEW to grant researcher privilege can be utilized in the examination of the drug/driving problem.

- Researchers engaged in and sponsors of accident investigation, driver survey, and evaluation research studies must be sensitized to the legal and ethical issues. Current efforts must be reviewed and future efforts planned with due regard to the protection of human subjects.

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DRUG/DRIVING RESEARCH REVIEW

SYMPOSIUM

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CHAPTER XI

A Report of the
Working Sessions on:

COUNTERMEASURE DEVELOPMENT FOR THE DRUG IMPAIRED DRIVER

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1.0 INTRODUCTION

This paper presents a summary of the discussions of the working group on countermeasure development for the drug-impaired driver.

The countermeasure topic was deliberately included within the conference agenda in spite of the fact that the information to support discussion was extremely limited. While information is available on general countermeasure programs targeted at drug abuse, reliable information on programs dealing primarily with drivers is almost nonexistent. A resource person who could speak with authority in this restricted area could not be identified, so the topic was dealt with generally by several speakers, and specifically only in the working sessions.

The decision to include working sessions on countermeasure development was made for two reasons. First, the literature does indicate a drug/driving problem and suggests that societal response is warranted. Second, countermeasures presently exist. Driving while impaired by drugs is prohibited by law in most states. Medical practitioners are warned in the medical literature that various drugs will or may impair driving performance. Other more general literature has warned the public of the possible deleterious impact of drug use on driving performance. The warning on nonprescription medications is an example of a general education approach commonly used.

Given the existence of countermeasures and a probability that more will be suggested or required, it appeared desirable to examine existing activity to suggest logical approaches for the future.

The discussion on countermeasure development was limited, not only by the lack of information on existing countermeasures, but perhaps more critically, by the lack of information on the precise nature and magnitude of the drug/driving problem.

At times this lack of information proved frustrating to the participants, but their frustration highlighted the need for careful investigation of the problem and supported the focus of the other working groups. In spite of the frustration and the inconclusiveness of existing information, the participants were able through their discussions to point out some directions for the future and some cautions for the present.

The following sections summarize the major discussion topics. The summarizations have been organized to facilitate communication and do not reflect the order of discussion. Any summary necessarily excludes some information or point of view. It must be noted that diversity of view was a characteristic of this working group, as is common in professional discussions. This summary should be read as a digest of discussion, and not as a presentation of a consensus of the participants.

2.0 DRUG USE-A SOCIETAL PROBLEM

In spite of the diversity of views expressed by the participants, a consensus emerged when the problems of drug use and abuse were discussed.

The drug/driving problem must be examined as an aspect of the overall use and abuse of drugs in society. The factors that create this highway safety problem also create other societal problems and flow from causes outside the Highway Transportation System.

Development of countermeasures that focus on individuals only when they are driving is probably a suboptimal solution. This does not suggest that such approaches should be ignored. However, an approach that would result in a drug impaired individual not driving would be most desirable. What is suggested is that the problem and countermeasure development be examined in the overall societal context to promote an integrated societal response.

An adequate response will require efforts on the community, state and national level and will necessarily involve many different agencies of the public and private sector. Independent efforts by a single agency not adequately coordinated could be counterproductive.

In this context, countermeasures that should be developed and implemented within the highway safety mission were discussed.

3.0 ALCOHOL ANALOGY

When drug impairment and driving is discussed, there is an immediate tendency to turn to society's experience with alcohol for potential solutions.

There are two pitfalls in attempting to develop analogs between alcohol and other drugs. First, alcohol use and

effects differ from other drugs. Second, the societal response to the alcohol/driving problem cannot be viewed as an outstanding success.

Alcohol is readily available as a licit drug. Illicit use is usually a function of the age of the user. Alcohol is widely used and knowledge of its effects also widely exists. Sudden, unexpected impairment by mature drivers is relatively infrequent.

In contrast, other drugs taken in a non-abusive manner may create sudden, unexpected impairment or unrecognized impairment in mature drivers. Alcohol/drug interactions resulting from licit drug use, as prescribed, and moderate alcohol ingestion may result in impairment.

Society's experience with alcohol and driving has led to identification of the heavy alcohol user as a significant risk. Heavy use or abuse appears to be a leading characteristic of the alcohol/driving problem. While drug abuse, in particular polydrug abuse (including alcohol), has been implicated in a number of crashes as a causative factor, use of licit drugs in the prescribed manner has also been implicated.

The present information on drugs and driving suggests that the population at risk may have significantly different characteristics than the alcohol-impaired driver population. In fact, the population at risk may well include drivers who are impaired because they failed to take required medication.

The nature of drug effects vary significantly from those of alcohol. Alcohol presence and impairment can be reasonably correlated, at least at higher concentrations of alcohol in the blood. Similar correlations cannot be established on the basis of existing evidence for many drugs that have the capacity to impair driving. Other drugs present detection problems that contrast sharply with alcohol, whose presence in a driver can be accurately and cheaply determined. These facts suggest that the development of legal countermeasures that rely on drug measurement, as for example, in the laws that make driving with a .10 BAC level illegal, will be difficult, if not impossible, in the immediate future.

Further, legal countermeasures historically tend to rely on intentional conduct before holding an individual liable. The application of legal sanctions to the driver

who is impaired because he has followed his doctor's instructions is likely to meet with societal resistance. Here, the analogy with alcohol may be closer if one examines the historical difficulty in obtaining driving-while-impaired convictions.

Educationally-based countermeasures may be more effective for drugs other than alcohol than for alcohol if it is true that a significant portion of the drug/driving problem flows from licit nonabusive use.

The relative lack of success of alcohol programs in dealing with the driver who is an alcohol abuser do not lead to high hopes for similar programs targeted at the drug abuser. Evidence from general drug abuse prevention programs is equally disheartening.

In summary, the existing evidence suggests that the user population and the drug effects associated with the drug/driving problem may be significantly different from the alcohol/driving problem, so that development of countermeasures by analogy may be inappropriate. In particular, use of legal approaches that rely on drug quantification and correlation with impairment do not seem feasible in the near future. The alcohol experience should not be ignored, but should be examined with the differences between alcohol and other drugs fully in mind.

4.0 THE ANALYTICAL APPROACH

The participants adopted a general analytical approach to the problem of countermeasure development. The overall approach discussed was the standard conceptual framework that appears in much of the evaluation and management by objectives literature. Such a framework may be set forth in five basic steps:

- Define the Problem
- Establish Goals and Objectives
- Identify Alternative Approaches to Meet Objectives
- Select and Implement the Most Feasible Approach
- Evaluate the Results

In attempting to apply this concept to the drug/driving area, the group necessarily involved itself in a discussion of problem definition. The absence of information has been previously noted. Thus, the group focused on the development of analytical approaches that would allow classifica-

tion of information as it became available and that would suggest information requirements for countermeasure development.

Various approaches were suggested which tended to reflect the experience and perspectives of the participants. Often, such perspectives were strongly held and resulted in debate.

Several schemes were suggested that hinged on the selection of the most critical independent variable.

4.1 Drug Classification Scheme

This approach used drugs as the independent variable and traffic crashes as the dependent variable. Information on driver/users would be classified in this scheme with other traffic crash related information.

While this appears a straightforward approach, it is not without problems. Drugs may be categorized in a number of ways: by chemical composition, by effects, by legal definitions, by availability, or by use.

Unfortunately, the chemical composition classification produces great complexity; the same drug has different effects in different users; legal definitions are arbitrary and often change; availability is a function of demand, perceived usefulness and legal restriction, among other factors. Use flows from an almost undefinable set of factors, but may be measured by consumption rates. Such use may be licit or illicit.

The discussions on drug-based classification scheme(s) led to the broad conceptual framework illustrated in Figure 1.

Members then advanced a drug classification scheme that categorized drugs by source into generally three groups: prescription, nonprescription, and street drugs. The first two groups were seen as subcategories of "licit drugs" while the last group was considered "illicit drugs." This scheme carried with it the idea that countermeasures might be targeted on drug sources. This classification seemed to have the greatest appeal although it has the weakness of not accounting for intended usage. Since it is possible to "illicitly use" a "licit" or prescription drug, subcategories were developed. The resulting matrix appears in Figure 1.

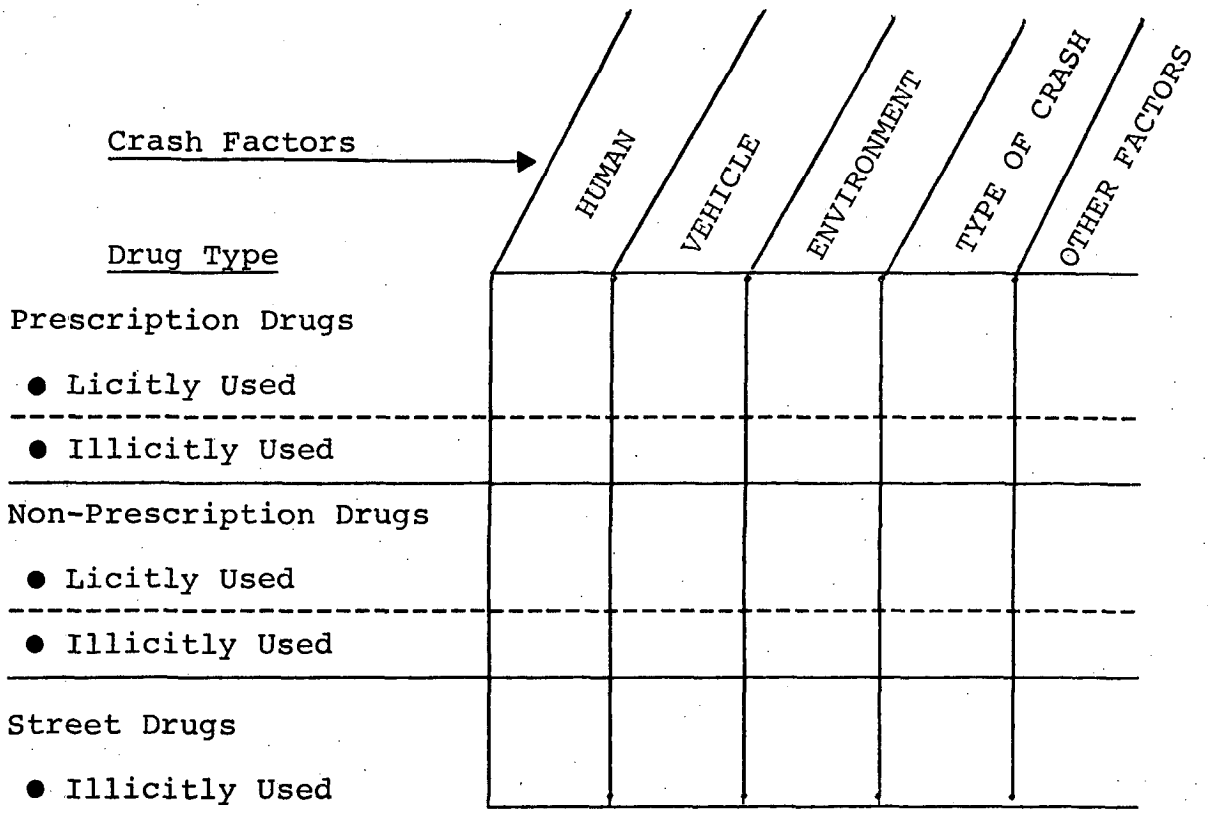

FIGURE 1: DRUG CLASSIFICATION SCHEME

4.2 User Classification Scheme

Those participants who were primarily involved with the drug user or abuser advocated a different emphasis for classification. They suggested the development of a scheme based on the user rather than the drug. The logic behind this approach is to develop a description of the at-risk population so that suitable communication campaigns could be devised.

While the concept is plausible, the limited information available on drug-impaired drivers made it difficult to illustrate the feasibility of the approach.

Critics were skeptical of the value of developing a classification approach geared to educational countermea-

sures in light of the lack of evidence supporting the effectiveness of mass communication efforts in the safety field.

4.3 Comprehensive Scheme

The articulation of various viewpoints and rigourous criticism of the two schemes presented led to the development of a third approach which reflected an integration of both approaches. This approach was conceptualized as a matrix and is illustrated in Figure 2. This matrix describes the types of information that the participants believed should be obtained to develop countermeasures.

Based on the data suggested by the matrix, the relationships of drug, user and crash variables should emerge. High values in a particular cell may suggest specific types of countermeasures and specific target areas.

The group viewed the matrix as representing an initial construct for use in discussion. Rigorous development of categories and identification of terms consistent with existing terminology and data would be required before the approach could be implemented. Thus, Figure 2 should be examined as illustrative of a concept and not as a developed plan for action.

Even in this initial stage of development, the information needed is far in excess of that available. This strongly suggests the need for more detailed examination of the problem before extensive countermeasure development or implementation is attempted.

5.0 COUNTERMEASURE PROGRAMS

Throughout the working sessions various countermeasures programs were suggested and discussed. The programs tended to fall into two broad general categories. The first, legal, would use the legal system to restrict availability of the drug and to sanction the drug-impaired driver. The second, education, would seek to restrict availability through dissemination of information to suppliers, dispensers, prescribers and users, and to reduce impaired driving through imparting general knowledge of the risk and special education/ rehabilitation programs for abusers.

Participants agreed and disagreed in part on each of the approaches contained in the categories.

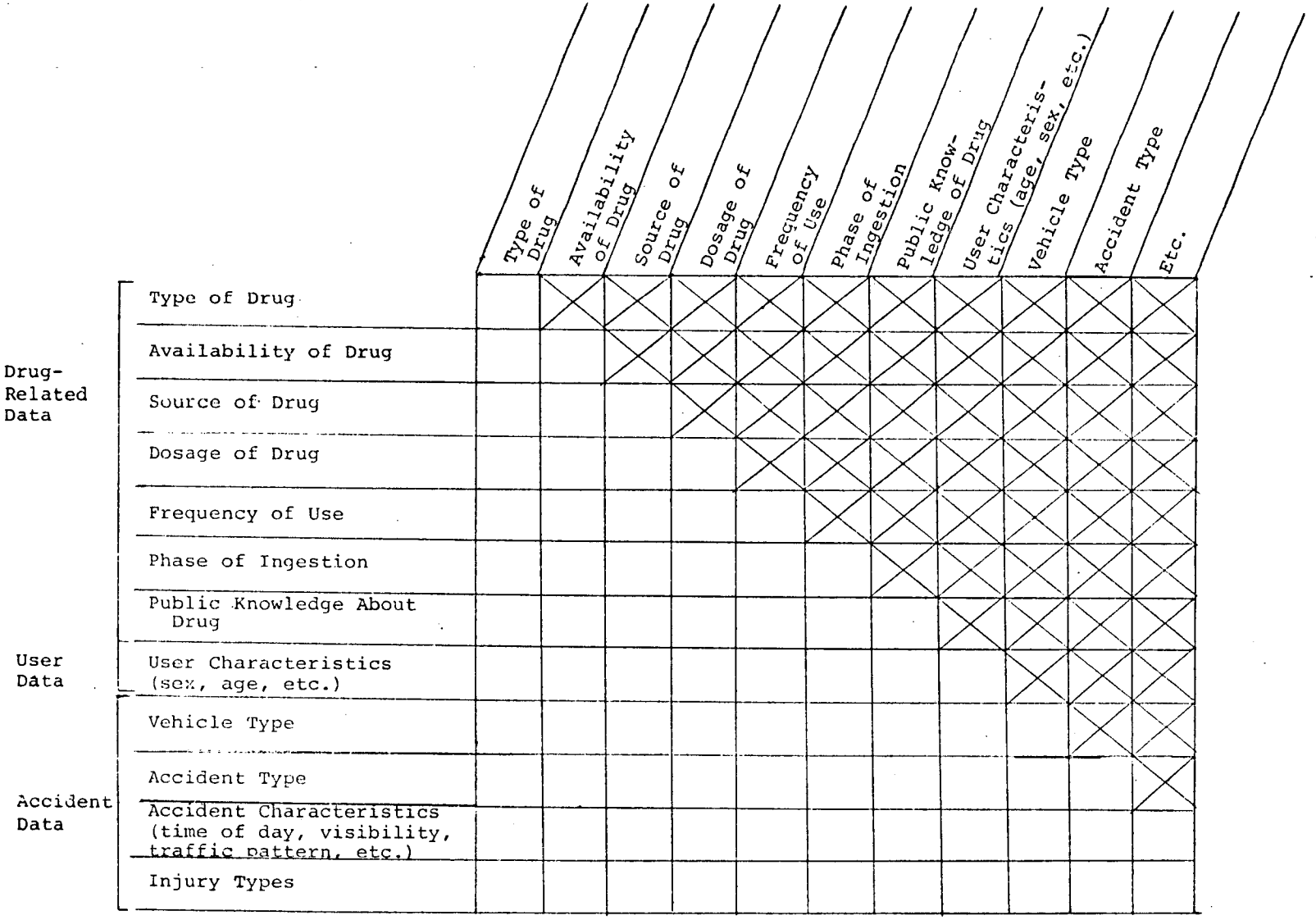

FIGURE 2 - INTERCORRELATION MATRIX OF DESIRED DRUG ACCIDENT DATA

The need for legally restricting drugs with a high potential for impairment was generally recognized. The effectiveness was questioned because of the lack of success in curtailing illicit drug use.

The legal restriction on availability tends to emphasize the non-causal nature of medical use and is believed to heighten the awareness of risk of both the physician and user. Thus, legal restrictions were believed desirable when clear evidence of risk associated with a particular drug (or drug group) has been developed.

The detection and apprehension of drug-impaired drivers by law enforcement was viewed as desirable, although the prosecution of those whose impairment was unintentional was questioned. It was suggested that more conventional tests for driver impairment which examine motor skills and psychomotor coordination be developed and implemented by law enforcement agencies rather than waiting for sophisticated drug measurement devices. Driver impairment resulting from drug abuse might well be documented by tests similar to those used to detect drinking drivers. Video tapes of driver performance on such tests may be the best available evidence of impairment given the current state of technology.

A general concern was expressed repeatedly by the group whenever educational countermeasures were discussed. The lack of information on the nature of the drug/driving problem suggests that any large-scale education campaign dealing generally with drugs and driving is not warranted. A premature campaign could easily backfire by stretching the credibility of the public, especially that portion of the population interested in recreational chemical use.

Specific information that is well supported by research findings should be disseminated. The need to warn physicians of potential drug risks was repeatedly suggested. The role of the pharmacist and community health professionals as influential and credible sources of information for the user was noted.

In general the group believed that reliable information should be disseminated to users through the health care professions. The professions' failure to disseminate available information at present was noted with concern, as was the overprescription and overselling of drugs.

The limited information available on the effectiveness of drug rehabilitation programs curtailed discussion of rehabilitation-based countermeasures. Concern was expressed that professionals responsible for the treatment of known drug abusers should be sensitized to the necessity of evaluating potential risks associated with the abuser's use of a vehicle.

In summary, the selective use of educational programs based on clear evidence of risk, as well as careful use of the legal system, were suggested as countermeasure approaches for the near-term future. Examination of existing countermeasure activities should be undertaken to determine effectiveness before undertaking expansion of countermeasure efforts.

6.0 CONCLUSIONS AND RECOMMENDATIONS

The lack of specific information on the nature of extent of the drug/driving problem limited the working group's recommendations on specific countermeasures. The discussions led to several general conclusions.

- A rigorous examination of the drug/driving problem must be undertaken before specific countermeasures can be developed.

- Based on a clearer definition of the problem, models and techniques for systematic countermeasure development must be identified. Research is required to establish effectiveness of countermeasures before any large scale implementation is attempted.

- The extent of knowledge of the health care professions about the drug/driving problem should be determined. Existing evidence suggests that an awareness campaign directed toward this audience to increase their perception of risk and to increase their patients' awareness of the drug/driving problem, is warranted.

- Large scale countermeasure programs do not appear warranted based on current knowledge of the drug/driving problem.

- Highway Safety Programs dealing with drugs and driving should be carefully coordinated with other federal, state and local programs to maximize effectiveness.

DRUG/DRIVING RESEARCH REVIEW

SYMPOSIUM

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CHAPTER XII

Speaker's Paper

THE PROBLEMS OF DRUGS AND DRIVING: AN OVERVIEW OF CURRENT RESEARCH AND FUTURE NEEDS

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1.0 INTRODUCTION

The effect of drugs on driving as a serious research area has a short history; in that history only a small amount of compelling information has been developed which would allow a radical change in the way drugs and driving are handled as social problems. We lack a wide variety of information which could lead us quickly to an understanding or a solution of drugs and driving problems. My aim here is to discuss some of the general issues in the whole area and in the specific areas concerned with risk identification, behavioral measurement of impairment, legal and practical constraints, drug measurement in the body, and countermeasure development. Compared to the theoretical and practical knowledge we have about alcohol and driving, research in these areas seems in a prolonged infancy. Some of the largest problems relate to the definition of a drug, the vast number of drugs to be considered and to the need for technological innovations in toxicology and biochemistry.

The problems of what is a "drug" and how many exist are considerable ones. According to several World Health Organization reports a "drug" is "any substance that when taken into the living organism, may modify one or more of its functions" (1). This would include all of the substances given on prescription and available over the counter as "medicines" but it would also include gases such as carbon monoxide, carbon dioxide, and oxygen. Probably it also includes foods of all descriptions since they are substances which modify body functions. Most people would not include foodstuffs as drugs if for no other reason than the legal entanglements of proceeding against "impaired driving" after eating. More common definitions restrict the term "drug" to chemicals which are connected with the treatment of illness, or to noxious substances with neurological ill effects. Dorland's Illustrated Medical Dictionary suggests that a drug is:

> "any chemical compound or any infectious biological substance not used for its mechanical properties, which may be adminstered 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."

This would appear to leave out noxious gases and certain recreational drugs such as cannabis, THC, mescaline, etc., but it is perhaps comprehensive enough. This is particularly the case when we realize how many "drugs" there might be in all. The British Pharmacopeia (1974) lists some 5,040 drugs but the American Drug Index lists over 20,000 (2) and the Merck Index lists over 41,000 (1966). Clearly, understanding the implications of 41,000 drugs for driving risk is a long-term or perhaps even impossible task. Decisions will have to be made to restrict our interests to those few classes of drugs for which there appears to be a major risk. Perhaps the best decision would be to concentrate all future efforts on the most commonly used psychoactive and hallucinogenic drugs, e.g., tranquilizers, sedatives and hypnotics, amphetamines, and the recreational drugs such as cannabis and (perhaps in the U.S.A.) the opiates. Even within these categories many new drugs are added each year to the pharmacopeia. If we were to concentrate efforts on these major categories all research related to risk-identification, assessment of impairment and detection in body fluids would be greatly facilitated.

2.0 RISK IDENTIFICATION

Several epidemiological studies in drug use indicate major trends which should be taken into account. Studies in both Canada and the United States indicate a considerable increase in the use of psychoactive drugs among adults. The major change for adults seems to be in tranquilizer use. Our own studies (supported by those of others) indicate that between 1971 and 1974 use of tranquilizers increased from involving 12.7% of adults to 19.0% of the population, whereas the frequency of barbiturate and hypnotic use remained unchanged and the use of amphetamines and other stimulants actually declined. The other area of greatest change is probably in cannabis use: in 1971 8% of adults in Toronto used cannabis at least once but the figure increased to 13% in 1974.

A similar trend is obvious in several studies of high school student populations. The trend seems to be in both Canada (3) and the USA (4) for the use of most illicit drugs to decline, (especially the hallucinogens and opiates) or remain the same. The only drugs showing a consistent increase among high school students are alcohol and cannabis. Naturally, these studies should lead us to concentrate our effort to understand how these drugs affect driving risk rather than being concerned with less frequently used drugs.

We are aware that drug use often precedes driving but it is difficult to determine the extent of drug use and driving from the available literature. From Milner's study (5) it seems that 57% of men and 35% of women on psychoactives ran the risk of drinking and driving while on psychoactives (7.1% of total population). However, this study has been done in only one area of the world. It does not give direct information about the proportion of drivers who have a drug in their system while they are driving. There are also indications that about half of the licensed cannabis users drive after smoking but for cannabis, too, the numbers of positives in non-accident drivers appears to be unknown. Without this sort of information it is difficult to assess the meaning of drug rates in accident drivers.

Numerous studies have been made of the rate of positive drug samples amongst both fatal and non-fatal drivers and victims (6,7). However, several were done a few years ago with less sophisticated testing than could be done now. These studies indicate a close connection between the presence of both alcohol and drugs in both impaired and accident drivers. They also suggest that some of the behavioral impairment assumed to be from alcohol may well be contributed by other drugs. Probably there is a need to specifically study impairment of drinking drivers to discover the excess impairment contributed by other drugs. Several studies have also found behavioral impairment among drivers with low or zero blood alcohol levels. An interesting study would be to administer behavioral tests to non-accident and accident drivers with no alcohol in their system, and to associate the impairment with various blood and urine drug levels.

Most drug and accident studies have screened for barbiturates and some tranquilizers but not for the stimulants, anti-depressants, or cannabinoids, partly because the tests for these substances are more difficult and less sensitive. There appears to be no large, dependable study which has examined fatal accident drivers or victims for evidence of hallucinogenic use, e.g., LSD, cannabis, DMT, etc. Such studies would be difficult to do as they would involve very large samples; perhaps n's of 5,000 to 10,000 would be required. A way around this problem might be to study only fatalities in high risk areas, e.g., only fatalities of persons under 25 or only accidents on campuses. A contribution would also be made by more studies of pedestrian accidents. Very few studies have included pedestrians and since elderly pedestrians have both high rates of psy-

choactive drug use and high accident rates, an interesting high-risk group may have been missed so far.

Another difficult area concerns actual impairment and accident responsibility. We tend to assume that if a given drug is found in an accident driver that its presence caused or contributed to the accident. Unfortunately for this assumption, some people may be better drivers with than without their drugs, especially if they are prescribed drugs. Demers and Heninger (8) made one of the very few behavioral impairment studies using actual patients who were prescribed the drugs. They tested manic-depressive patients on a variety of cognitive and psychomotor tasks and found little impairment when speed was not an important element in performance. With normals lithium salts would produce some confusion and disorientation. Clinical judgment and some experimental studies indicate that excited, anxious persons prescribed tranquilizers may be better drivers after they have taken their drugs, than without them. The same may be the case for abstracted, depressed persons put on anti-depressants. It is known that drug effects depend a great deal on physiological state, expectation and previous experience. However, no study appears to have related actual driving errors or accident responsibility to drug use.

The problem of determining whether drug users and abusers of various types have higher accident rates than expected is also difficult to solve. Only one study has been made of accident rates among psychoactive drug users (9) and it involved a small total sample and even smaller sub-categories of similar drug users. It should be repeated with a much larger sample. Studies of heroin addicts and cannabis users have given rather inconsistent results but the variables to be controlled are considerable. Many of these studies have not had good data on accident exposure in terms of miles driven. However, a more interesting problem is to determine accident rates per unit of drug-related exposure, or miles driven while drug-influenced. A recently completed study in Toronto (10) indicated that cannabis users have nearly as many accidents under cannabis as under alcohol, taking exposure into account. Unfortunately, multi-drug use is the norm rather than single drug use. Most cannabis users are also drinkers and about one-third of their cannabis use occasions had also been drinking. This problem will be even more marked with heroin addicts who are heavy users of alcohol, barbiturates, hypnotics as well as opiates.

A last area of interest would be the types of accident occurring under drug effects. Several types of drugs, e.g., cannabis, tranquilizers, lithium, etc., appear to increase errors but not speed in simulator tests. This would suggest that drug-related accidents should less often be highspeed passing accidents and perhaps more often rear-end collisions or running-off-the-road accidents. Injury and fatality rates depend substantially on the type of accident occurring. The apparent low rate of drugs among fatal accident drivers may be far lower than among drivers in minor accidents.

3.0 BEHAVIORAL MEASUREMENT OF IMPAIRMENT

Naturally, information is not available on how all or even most of the 40,000 or so drugs affect driving skills and risks. However, many of the major psychoactive and hallucinogenic drugs have been tested for their effects on cognitive and psychomotor skills. The tests used include short laboratory tests such as pursuit-rotor and visual acuity, driver-trainer or simulator tests, closed course or parking lot studies and a few actual tests in real traffic situations. There are great difficulties in summarizing and interpreting all of these studies for their contribution to the drugs and driving area. Problems exist with the sheer number of drugs and drug combinations used and with some experimental design aspects. In general, the results of research indicate that most tranquilizers, cannabinoids, anti-depressants, barbiturates and hypnotics tested so far can impair psychomotor skills (probably) involved in driving. The impairments seem greatest where alcohol is also involved and where the tasks are long or boring. The majority of studies of such drugs suggest that they will contribute to accidents more through creating inattentiveness and errors, than through increasing speed or risk-taking, particularly in combination with alcohol. It would be of interest to conduct studies which examine relative effects on risk-taking and attentiveness, especially when the drugs are combined with alcohol. In fact, it could be argued that all drug toxicity studies should allow for testing of the drug-alcohol effects.

There are considerable difficulties in deciding what laboratory or simulator methods are most appropriate for assessing driving risks. Studies with instrumented cars depart from the artificiality of the laboratory but many driving tasks are difficult to simulate, e.g., highspeed passing on a hill. Most laboratory and closed course studies are made under the best conditions; for example, there is no snow, rain, (fog) or darkness the roadway is not slippery

and there is no really threatening traffic. Usually the sessions are short and the drivers are not tired.

A larger problem is that we are not certain what skills are needed to produce "safe" driving or how to simulate it. The tendency in behavioral toxicity on drugs has been to test psychomotor, visual and cognitive skills and to pay almost no attention to personality or motivational variables such as aggression, assertiveness, risk-taking, etc. Such variables are probably just as important in simulated and real driving. The validity of "simulators" is in considerable doubt. Edwards, Hahn and Fleischman (11) found almost no correspondence between simulator behavior and actual driving. However, Crancer (12) found that simulator driving was related to 5 year accident records, with good performers having fewer accidents. However, behind-the-wheel tests such as ones used in licensing examinations had no relation to accidents. Real progress in the drugs and driving area would be facilitated by more information on how to simulate safe driving. An alternative might be to use the methods of Klonoff (13) who had subjects driving cars on the streets of Vancouver after cannabis use. The provision of dual control cars, driver observers and careful subject screening make this much less risky than it might seem at first.

Another improvement in experimental design would be to enlarge the subject pool for drug-driving studies. The tendency in most studies is to use male college students or professional drivers (14), or army personnel (15). Known accident drivers, inexperienced drivers, those over 65 and women are almost never used. Subjects are always well rested and are often screened for emotional disturbance. Some studies with the neglected groups would be helpful, especially because they tend to be more frequent drug users.

Patients receiving psychoactive prescriptions have only been used in very few studies relevant to driving (8). However, tolerance is known to greatly affect drug impairment especially of drugs with RAS effects. Most drugs and driving studies with psychoactives are done with persons receiving the drug for the first time with no opportunity to develop tolerance. The effects of anti-depressants, barbiturates or tranquilizers on the driving of people who have been taking them for a long time seems completely unknown -- some behavioral as well as physical tolerance is likely.

A last area of concern is around the time intervals being investigated. The most common approach seems to be for testing two or three hours after the drug has been

administered. However, psychoactives can be found in the system long after a few hours and can have clinical effects for 8 to 10 hours in the case of major tranquilizers. Very few studies have examined the "hangover" effects of drugs such as hypnotics on driving skills. Walters and Lader (16) examined the effects of nitrazepam and amylobarbitone on psychomotor and cognitive tasks after 12 hours and found considerable impairment. Our knowledge would be increased by a variety of dose-response studies with testing time intervals up to 3 or 4 days.

4.0 DRUG MEASUREMENT METHODS

The past 10 years have seen the rapid development of methods of analyzing drugs in body fluids. Much of the impetus for this work came from the need to detect illicit drug use among opiate addicts in methadone and other maintenance programs. The aims of this work were originally to provide information on the existence or non-existence of barbiturates and opiates in the urine of addicts. Usually, the amounts taken or the time at which they were taken was of little interest. Currently, a vast number of techniques of analysis are undergoing study, e.g., spectrophotometric methods, gas chromatography, immunoassay methods and the like. From an original interest in only a few drugs desired by addicts there have developed many methods for almost all major psychoactives and hallucinogenics. Unfortunately, much of the work in this area has not reached the point where it is of practical utility in the drugs and driving area.

Following administration, drugs are absorbed into the blood, distributed in body fluids and metabolized, then excreted. Alcohol, the drug of greatest interest in traffic research, is partly excreted in the breath, with a known relationship between breath and blood levels. It is rapidly excreted and disappears in unchanged form in less than 12 hours. Unfortunately, no other major psychoactive or hallucinogenic has these properties. The prospects for breath tests for drugs appear near zero for any important drug except cannabis. Also, the long excretion times make decisions about when the drug was taken nearly impossible.

Detection of drugs in the body varies considerably from one drug group to another. Most opiates, including heroin, methadone, pethidine, etc., can be easily detected with a variety of methods using urine. However, some methods (1) detect a single dose of heroin after 3 to 5 days. Of course

this would be long after the impairing effects of that dose had worn off. If one were to detect a small amount of morphine in the urine of a fatally injured driver one could conclude that the driver had taken a small amount just prior to the accident, a large amount 3 to 5 days prior, or several small amounts over time before the accident. The implications for driver impairment of any positive test are of course uncertain. It would be of interest to combine interview methods (with relatives) with studies of heroin levels in accident drivers.

Unfortunately, many of the problems with opiate tests are just as acute with other drugs. For example, the half-life of some barbiturates in plasma is 3 1/2 days (1) and excretion in urine may be detected for at least 6 weeks. Chlordiazepoxide and diazepam are not excreted unchanged in the urine and a variety of metabolites must be detected. For diazepam, positive reactions for as long as 8 to 9 days have been found after a single 5 mg. dose and this is a relatively small dose. Examples could be multiplied for other psychoactives but a clear research problem has emerged for those interested in accident research, that is, how to relate the presence of a drug in an accident driver or victim to this impairment. What we need is behavioral impairment studies which tell us about impairment at various body fluid levels rather than after a given dose.

There are also drugs, probably important in traffic accidents, for which there is no sensitive, reliable test. There are no presently acceptable methods for detecting cannabis, D^{9}THC, LSD or naltrexone. Although many methods have been attempted with cannabis none is sufficiently well-developed to have practical utility (1). A recent World Health Organization Meeting of Investigators, concerning the detection of drugs, decided that two of the major research needs were:

(1) The development of suitable test procedures for demonstrating drugs in body fluids when no satisfactory method is available; such drugs include cannabis, lysergide and naltrexone.

(2) The correlation of drug use with impaired driving skill in relation to traffic problems.

Several further practical needs are obvious in the drugs and driving area. Many of the tests for drugs now currently in use are extremely sophisticated and cannot even be done by technicians. Several can be done in only a few

places in North America (e.g., mass fragmentography, immuno-assays). Both the capital costs for equipment and sample testing costs are high if a variety of unknown drugs are being screened for in samples. The traffic area is probably most in need of cheap, roadside detection methods just when these will be available is uncertain.

5.0 LEGAL AND PRACTICAL CONSTRAINTS

Some of the probable legal and practical constraints for the drugs and driving area have already been suggested. Many jurisdictions already have laws which prohibit driving while under the influence of drugs, or while impaired by them. In fact, very few charges are ever laid under such laws. Usually, not more than a few each year are laid in Ontario, an area where there are some 30,000 impaired driving charges per year. It is possible that we are not even aware yet of what the legal constraints are in creating and enforcing drugs and driving laws. I could suggest only a few of the most obvious problems at present:

(i) There probably will be difficulties around the definition of a "drug". The laws frequently have not attempted a sophisticated definition. Challenges to laws which do not define a drug are possible;

(ii) The difficulty of proving "under the influence" of a drug is considerable unless there is to be reliance on behavioral and physiological signs, e.g., staggering, "on the nod", coma, slurred speech, sleepiness, etc. The most obvious signs are similar to those of alcohol intoxication. If breath tests are negative and drug use is not admitted it is doubtful whether many current drug tests would stand a strong court challenge;

(iii) Many drug tests require blood or urine or both. Only those for cannabis (facial wipes) perhaps will not. Laws compelling the surrendering of blood and urine for self-incrimination would have strong civil rights opposition in many areas. In some cases, such samples could be obtained from hospital emergency wards but many would be reluctant now to surrender the fluids or the results of tests on them;

(iv) Research on behavioral impairment is not sufficiently well-developed to be sure that driving

impairment is certain with all drugs and all drug users. If a long time tranquilizer user maintained that his driving was better after meprobamate than before, could expert testimony refute this assertion?

In conclusion, it may be best to have legal controls and enforcement await the development of more research on impairment and better detection tests.

The second area of legal concern is that relating to legal entanglements for researchers on drugs and driving. It seems likely that researchers will rarely have the privilege of protecting their data from subpoena, unless these privileges are specifically granted. Current changes in the ethical standards required in human research make researchers more open than ever to criminal and civil suits. The type of informed consent forms now being required will certainly make some types of research impossible, e.g., experiments with newer drugs, high dosages, chronic administration or those involving disturbed persons. The problem of who can give informed consent has not been settled and researchers will probably have to await the outcome of case law on these issues, or negotiate some protection from law enforcement or granting agencies.

6.0 COUNTERMEASURES DEVELOPMENT

A variety of countermeasures against drugs and driving risk can be suggested which do not involve legal constraints or increased enforcement. Most of these would involve educational or persuasive techniques. We do not have effective techniques for educating about drugs and driving at present however, a number of approaches could be taken, especially with physicians. Much of the drug-driving problem will turn out to involve psychoactive drugs given on prescription. Illicit drug use, except for cannabis, is probably decreasing in many parts of the world already. There are prospects for developing effective school drug education programs which include information on drugs and driving. Many of these will be school-based and established chiefly for young people.

Some efforts could be made to warn psychoactive drug users about driving hazards. Milner (5, 17) has suggested: (i) warnings by physicians about driving after drug use; (ii) that physicians not prescribe drugs for patients who are likely to drink and drive or to be accident risks; (iii) prescribing drugs only for patients with a low impairment potential; and (iv) shorter courses of therapy for some

drugs. All of these approaches might be helpful. However, there are several recent instances of warnings being ignored. Goldstein (18) pointed out that warnings were provided on the harmful side-effects of chloramphenicol, i.e., warnings by the manufacturer, the FDA, the AMA, on the product itself, and in the Physician's Desk Reference. However, in 1972 approximately 600,000 patients received it in the U.S.A. even though many had trivial infections and many malpractice lawsuits were filed (for aplastic anemia). Without a clear and unambiguous benefit to all concerned, warnings about drugs and driving might also be ignored.

A larger question concerns the need for so much psychoactive medication. Many people have pointed out that society is being over-medicated. It has been estimated that 60% of hospital patients getting drugs don't need them. Seidenberg (19) and others have pointed out how often psychoactive advertisements in medical journals and in direct mail to physicians recommend drugs for the anxieties of everyday life.

Some physicians would maintain that all psychoactives are prescribed for real symptoms. However, prescribing among physicians relates to his own drug use, his experience, his age, the number of patients he has and how much administration he had to do (see Blum, (20) for a review). When drugs are not prescribed physicians have to spend more time with patients and this might be difficult in busy consulting rooms and hospitals.

Fejer and Smart (21) attempted to determine the use of tranquilizers among "well" persons. Among adults in one of our surveys we found that 26% who had taken tranquilizers had good or excellent health, had no serious health problem in the past year, no serious illness in their family, and had never consulted anyone for a psychological problem. These people look surprisingly "well", certainly well enough not to require treatment. However, they are at risk for a drug related accident. It may be that much of the drugs and driving problem could be ameliorated by a reduction in drug prescribing and limiting psychoactives to only those who require them. In some countries, e.g., the U.S.A., a start could be made as in several other countries by banning amphetamines and other stimulants.

7.0 CONCLUSIONS AND RECOMMENDATIONS

By way of summary the major research needs are for:

- some restriction of research to the major psychoactive and hallucinogenic drugs, i.e., tranquilizers anti-depressants, and cannabis;
- more studies of the level of drugs in various non-accident populations and among accident-involved pedestrians and passengers;
- more studies of the proportions of fatal and non-fatal accident drivers with opiates, anti-depressants, amphetamines and cannabinoids in their system;
- some study of how accident responsibility relates to drug levels in drivers;
- more studies of behavioral impairment from drugs involving older subjects, females, patients and less experienced drivers, preferably some in real life driving situations and after long intervals since drug ingestion;
- the development of methods of detecting cannabis and LSD in body fluids;
- research on how body fluid-drug levels relate to actual behavioral impairment;
- some experimentation with efforts to have physicians prescribe fewer psychoactive drugs or to give effective warnings about driving to their drug using patients;
- studies of why people appear to need so many psychoactive drugs and what can be done to decrease their needs.

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APPENDICES

Appendix A

Symposium Attendees

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APPENDIX B

SYMPOSIUM AGENDA

Tuesday, April 8, 1975

Conference Registration - concurrent with lodging registration at Fireside Inn, Bloomington, Indiana. From noon.

5:00-7:00 pm	Dinner - Fireside Inn Dining Room
7:00-9:00 pm	Informal Mixer at Fireside Inn

Wednesday, April 9, 1975

8:30-9:00 am	Introduction and Welcome
9:00-10:00 am	Gerald Milner, M.D. - An overview of the problem of drug use and highway safety
10:00-10:30 am	Coffee Break and Informal Discussion
10:30-noon	Working Group Session I
noon-1:30 pm	Lunch
1:30-2:30 pm	Maressa Hecht Orzack, Ph.D. - A review of the problems of measurement of drug effects on human behavior.
2:30-3:00 pm	Coffee Break and Informal Discussions
3:00-5:00 pm	Working Group Session II
6:30-8:00 pm	Informal Mixer and Dinner

Thursday, April 10, 1975

9:00-10:00 am	Roger P. Maickel, Ph.D. - A review of the available methodology for quantitative determination of drugs in biological materials.
10:00-10:30 am	Coffee Break and Informal Discussion
10:30-noon	Working Group Session III
noon-1:30 pm	Lunch
1:30-2:30 pm	Joseph Little, J.D. - A review of major legal issues associated with drug/driving research.
2:30-3:00 pm	Coffee Break and Informal Discussion
3:00-5:00 pm	Working Group Session IV
6:30-9:00 pm	Informal Mixer and Dinner

Friday, April 11, 1975

9:00-10:00 am	Working Group Session V
10:00-10:30 am	Coffee Break and Informal Discussion

10:30-11:30 am	Working Group Session VI
11:30-12:30 pm	Dr. Reginald Smart - An overview of the status of research on Drugs/Driving and suggested future directions for research in light of the Symposium discussions. Closing remarks will be made by NHTSA and Indiana University personnel.
12:30-1:30 pm	Lunch