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Strategies for Research on the Interactions of Drugs of Abuse

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Strategies for Research on the Interactions of Drugs of Abuse

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Introduction and Overview

Monique C. Braude, Ph.D., and
Harold M. Ginzburg, M.D., J.D., M.P.H.

Ten years have passed since the Proceedings of the first Conference on Interactions of Drugs of Abuse, held at the New York Academy of Sciences, was published (Vesell and Braude 1976). Some of the participants in the 1976 conference, such as Drs. Hollister. Kreek, Mitchell, and Vesell, who have continued and expanded their interest in the interaction area, also participated in the Technical Review on "Strategies for Research on the Interactions of Drugs of Abuse" which was held in Rockvllle, Maryland, October 29-30, 1984. This Research Monograph is a summary of the papers and discussions of the invited experts who participated in this 2-day meeting.

In the past two decades a large part of the counterculture has been involved in self-experimentation with drugs, and the concurrent self-administration of multiple substances of abuse, by a variety of routes, has become normative behavior. Recently, for instance, the use on the street of a combination of tripelennamlne and pentazocine (Ts and Blues) elicited concern which was promptly remedied by the pharmaceutical industry by the addition of naloxone to pentazoclne.

Since the early 1970s the National Institute on Drug Abuse (NIDA) has supported a program encompassing interactions of drugs of abuse (such as marijuana, stimulants, and depressants) or of new therapeutic modalities. such as naltrexone, with other compounds used either on the street or therapeutically. The need for this type of research has increased with the use of polypharmacy by drug abusers and also their simultaneous use of alcohol, which has proved in many cases to be a potentiating agent for abused substances.

While the literature dealing with drug interactions from the pharmaceutical standpoint is extensive, it often consists of testimonial reports of adverse interactions and lacks in-depth studies of the mechanisms underlying these effects. A more recent approach has been to investigate interactions not simply from a forensic standpoint but rather to obtain epidemiological and clinical data to study pharmacological and behavioral interactions.

In as much as the first conference was about equally divided between preclinical and clinical studies, the emphasis at this second meeting was on clinical experimental and epidemiological data and strategies to be used for future studies in this research area.

In the opening chapter of this monograph, Dr. Adler lists the critical factors that would have to be adhered to in order to obtain reproducible and meaningful information about interactions among drugs of abuse. These include the necessity of performing full dose response curves as most of these drugs, such as the barbiturates and the cannabinoids, may have biphaslc effects at different dose levels. This was discussed at length by the group, and it was the general feeling that clinical studies cannot adhere to the rigorous criteria set by Dr. Adler for preclinical studies. For instance, a full dose response range may not be practical and would be too expensive to use in clinical studies if one would want to look only at the therapeutic (or abuse) range for treatment compounds. However, for illicit drugs, often used in the street in the toxic dose range, interaction studies cannot be done clinically and animal models have to be used.

The group also noticed that basic science studies have not provided any complex models for understanding drug interactions and that no model to replicate the "street environment" of multiple drug use has been developed. Too often, most of the preclinical studies have used a single-drug or at most a two-drug dosing regimen while, actually, street abusers as well as therapeutic users often use multiple drugs simultaneously or sequentially. On the other hand, clinicians have had difficulty in developing research protocols with a definite set of hypotheses which would not be too costly to be approved with high priority by a review committee.

Initial epidemiologic studies, which are descriptive, can provide evidence of what types of drug interactions will precipitate individuals into seeking treatment as well as demonstrate the generallzabllity of laboratory findings. In the second chapter, Dr. Hubbard and colleagues describe the multiple use patterns of a treatment population of drug abusers, observed in the Treatment Outcome Prospective Study (TOPS). This data, coupled with the Drug Abuse Warning Network (DAWN) data, provides the basis for determining new toxic drug interactions that will require careful study both to develop therapeutic interventions that will minimlze morbidity and to better understand the pharmacological reasons for individuals wanting to use a given set of psychoactive substances. Dr. Hubbard also emphasizes that, in order to understand the complex nature of multiple drug use, a multidisciplinary approach is needed with greater collaboration between epidemiologists, clinicians, and pharmacologists.

Dr. Mitchell describes step by step the statistical approaches which can be used to measure interaction quantitatively. Most often used are the potency ratio and the isobolographlc methods. Both approaches have the same conceptual basis. but the lsobolographic method is more tedious and more difficult to use in clinical studies.

Dr. Frecker brought an interesting new perspective to the group, that of an ophthalmologist with a doctorate in pharmacology who is interested in developing engineering systems for biomedical studies in humans. He identified some critical elements of the "man-machine interface" as they relate to drug-effect measurements and described what he considers to be the attributes of an "ideal" pharmacodynamic measurement technique. Although his paper is mainly on pharmaco-dynamics, i.e., the study of drugs in organisms, he also reminds us that pharmacokinetic parameters which provide indicators on, for instance, the time course of drug effects should be taken into consideration.

The pharmacokinetic mechanisms of alcohol-psychotropic drug interactions were described by Ciraulo and Barnhill and relevant examples cited. Alcohol alters drug metabolism through its effects on hepatic biotransformation, and the concept of hepatic extraction is important in predicting the effects of metabolic interactions. (Excellent reviews on the pharmacokinetics of drug interactions by G. Levy and J.R. Gillette were also included in the 1976 publication of the New York Academy of Sciences and can be referred to for additional information on that topic.)

The importance of dietary factors which can alter drug response by changing several pharmacokinetic factors was reviewed by Dr. Vesell. Large individual variations, from three to elevenfold, can be observed in different subjects even when the same dose of a drug is given by the same route and under the same environmental conditions. Furthermore, food affects the absorption of drugs by enhancing gastric blood flow and retarding gastric emptying. In this monograph, Dr. Vesell discusses various approaches to assessment of dietary contributions to the interindivldual variations in drug disposition observed in many clinical studies.

The next two papers, by Dr. Hollister and Drs. Mendelson, Mello, and Lex, illustrate the problem of making positive conclusions about possible interactions of two drugs of abuse such as alcohol and marijuana. In reviewing the interactions of cannabis with other drugs in man, Dr. Hollister reports that only THC. the psychoactive component of marijuana, shows a significant pharmacodynamic interaction in man and animals with alcohol and that the interactive effect tends to be additive. However, the data presented by Drs. Mendelson and Mello regarding the concordant use of marijuana by men and women shows that when alcohol and marijuana are concurrently available, marijuana appears to affect alcohol use more dramatically than alcohol influences marijuana use, and that the consumption of alcohol is reduced during marijuana use even in heavy alcohol drinkers. These data indicate that the simultaneous availability of two recreational psychoactive drugs does not necessarily increase drug use. As THC is known to affect cell membranes, Dr. Hollister also feels that it would be of interest to study interactions between THC and drugs, such as lithium. that alter membrane lipids.

Dr. Reese Jones in his critical review of cocaine Interactions reminded the group that both nicotine and caffeine consumption need

to be taken into account when investigating the effects of cocaine with other drugs. He believes that the most realistic conditions for studying cocaine and other drug interactions are after repeated use of both drugs of interest. Rapidly acquired tolerance and the likelihood of cross tolerance to other drugs complicates any design involving repeated administration of a drug in drug interaction studies. In a repeated dose paradigm lasting more than a few days, new signs and symptoms appear which are different from those observed after acute or early drug effects. The mechanisms of these long-term interactions are complex and difficult to delineate.

The chapter by Drs. Mello and Mendelson further demonstrates the complexity of interaction studles. In studying the effect of cigarette smoking on alcohol, opiates (heroin and buprenorphine), and marijuana use, they confirm that a number of drugs from diverse pharmacological classes influence tobacco smoking. Alcohol and opiates increase cigarette smoking, whereas marijuana has no apparent effect on tobacco use. Opiate antagonists like naltrexone do not appear to alter cigarette smoking significantly. They suggest that polydrug use may have less to do with the pharmacological properties of the drugs or their anticipated effects than with their capacity to produce some change in subjective states. Change may be the goal of the polydrug user, as it appears that any drug or drug combination that has definitive stimulus properties and behavioral effects for the user may have abuse potential.

Dr. Kornetsky reports the results of a series of experiments on the effects of various drug combinations on the threshold for brain-stimulation reward and brain-stimulation escape (pain). These studies show that combinations of drugs often lead to synergism or potentiation of effects which are manifested not only in the euphoriant action of drugs but also in their analgesic action, as with the enhancement of morphine analgesia by d-amphetamine.

Dr. Kreek in her extensive review of the interactions of methadone with various drugs in humans shows that combined treatment of a methadone-maintained patient with a second drug, such as rifampin or phenytoin, can produce severe withdrawal symptoms due to pharmacoklnetic interactions. In developing a strategy to identify, define, and elucidate the mechanisms of interactions between drugs of abuse or those used in treatment, Dr. Kreek concludes that the most urgently needed studies are those which can be carried out in humans to document pilot data obtained in in vitro or preclinical studies.

In the final analysis, however, the question is: What do we want to learn from interaction studies? Are we interested in understanding the cellular effects of drug interactions to develop better treatment interventions or are we interested in the pathophyslology of multiple concurrent drug use, independent of developing therapeutic interventions? On the other hand, are we interested in being able adequately to describe the phenomena as markers for the effectiveness of interventions (primary, secondary, and tertiary)?

In summary, the review participants were very enthusiastic about continuing research in the drug interactions area. They felt, however, that this field needs to be encouraged by NIDA and that the supportive group of clinical and preclinical research scientists already involved in this type of research needs to be nurtured and its ranks enlarged.

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Critical Factors in Studying Drug Interactions

Martin W. Adler, Ph.D.

INTRODUCTION

This technical review met to develop etrategies that can be used to study interactions involving drugs of abuse. The need for information on this subject is obvious, both from a therapeutic and a toxicological viewpoint. If we look at the list of pharmacological agents that we consider under the heading of drugs of abuse, we see a variety of drugs and drug classes, including the opioids, cannabinoids, alcohol, cocaine, amphetamine, PCP, hallucinogens, barbiturates, anxiolytics, and nicotine. Many of these agents have important therapeutic uses, while others are of interest primarily because of their nomedical use. While there is a paucity of information about the interactions of these substances with all sorts of other drugs, perhaps the greatest deficiency in knowledge lies in interactions among the various drugs of abuse. When there drugs are used therapeutically, interactions can lead to either a desired increase in efficacy or to adverse effects. When used nonmedically, they can interact to alter the euphoric or dysphoric effects. If one thinks in terms of basic pharmacological principles, it is often possible to predict what will occur if two or more drugs are administered concurrently or, at least, to understand unexpected consequences of drug combinations. With that in mind, I will review some of the factors that should be considered.

GENERAL CONSIDERATIONS

In general, one drug may be synergistic with (additive or potentiated) or antagonistic to another drug by acting at the same receptors, by acting at different receptors or systems, by interacting chemically or physically, or by altering pharmacokinetics. A word of caution should be given at this point, however. Just because an interaction occurs, one rhould not necessarily conclude that the interaction is meaningful either in terms of clinical efficacy or toxicological consequencer; that determination is dependent on a variety of considerations, such as the degree of interaction, the therapeutic ratio, the shape of the dose-response curve, and the general status of the subject.

A natural way to proceed in this discussion might be to dissect and explore in detail the pharmacokinetic and pharmacodynamic factors which are vital elements in evaluating and predicting drug interactions. For example, a consideration of drug absorption, distribution, metabolism, and excretion is important. Good discussions of these pharmacokinetic factors may not only be found in any authoritative text in pharmacology, but also in three excellent papers presented at the New York Academy of Sciences symposium entitled "Interactions of Drugs of Abuse" (Reidenberg 1976; Levy 1976; Gillette 1976). Although this chapter will address these and other basic considerations, they will be used in a somewhat different way in order to focus attention on those aspects that may be moat important in terms of preclinical and clinical studies with the drugs of abuse.

CRITICAL FACTORS

Table 1 summarises some of the factors which should be taken into account when conducting drug interaction studies.

TABLE 1
Critical Factors in Drug Interactions

1. Ability of a Drug to Reach its Site of Action
2. Time Course of Drug Effects
3. Full Dose-Response Curves
4. Circadian and Seasonal Variations
5. Environment
6. Sex and Age
7. Choice of Endpoint
8. Route of Drug Administration
9. Choice of Vehicle and Proper Controls
10. Tolerance and Cross-tolerance
11. Effects on Neurotransmitter Systems
12. Appropriate Statistical Analysis

Reaching the Site of Action

The ability of the drugs to reach their sites of action is a vital concern in interpreting the interaction or lack of interaction Of drugs. Figure 1 diagrams the pharmacokinetics of a drug in relation to its rite of action. Anything that might affect the absorption of a drug, its binding to plasma proteins, its metabolism, or its penetration into the central nervous system could affect the final result and assessment.

Time Course

Due consideration must be given to the time course of the effects of the drugs in terms of onset of action, time of peak effect, and duration of action. The investigator must make aure that the pharmacological effects of the drugs are being evaluated at a time when both drugs are exerting their maximal effects, Looking at interactions when one drug is just beginning to exert its effects and the other drug's effects are on the wane can result in meaningless conclusions.

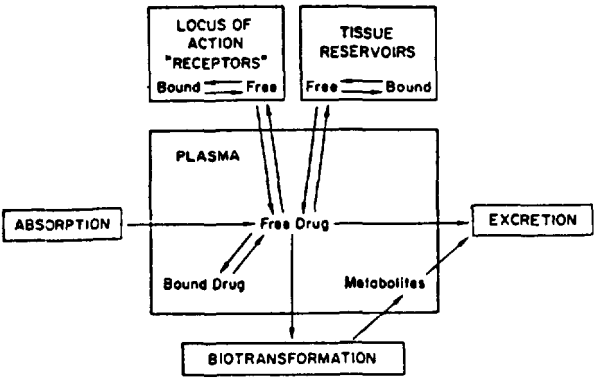

FIGURE 1

Schematic Representation of the Interrelationship of the Absorption, Distribution, Binding, Biotransformation, and Excretion of a Drug and its Concentration at its Locus of Action. Possible distribution and binding of metabolites are not depicted.

From Mayer, S.E.; Melmon, K.L.; and Gilman, A.G. Introduction: The dynamics of drug absorption, distribution and elimination. In: Gilman et al. 1980. Copyright 1980, Macmillan Publishing Co.

Dose-Response Relationship

The necessity of utilizing full dose-response curves when evaluating drug interactions is too often ignored. Conclusions are sometimes reached on the basis of experiments using only one or two doses of the drugs involved. Not only can such experiments yield false negatives in terms of drug interactions, but they also fail to provide the quantitative data needed for a full evaluation of a positive effect. As an example, one can take the question of whether there is an interaction between the opioid drugs and the barbiturates, using analgesia (or antinociception) as the endpoint. Various reports in the literature concluded that there was synergism (Barlow and Duncan 1933; Keats and Beecher 1950; Lesher and Spratto 1978; Smith et al. 1943), l antagonism (Clutton-Brock 1961; Dundee 1960; Neal 1965; Shapero and Wilson 1964), or no interaction (Hart and Weaver 1948) between the drugs in terms of analgesia. The studies differed from each other in terms of the particular drugs used, the doses, the species, the dose range tented, and the number of times the drugs were administered. We decided to investigate the problem by using the rat, one test of antinociception (tail-pressure), a full dose range of morphine, a full subanesthetic dose range of pentobarbital, and by giving the drugs at the time of peak effect. One study was done in animals that were drug naive and another in rats tolerant to morphine. Although we raw an isolated instance of decreased analgesia in one dose pair, the results were clear--subanesthetic doses of Na pentobarbital had neither antinociceptive nor hyperalgesic properties, and the barbiturate had no effect on the antinociceptive

action of morphine in either morphine-tolerant or nontolerant rats (Geller et al. 1979). Bad we chosen only one dose combination, we might have concluded otherwise.

Circadian and Seasonal Effects

The influence of circadian and seasonal variations on the effects of one or both drugs must be assessed. Some drugs may have markedly different quantitative actions depending on the time of day the drug is administered. For instance, there is a diurnal rhythm in responsiveness of mice to the hyperalgesic activity of naloxone (Frederickson et al. 1977) and in lorazepam-induced neurologic deficits (Henauer et al. 1984). A study by Morris (1980) in mice and rats is intriguing. He found that several drugs (e.g., cocaine, PCP, and morphine), when combined with alcohol, markedly increased lethality depending not only on time of day, but also on the phase of the moon. The circadian variations in drug effect are thus important to consider in evaluating drug interactions. Likewise, seasonal variations in response to drugs have long been known in animals and are likely to occur in human subjects as well. As an extreme example, I can cite recent studies demonstrating that dependence to morphine could not be produced in hibernating animals (Beckman et al. 19811.

Environment

The environment of the subject can play an important role in the response to drugs. Thus, housing has been found to be one of the determinants of the lethal dose of amphetamine; low humidity may lead to infections and the consequent general debilitation may modulate drug effects; high humidity can add to stress-induced effects of high temperatures; lighting can alter circadian rhythms; and ambient temperature can affect a variety of measures such as the changes in body temperature produced by morphine in rodents. Alterations in any of these environmental conditions could thus markedly modify the results seen with interactions of drugs of abuse.

Sex and Age

Sex and age of the subject are important considerations in looking at interactions. One must be aware that a drug can have markedly different effects depending on the sex of the subject. For example, the toxicity of drugs such as cocaine seems to be determined, in part, by the sex of the subject (Thompson et al. 19841. Based on studies which reveal a differential sensitivity of leutinizing hormone to naloxone and morphine in males and females at different points in development, it has been recently postulated (Cicero et al., in press) that opioids may be responsible for the regulation of endocrine profiles. As for age, we are becoming increasingly aware that the response of older individuals to drugs, especially those affecting the CNS, is markedly different from that seen in younger adults because of a combination of pharmacokinetic and pharmacodynamic factors. We

have long known that subjects with immature nervous systems respond differently to centrally acting drugs than do mature subjects. Yet, these factors are too often ignored, especially in studies with mice and rats.

Endpoint

Choice of the endpoint to be rtudied is extremely important. Drugs usually have multiple effects mediated through a variety of different receptors and systems. Drug interactions may thus be seen for some effects but not others.

Route of Administration

Route of drug adminstration is important in determining if interactions occur. Not only does the route of administration affect the amount of drug reaching its site of action and thus influence the quantitative effect, but the route may alter the qualitative effect. For example, studies in rats in our laboratory have demonstrated that meperidine increases brain excitability vhen administered subcutaneously (s,c.) but decreases excitability when given intracerebroventricularly (i.c.v.) (Tortella et al. 1984). Table 2 compares effects on flurothyl seizure thresholds and the action of naloxone on these responses for several opioids given by the two routes. Similarly, body temperature studies reveal that high doses of morphine s.c. produce hypothermia, but these doses administered i.c.v. produce only hyperthermia (Adler et al. 1985b). Whether the differences are due to the temporal sequence in which the drugs reach the receptors or to some other mechanism in not yet known. In any case, interactions may occur between drugs given by one route but not by another.

TABLE 2

Influence of Route of Administration on Opioid-Induced Changes in Flurothyl Seizure Threshold in Rats

DRUG	ROUTE OF AMINISTRATION	CHANGE IN SEIZURE THRESHOLD	EFFECT WITH NALOXONE
Morphine	SC	↑	Blocked
	ICV	↑	Blocked
Meperidine	SC	↓	Potentiated
	ICV	↑	Blocked
Pentaxocine	SC	↓	Potentiated
	ICV	↑	Unchanged
Normeperidine	SC	↓	Unchanged
	ICV	↓	Potentiated

Vehicle and Controls

Choice of vehicle and proper controls for the possibility of interactions between the vehicles and the drugs is often overlooked or given scant attention. Many chemicals used as vehicles have effects by themselves and the possibility exists that, when given together, those compounds can synergize with or antagonize the actions of the drug or drugs being tested. As an example, one can refer to studies involving delta-9-THC. This agent is usually administered either in alcohol, emulphor, Tween 80, pluronic, or some combination of the above. All of these agents have effects on the CNS. What started out as a straightforward experiment in our laboratory to determine the effects of THC on the pupil in the rat became a major effort when we discovered that accompanying the change in pupil size with THC was an increase in pupillary oscillations. The vehicles themselves also caused some oscillation, although less than that seen with the vehicle-THC combination (Adler et al. 1985a). In attempting to determine whether there is an interaction between opioids and THC on the pupil, we face a problem because opioids also produce very profound pupillary fluctuations in the rat. In fact, the degree of fluctuation is one means we use in postulating whether an effect is exerted at a mu, kappa, or sigma receptor (Robin et al. 1985).

Tolerance and Cross-Tolerance

Tolerance to a drug as well as cross-tolerance to other drugs may develop. The tolerance may be due to pharmscokinetic or to pharmacodynamic factors and may occur as the result of the administration of a single drug or the previous or concurrent administration of other drugs. There may be tolerance to some of the effects of a drug and not to other effects, and there may be reverse tolerance (increased responsiveness to an action of a drug). A good example is seen with amphetamine vhere tolerance occurs to effects such as the hyperthermic and the anorexic actions (Gilman et al. 1980), while an increased sensitivity to some stereotypic behaviors (Segal et al. 1980) can develop. Repeated administration of cocaine leads to an increase in sensitivity to its lethal effects. Such factors are of obvious significance in evaluating the drug interactions that may occur.

Effects on Neurotransmitters

Effects on a neurotransmitter system by one drug may affect the actions of another drug. Thus, a drug affecting the adrenergic system by altering levels of norepinephrine or by acting at postsynaptic receptors can markedly modify the actions of drugs of abuse, such as cocaine or amphetamine.

Statistical Analysis

Finally, correct statistical analysis of the data is not an easy problem. This is especially true if one is trying to determine

if an interaction between drugs is an additive effect, an effect that is something less than additive, or an effect that is greater than additive, a true potentiation. There are several ways that this problem can be approached and Dr. Mitchell addresses this topic elsewhere in this volume.

CONCLUDING REMARKS

If future studies adhere to the criteria set forth above, I believe that we will obtain reproducible and meaningful information about interactions among drugs of abuse. To conduct such studies properly is admittedly tedious, time-consuming, and expensive. Of course, not all studies can control all of the factors I have discussed. This is especially true of clinical studies with all their inherent difficulties. In such situations, however, it would be useful if the investigators at least took these factors into consideration when drawing conclusions. Pointing out potential pitfalls in interpretation vould be most helpful to other researchers in the field and would aid in resolving differences between studies and in determining the significance of the drug interactions.

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Issues in the Assessment of Multiple Drug Use Among Drug Treatment Clients

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Use of such drugs as marijuana, cocaine, and heroin continues to be a significant problem, crosscutting health, legal, and behavioral domains. The use of multiple drugs of abuse, especially marijuana and cocaine in combination with alcohol, appears to be increasing in some segments of the population. Among persons entering treatment, patterns of use are becoming more complex.

More effective approaches to prevention, intervention, and treatment may be developed and implemented with a better understanding of multiple drug abuse patterns. Increased understanding of use patterns of "street pharmacologists" could suggest hypotheses for pharmacological studies in the laboratory. In addition, epidemiological studies can demonstrate the generalizability of laboratory findings.

Drug abuse treatment clients are the extreme in the continuum of the drug-using population. Information on their muliple use patterns may be useful and important. The Treatment Outcome Prospective Study (TOPS) obtained detailed drug use histories of 11,750 clients entering 41 detoxification, methadone, residential, and outpatient drug-free treatment programs in 10 cities from 1979-81 (Hubbard et al. 1984). A sample of 5,000 of these clients was followed up 1 to 3 years after treatment.

The purpose of this chapter is, first, to describe the multiple use patterns of treatment population; second, to outline factors that need to be considered in epidemiological studies of multiple drug use; and, finally, to suggest some strategies for a comprehensive and integrated approach to the study of multiple drug use.

A COMPREHENSIVE ASSESSMENT OF DRUG USE

The complexity of current drug use patterns requires a thorough assessment of use of alcohol and a variety of types of licit and illicit drugs. The information needed for assessment includes specific data on medical and nonmedical use of different types of

drugs as well as specific drugs. The history of use for the major types of drugs should include the initiation of use, current use, and the termination of use. Frequency, quantity, route, and concurrent use of other drugs provide data critical for assessment of multiple use pattern.

Assessment of Drugs Used in TOPS

Clients were asked to provide information about their backgrounds, alcohol and drug use treatment, mental health, criminal behavior, and employment in personal interviews conducted when they applied for admission to a TOPS program. The data used to develop drug use measures in TOPS are from the comprehensive assessments of nonmedical drug use obtained in the interviews. Clients were told, "In this section we would like to ask about your nonmedical use of drugs--without a doctor's prescription or not according to directions." Clients were then asked, "Have you ever used [drug type]?" for each of the types of drugs listed below.

1. Marijuana, hashish, THC
2. Inhalants-such as glue, gasoline, paint thinner
3. Hallucinogens or psychedelics-such as LSD, DMT, mescaline, PCP
4. Cocaine
5. Heroin
6 Street or illegal methadone
7. Other narcotics or opiates-such as opium, morphine, codeine, Demerol, Dilaudid, Talwin
8. Minor tranquilizers-such as Librium, Valium, Miltown, Equanil
9. Major tranquilizers-such as Thorazine, Stelazine, Lithium, Mellaril
10. Barbiturates-such as Nembutal, Seconal, Tuinal
11. Sedatives and hypnotics - such as Doriden, Noludar, Quaalude, Sopor
12. Amphetamines, speed or diet pills - such as Benzedrine, Dexedrine, Preludin
13. Any other drugs (Specify) _____

The drug type and examples of each type were read to the client. Color pictures of tranquilizers, barbiturates, sedatives and amphetamines were shown to the client. If a client reported use of hallucinogens, minor tranquilizers or amphetamines, he or she was asked about use of a specific drug within the general type-PCP, Librium/Valium and Preludin, respectively.

Frequency of use of alcohol and frequency of use of drugs for nonmedical purposes during the 3 months and 12 months before treatment were obtained for all drug types. Clients were asked to report their frequency of use on the following 9-point scale:

0	None
1	Less than 1 time a month
2	1 to 3 times a month
3	1 time a week
4	2 to 3 times a week
5	4 to 6 times a week
6	Daily/1 time a day
7	2 to 3 times each day
8	4 or more times each day

The 12-month period preceding treatment was chosen as the base period for the TOPS analyses because it should allow a more complete assessment of drug use than the 3 months immediately preceding treatment. Although a client's life history of drug use could also be considered, a period of a year prior to treatment should be a more appropriate baseline for examining change during and after treatment. Detailed questions were asked on the initiation of use. The nature of the drug problem and the types of problems associated with use were also addressed.

At months 1, 3, and quarterly thereafter for up to 2 years while the clients remained in treatment, additional indepth assessments of drug use and other behaviors were conducted. These assessments are being continued in the posttreatment period by followup interviews up to 3 years after termination.

Types of Drugs Used by Treatment Clients in TOPS

The need for a comprehensive assessment of drug use is shown in table 1. In the year before treatment, clients in all modalities used a variety of drugs weekly or more often. Weekly use of alcohol and marijuana was quite common. Given the extent of multiple drug use, weekly rather than daily use provides a more appropriate measure for multiple use. The great variety of drugs used suggests that use patterns may be episodic and considerable substitution may occur. Consequently, a focus only on consistent daily use may seriously understate the extent of multiple use and the potential for drug interactions.

TABLE 1

Weekly or More Frequent Drug Use in Year Before Intake: 1979 and 1980 Cohorts

Drug(s)	Outpatient Methadone (n=2660)	Outpatient Drug-Free (n=2014)	Residential (n=1789)
Alcohol	46.8%	62.0%	63.8%
Marijuana	57.3	67.5	65.9
Inhalants	0.4	1.4	2.0
Hallucinogens	1.3	5.6	10.6
(PCP)	0.5	2.6	8.1
Cocaine	27.4	15.6	28.1
Heroin	63.9	10.5	30.2
Methadone	19.8	2.0	5.0
Other narcotics	26.8	15.6	29.2
Minor tranquilizers	25.3	18.1	28.3
(Chlordiazepoxide/Oiazepam)	23.9	16.6	27.4
Major tranquilizers	1.3	1.9	3.9
Barbiturates	6.4	7.9	15.1
Sedatives	5.6	11.2	16.5
Amphetamines	10.2	22.0	28.5
(Phenmetrazine)	5.0	3.6	11.9

In table 2, we see that, even after treatment, many clients continued their use of multiple substances. Marijuana was used weekly by almost half of the former clients. These data on the extensive use of a variety of drugs provide the base from which a description of multiple drug use must be made.

TABLE 2

Clients' Drug Use Weekly or More Often During the First Year After Treatment: Followup Samples of 1979 and 1980 Cohorts

Drug(s)	Outpatient Methadone (n=835)	Residential (n=731)	Outpatient Drug-Free (n=854)
Heroin	21.4%	14.5%	7.5%
Cocaine	18.0	17.5	9.8
Marijuana	47.0	49.1	53.4
Other non-opiates*	21.8	24.8	23.2

*Amphetamines. sedatives, barbiturates, minor tranquilizers

DESCRIPTION OF MULTIPLE USE PATTERNS

Many research efforts have been directed toward assessing multiple drug use, but no widely accepted system has emerged. Numerous factors contribute to this situation: (1) many studies focused on special populations or individual treatment programs and have limited generalizability; (2) many studies have had measurement shortcomings, mainly covering brief periods of use that do not fully reflect the extent of multiple use; (3) the number of possible drug combinations has resulted in varied and complex patterns; (4) only a few drugs have been surveyed in some research, e.g., Client Oriented Data Acquisition Process (CODAP) data; and (5) selection of measures has varied, depending on the purposes of research. In order to adequately assess and compare the results of various studies, some common, comprehensive, and meaningful measures are needed.

Issues in Describing Drug Use

Three key issues are central to the development of descriptions of multiple drug use:

1. Emphasis on description of single drug use (such as heroin) versus multiple drug use involvement;

2 Quantification (interval or ordinal scales) versus classification (categories or patterns) of drug use; and

3. Clinical versus analytic usefulness of the description.

In the following paragraphs, we discuss each issue and its impact on the development of useful descriptions.

Single versus multiple drug use. Many previous studies have focused on the use of a single drug, generally heroin or other narcotics/opiates. Implicit in such studies is the belief that heroin use is the most serious type of drug use and that knowing the level of involvement with heroin or other narcotics/opiates would be adequate for describing drug use involvement. The parsimony of this approach must be weighed against evidence of the prevalence of multiple drug use. Use of heroin and other narcotics/opiates alone may no longer fully describe the intensity of drug use. Many addicts, for example, substitute other drugs when heroin is not available and use many other drugs at various levels of intensity throughout their drug-using careers. Thus, even the most complete data on use of a single drug may not adequately describe the nature and extent of multiple drug use.

Quantification versus classification. Approaches to assessing drug use are, generally, either attempts to quantify the extent of use or to develop classifications of use (i.e., patterns or typologies). The resulting measures and classifications, for the most part, have been developed independently by separate investigators working with different data sets. To date, there has been little effort to compare and contrast these measures or to examine their relative utility for research in different populations of drug users (Clayton and Voss 1981). For quantifiable measures, comparisons of the composite indices that are based on a linear combination methodology would be particularly useful to demonstrate the utility and/or interchangeability of these measures. A quantifiable measure of multiple drug use also has advantages for empirical analysis using parametric statistics. Of course, it should be evident that, despite the advantages of the composite indices, they also have limitations. They provide a univariate summary of drug involvement, for example, but do not permit the specification of which drugs or drug combinations are involved. Since drug combinations are of considerable interest in understanding multiple drug use, it is useful to be able to identify which drugs contributed to the index score.

Classification of drug use by patterns and typologies has focused, respectively, on frequency of use of selected drugs and on the specification of comprehensive typologies of drug use. As with the quantifiable measures, few comparisons have been made across samples to test for the stability and generalizability of patterns and typologies. Furthermore, the utility of clustering approaches has not been adequately demonstrated on large samples and complex use patterns. Clustering algorithms which are designed to detect stable patterns and typologies within data sets may not produce robust or stable solutions among clients with complex multiple drug use patterns. Additional work is needed on large samples that assess the full domain of drug use.

Clinical versus analysis use. The purpose for which a measure will be used must be considered in its development. Two major purposes of most drug abuse measures are: (1) to help make judgments about treatment, and (2) to provide a useful analytic tool. Ideally, a measure would serve both purposes. However, the method of developing measures often emphasizes one purpose over the other.

Approaches emphasizing clinical applications would more likely focus on comprehensive use patterns or the use of particular combinations of drugs. Such measures or patterns of use may not be easily included in statistical analysis. Except for extreme use patterns (such as heavy heroin and other drug use or solely marijuana use), it may be difficult to scale or order these categories for parametric analysis.

The analytic method often relies on statistical techniques to structure the data. While such methods provide data in a form that may be very useful for statistical analysis, the data may not be readily interpretable by clinicians or program managers. In addition, the analytic methods may be susceptible to small statistical variations in the data that would not reflect clinically useful differences.

Measures of Single Drug Use

Measures that tap use of single drugs generally consist of the percentages of persons who use particular drugs within a given time frame (e.g., a week, a day) or examine use of the principal problem drug. Such measures are useful when the focus is on use of a particular drug (e.g., heroin) or when the primary drug problem dictates the treatment strategy to be followed. Such single use measures were predominant a decade and more ago when intensive use of single drugs was the modal pattern among clients.

Primary drug of abuse was a major category of analysis in the COOAP system. Tyler and Sheridan (1980) examined the relationship of various demographic characteristics and primary use of such drugs as heroin, amphetamines, cocaine, or marijuana for 162,062 CODAP clients. They observed an interesting relationship between age at first use and primary drug used: clients who began use at age 15 or younger showed most frequent use of marijuana (45%) followed by heroin, amphetamines, and cocaine; clients who began use at age 16 and older showed heroin as the primary drug most often (69%) followed by marijuana, amphetamines, and cocaine. Blacks were found to abuse heroin more than whites or Hispanics. Such data potentially have important implications for the targeting and focus of prevention and intervention strategies.

The usefulness of primary drug as an outcome measure seems apparent, though the exact nature of its usefulness is unknown. The ability and willingness of clients to substitute other drugs in whole or in part for the primary drug of abuse would greatly diminish the usefulness of this measure. To better understand the utility of primary drug as a measure, results from analyses using only primary drug data and analyses using more Complete drug use information should be compared.

Indices of Multiple Drug Use

Greater attention has been given recently to the development of indices that capture multiple drug use. The approaches that have been developed can be conveniently classified as procedures that use scaling techniques or procedures that use some form of linear combination of variables.

Scaling approaches. The attempts to use scaling for indexing drug involvement have typically relied on Guttman scaling procedures (scalogram analysis) to form a unidimensional construct (Guttman 1950). For drug use, such a scale assumes that different drug types are nearly always used in a hierarchical progression, such as alcohol to marijuana to heroin. Successful scaling indicates that users of any particular drug type are also users of drug types preceding it in the ordering sequence. For example, users of heroin in an ordering of alcohol, marijuana, and heroin could be assumed to also use marijuana and alcohol.

Most of the studies that have successfully used Guttman scaling procedures have focused on student and young adult populations. Although they were unable to scale use patterns for their total sample, Loiselle and Whitehead (1971) were successful in scaling adolescent drug use patterns for the subset of subjects that had smoked marijuana. The resulting four-item scale consisted of stimulants, tranquilizers, hallucinogens, and opiates. Single and coworkers (1974), analyzing survey data from 8,206 high school students in New York State, found Guttman scaling useful in describing drug use patterns in a series of analyses. The best scale (based on a reproducibility coefficient of .98 and scalability coefficient of .82) consisted of seven categories: no drugs, any legal drug, cannabis, "pills," psychedelics, cocaine, and heroin. Donovan and Jessor (1983) found problem drinking to be a key stage after marijuana use in a Guttman analysis of a national sample of high school students.

Other investigators have found Guttman scaling procedures useful for identifying sequences and stages of drug use among high school students (Gould et al. 1977; Kandel 1975; Kandel and Faust 1975; Kessler et al. 1976).

Linear combination approaches. The other tack followed in developing measures of multiple drug use has been to use some variant of linear combinations. Two general approaches have been followed: (1) a multivariate procedure, such as factor analysis or principal components analysis (e.g., Kessler et al. 1976); or (2) a specially constructed index based on conceptually or empirically derived weights for drugs used by an individual. Most efforts in this domain have followed the latter approach (Clayton and Voss 1981: Douglass and Khavari 1978; Lu 1974; Phin 1978) and are similar in that they have used a composite index of weighted elements (drugs). These measures are distinct, however, in the weighting scheme that is applied to the drugs to reflect the risk or seriousness associated with the use of that drug.

Comparisons of multiple use indices. Five indices of multiple drug use have been considered in TOPS: the Lu Index, the Douglass/Khavari Index, the Number of Drugs Index, the Severity Index, and the Illicit Drug Use Index. These indices share a

linear combination methodology in their construction. They all attempt to derive a single number that represents the extent of user involvement with the entire array of drugs being considered. In general, the methodology multiplies the frequency of use scores by the weights assigned to each drug and then combines these products either by summing or averaging across the set of drugs to obtain a final index value.

The principal difference among the indices is the procedure used to obtain the weights associated with the drugs. The Number of Drugs Index uses equal (unit) weights for each drug; the Lu Index uses an empirical derivation based on frequency of use of each drug in the population; the Douglass/Khavari Index uses a standardization procedure; the Severity Index uses conceptually based weights; and the Illicit Drug Use Index uses weights derived from national data sets.[1]

The similarity in construction of the various indices suggests that there may be considerable overlap among the measures themselves. To address this question more directly, the intercorrelations of the indices were computed along with the correlations of selected drugs and are presented in table 3. As shown, the Number of Drugs Index, the Lu Index, the Douglass/Khavari Index, and the Severity Index are all highly related. For these four indices the correlations range from .80 to .93, with an average correlation of .89. Thus, it appears that the various weighting schemes used to construct these indices have very little effect on the final index. These four indices provide reasonably comparable estimates of multiple drug use. Relationships are considerably lower, however, between these four indices and the Illicit Drug Use Index which appears to be a better indicator of heroin use than a total involvement index.

Table 3 also shows correlations between the five drug use indices; the primary drug of abuse; the number of drug problems; and the alcohol, marijuana, heroin, and barbiturate use during the year prior to treatment. As already noted, heroin use is strongly related to the Illicit Drug Use Index. For the other indices, barbiturate use shows the highest relationship. Perhaps barbiturates are a marker, in that clients who use barbiturates tend also to use several other drugs, whereas those who do not use barbiturates tend to use only a few drugs.

In selecting among indices, the three most important criteria are construct validity, parsimony or simplicity, and conceptual appeal. Examination of the five multiple use indices with respect to these criteria in TOPS led to the conclusion that the Severity Index is the preferred multiple use index in the drug treatment population.

TABLE 3

Correlations of Multiple Drug Use Indices and Selected Other Drug Use Measures: 1979 Cohort

Selected Drug Use Measure	Multiple Drug Use Index				
	Number of Drugs	Lu	Douglass/ Khavari	Severity	Illicit Drug Use
Number of Drugs Index	1.00				
Lu Index	.80	1.00			
Douglass/Khavari Index	.88	.91	1.00		
Severity Index	.89	.93	.93	1.00	
Illicit Drug Use Index	.48	.42	.45	.59	1.00
Primary Drug Frequency	.39	.35	.39	.43	.55
Number of Drug Problems	.32	.35	.36	.36	.19
Alcohol Frequency	.37	.21	.17	.23	-.02
Marijuana Frequency	.46	.52	.44	.38	. 10
Heroin Frequency	.34	.26	.24	.43	.90
Barbiturate Frequency	.50	.56	.62	.53	.08

DRUG USE PATTERNS AND USER TYPES

Several approaches were used in TOPS analyses to examine drug use patterns and user types based on use in the year prior to treatment: primary drug of abuse, Guttman scaling, pattern frequency counting, development of general drug use patterns, and cluster analysis.

For the primary drug index, a frequency analysis was first conducted to determine the pattern of drug use accompanying use of a specified primary drug. Use of eight drug types (heroin/illegal methadone, other narcotics, barbiturates/sedatives, cocaine, amphetamines, minor tranquilizers, marijuana, alcohol) was examined for clients who reported each of the primary drug groupings (heroin/illegal methadone, other narcotics, cocaine, barbiturates/sedatives/minor tranquilizers, amphetamines, alcohol/marijuana). Discriminant analyses using these patterns misclassified 32% of the clients, thus showing this approach to be insufficient.

Guttman scaling analysis, which provides information to determine if clients use drugs in a particular cumulative sequence, was also explored. If the drugs are able to be scaled, the analysis indicates hierarchy of use, and specifies the set of drugs expected to be used by a client who appears at any point in the scale. Weekly or greater use of eight drug classes reported by TOPS clients was examined: heroin, other narcotics, barbiturates/ sedatives, cocaine, amphetamines, minor tranquilizers, alcohol and marijuana. The results of the analysis showed that clients use of these drug classes did not meet requirements for Guttman scaling. The coefficient of scalability (which ranges from 0 to 1) was only .22, far below the minimum acceptable level of .60.

For pattern frequency counts, TOPS drug use data were first recoded and compared to 28 patterns used in the Drug Abuse Reporting Program (DARP) (Simpson 1974, 1976). Eight of the major drug classes were considered (heroin, other narcotics/ opiates,[2] barbiturates, cocaine, amphetamines, hallucinogens, marijuana, and other drugs) for four categories of use (no use, less than weekly use, weekly use, daily use). Results showed that the DARP patterns did not adequately describe the drug use of the TOPS clients. The major difference was greater multiple drug use in TOPS. Twenty-eight percent of DARP clients were heroin only users as compared with 3% of TOPS clients. In contrast, 5% of DARP clients fit the "poly" pattern (i.e., used heroin and other narcotics [opiates] less than weekly and three or more nonnarcotics at any level) as compared with 19% of TOPS clients. Similarly, 8% of OARP clients as compared with 14% of TOPS clients were classified in the pattern "opiates plus" (any use of heroin or other opiates along with any use of one or two nonopiates).

A second approach was to examine a set of 25 drug use patterns adapted from the DARP classification scheme. These 25 patterns were based on the eight frequently used drug classes: heroin, other narcotics, barbiturates (including sedatives/hypnotics), cocaine, amphetamines, minor tranquilizers, marijuana, and alcohol. This drug set was examined using the 4-point use scale noted above. Results showed that two-thirds of the clients from both the 1979 and 1980 cohorts fell into three complex multiple use patterns. However, these patterns were viewed as unsatisfactory because the classification rules (1) grouped clients together who had wide variability in amount and kind of drug use, and (2) defined some patterns which did not appear discriminably different from others.

Close examination of frequencies of the specific combinations of use of the eight drug types revealed a complex picture. For example, over 740 unique patterns were reported by the 3,389 clients of the 1979 cohort. This suggested that broad, rather than specific, patterns may be required to describe drug use. Thus, an alternate approach to using the eight drugs and the

4-point use scale focused on a more limited set of clinically useful patterns. Patterns were defined by hierarchical rules that emphasized weekly or greater use of key drugs or drug types. The conceptually based rules produced seven patterns, which appear in table 4 along with their respective percentages of clients from the 1979 and 1980 cohorts. It should be noted that the greatest number of clients fell in the heroin class and that the majority of clients (58%, 1979; 55%, 1980) fell in the first three classes which describe heavy narcotics users.

The defining characteristics of the patterns do not describe all drugs used by the clients. Rather, they indicate the key drugs and the use levels of these particular drugs. Additional illustration of the use of different types of drugs within the seven patterns is provided in table 5.

It should be noted that a sizeable proportion of clients entering treatment, including methadone treatment, were not active heroin users in the year prior to their admission to the TOPS program. We identified an eighth pattern of those who used heroin daily at some time in their lives. Depending on the purposes of a study, it might be advisable to separate these Former Daily Users from individuals in the other pattern.

The last approach employed cluster analysis to identify some general types of drug use clients. Several alternative clusterings were conducted and assessed according to their reproducibility and face validity. The best cluster solution based on these criteria identified three major types of drug abuse clients. The first type, comprising 37% of the TOPS clients, was viewed as traditional heroin users. The use pattern of this group involved daily use of heroin coupled with periodic use of cocaine, marijuana, and alcohol. The second type, comprising 23% of the clients, was described as heavy multiple users, characterized by weekly or more frequent use of the eight drugs. Finally, the third type, which made up 40% of the sample, was characterized by low average frequency of use of all drugs except alcohol and marijuana Multivariate analysis of variance and discriminant analysis results confirmed that the clients in these three clusters were reliably different from one another in terms of their drug use.

These analyses, however, did not provide discrimination among the user types that would be very useful for clinicians or researchers. Thus, for descriptive purposes, the seven drug-use patterns described above seem to be the most useful approach.

TABLE 4

Distribution of Seven Patterns: 2979, 2980, and 1982 Cohorts

Drug Use Patterns	Defining Characieristics of Groups[a]	Cohort Prevalence 1979 (n=3389)	1980 (n=3908)	1981 (n=3729)
Heroin/other-narcotics	Weekly or greater use of heroin or illegal methadone and other narcotics	11.2%	10.3%	15.4%
Heroin	Weekly or greater use of heroin or illegal methadone and no use of other narcotics as often as weekly	37.1	33.0	34.0
Other narcotics[b]	Weekly or greater use of other narcotics but less than weekly use of heroin/methadone	9.7	12.1	11.6
Multiple non-narcotics[c]	Weekly or greater use of at least two nonnarcotics in addition to marijuana and alcohol use	6.0	6.7	7.4
Single non-narcotic[c]	Weekly or greater use of one nonnarcotic in addition to marijuana and alcohol use	10.4	13.5	11.9
Alcohol/Marijuana	Weekly or greater use of alcohol and/or marijuana. No other drug used as often as weekly	19.5	17.7	14.2
Minimal (residual)	All remaining clients	6.1	6.7	5.5
		100.0%	100.0%	100.0%

Note: Patterns were defined hierarchically in their tabled order. Thus, for example, a client appears in a pattern 5 in the table only if he did not qualify for any of the preceding patterns (1 to 4).

[a]Defining characteristics do not describe all drugs used by these clients. Rather, they indicate the key drugs and use levels for classification.

[b] Other narcotics are defined as opioids other than heroin and methadone. Included in this category are codeine, propoxyphene (Darvon), meperidine, hydromorphone, morphine, opium, paregoric, oxycodone (Percodan), and pentazocine.

[c]The nonnarcotics included in constructing these patterns were barbiturates/sedatives/hypnotics, cocaine, amphetamines, and minor tranquilizers.

TABLE 5

Use of Selected Drugs within Drug Pattern: 1979, 1980, and 1981 Cohorts

Drug Type	Use During 12 Months Before Intake			
	No Use	Monthly	Weekly	Daily
Heroin/Other-Narcotics (n=1379)				
Heroin	2.1%	2.6%	29.0%	66.3%
Other narcotics	0.0	0.0	40.0	60.0
Barbiturates/sedatives	49.8	27.0	14.3	8.9
Cocaine	26.3	40.1	20.3	13.3
Amphetamines	52.2	20.9	12.2	14.7
Minor tranquilizers	28.7	26.0	23.9	21.4
Marijuana	15.8	21.1	25.2	37.9
Alcohol	16.0	27.9	29.7	26.4
Heroin (n=3854)				
Heroin	3.8	2.7	20.9	72.6
Other narcotics	80.5	19.5	0.0	0.0
Barbiturates/sedatives	81.8	11.7	4.4	2.1
Cocaine	29.2	29.3	21.1	20.4
Amphetamines	84.3	9.4	3.4	2.9
Minor tranquilizers	59.9	22.5	11.4	6.2
Marijuana	22.1	20.9	27.9	29.0
Alcohol	23.1	22.8	30.1	23.9
Other Narcotics (n=1259)				
	66.4	33.6	0.0	0.0
Other narcotics	0.0	0.0	40.0	60.0
Barbiturates/sedatives	46.5	25.6	15.7	12.1
Cocaine	42.5	39.8	11.1	6.5
Amphetamines	45.9	20.6	16.4	17.1
Minor tranquilizers	32.3	26.5	24.5	16.7
Marijuana	17.1	19.5	23.7	39.7
Alcohol	14.7	26.8	32.5	26.0
Multiple Nonnarcotics (n=750)				
Heroin	78.9	21.1	0.0	0.0
Other narcotics	54.6	45.4	0.0	0.0
Barbiturates/sedatives	18.1	16.1	42.8	22.9
Cocaine	18.1	29.2	36.4	16.3
Amphetamines	20.3	17.1	34.7	27.8
Minor tranquilizers	19.9	23.1	35.5	21.5
Marijuana	7.5	12.2	26.5	53.8
Alcohol	6.3	21.4	36.7	35.6

(Continued)

Table 5 (Continued)

Drug Type	Use During 12 Months Before Intake			
	No Use	Monthly	Weekly	Daily
Single Nonnarcotic (n=1334)				
Heroin	83.1	16.9	0.0	0.0
Other narcotics	73.8	26.2	0.0	0.0
Barbiturates/sedatives	52.9	27.6	12.2	7.3
Cocaine	33.9	41.0	18.0	7.1
Amphetamines	43.5	20.4	20.9	15.3
Minor tranquilizers	49.4	30.4	11.0	9.2
Marijuana	13.7	17.9	30.1	38.3
Alcohol	11.9	24.4	38.7	25.1
Alcohol/Marijuana (n=1901)				
Heroin	85.0	15.0	0.0	0.0
Other narcotics	81.2	18.8	0.0	0.0
Barbiturates/sedatives	74.5	25.5	0.0	0.0
Cocaine	58.4	41.6	0.0	0.0
Amphetamines	68.3	31.7	0.0	0.0
Minor tranquilizers	72.6	27.4	0.0	0.0
Marijuana	10.8	13.7	39.4	36.1
Alcohol	8.2	21.1	46.4	24.3
Minimal (n=675)				
Heroin	85.7	14.3	0.0	0.0
Other narcotics	91.6	8.4	0.0	0.0
Barbiturates/sedatives	89.6	10.4	0.0	0.0
Cocaine	81.4	18.6	0.0	0.0
Amphetamines	92.2	7.8	0.0	0.0
Minor tranquilizers	86.2	13.8	0.0	0.0
Marijuana	58.0	42.0	0.0	0.0
Alcohol	46.4	53.6	0.0	0.0
Former Heroin Users (n=2176)*				
Heroin	60.4	39.6	0.0	0.0
Other narcotics	56.9	15.9	9.2	18.0
Barbiturates/sedatives	71.0	17.7	6.3	4.9
Cocaine	49.2	34.6	10.9	5.3
Amphetamines	70.0	15.9	6.8	7.2
Minor tranquilizers	54.5	23.5	12.7	9.3
Marijuana	23.2	22.9	26.6	27.3
Alcohol	22.1	27.9	27.4	22.6

Note: Rows sum to 100%.

*The Former Heroin Users pattern is a supplementary classification which includes individuals from five of the seven patterns.

DYNAMIC NATURE OF MULTIPLE USE PATTERNS

The patterns of multiple drug use are dynamic. In TOPS, the focus was on the pattern in a 1-year period. Over an individual's life, however, a number of patterns may be experienced. Three sets of results demonstrate the dynamic nature of drug use patterns.

A Decade of Changing Patterns

As previously noted, the drug use patterns of OARP clients entering treatment in 1969-73 were markedly different from those for TOPS clients entering treatment in 1979-81. As shown in table 6, the TOPS clients were much less likely than DARP clients to use only opioids on a daily basis regardless of the modality they entered. In methadone programs, TOPS clients were more likely to be daily opioid users who also used nonopioids. In the other modalities, nonopioid use was much more common among TOPS clients than among DARP clients. More detailed analysis also demonstrated the more extensive use of multiple substances among TOPS clients than among DARP clients. These results suggest the need for monitoring trends in multiple use patterns to determine changes in patterns, especially patterns that might adversely affect treatment outcomes.

Substitution

In TOPS, clients were asked about any drugs they used as a substitute for heroin. As table 7 shows, substitution was common. Over one-third of the clients who had a history of daily heroin use reported using illegal methadone or other narcotics to substitute for heroin. About one in four used diazepam or chlordiazepoxide. These reports of substitution suggest that the life history of use should be carefully considered in order to accurately describe multiple use patterns. A number of clients entering treatment had not used heroin in the year prior to admission. Thus, a limited assessment might misclassify them as nonopioid users. The TOPS data suggest that former daily heroin users should be identified and their use patterns described separately from users who have not used heroin. Reasons for abstinence from heroin also need to be ascertained for the former daily users to better understand the nature of their current use patterns.

TABLE 6

Classification of Pretreatment Drug Use: DARP and TOPS Clients, 1979-1981

Drug Use Classification	Outpatient Methadone		Residential		Outpatient Drug Free	
	DARP (n=11,023)	TOPS (n=3223)	DARP (n=4505)	TOPS (n=1192)	DARP (n=5785)	TOPS (n=1949)
Daily opioid use only	45	21	22	6	19	2
Daily opioid use; some nonopioids	49	60	40	24	16	8
Less-than-daily opioid use	5	15	20	29	17	26
Nonopioid use only	1	4	17	41	48	64
Total	100	100	99	100	100	100

Note: DARP data are for the 2 months before admission. TOPS data are for the 3 months before admission. Data are for comparable TOPS and DARP samples of clients using drugs in the 2 to 3 months before treatment.

TABLE 7

Nonmedical Use of Substitutes for Heroin by Heroin and Cocaine Use in the Year Before Intake: 1979, 1980, and 1981 Cohorts

Substitute Drug	Weekly Heroin Use		Former Daily Users	
	Weekly Cocaine (n=2069)	No Cocaine (n=3069)	Weekly Cocaine (n=445)	No Cocaine (n=2173)
Illegal methadone	44.9%	34.0%	33.8%	34.0%
Other narcotics	29.4	39.2	40.5	38.9
Diazepam or chlordiazepoxide	19.5	23.8	25.0	23.0
Barbiturates	7.9	10.7	17.6	14.7

Change in Patterns Before and After Treatment

Table 8 shows considerable shifting in use patterns. The data for residential clients are presented because there is a distribution of clients in each pattern. As can be seen from the data for clients staying 1 week or less, about 65% of the opioid users move to a less serious use pattern. However, 24% of nonopioid users before treatment use opioids weekly in the year after treatment. About one-third of the marijuana/ alcohol/minimal user group increases use to weekly opioid or other nonopioid use. The table also shows a clear tendency for clients with longer treatment stays to move to less serious patterns of use. The consideration of multiple use patterns after treatment provides a more complete description of the effects of treatment on drug use patterns.

TABLE 8

Drug Use Pattern in the Year After Residential Treatment by Drug Use Pattern in the Year Before Intake: Followup Samples of 1979 and 1980 Cohorts

Duration of TOPS Treatment	n	Weekly or Greater Pattern After Treatment: Opioids	Non-opioids	Alcohol/ Marijuana	Minimal
Weekly or Greater Heroin and/or Opioid Users (n=354)					
1 week or less	26	35%	15%	23%	27%
2-13 weeks	153	39	19	25	17
14-52 weeks	153	39	19	35	22
More than 2 years	48	13	10	40	37
Weekly or Greater Nonopioid Users (n=202)					
1 week or less	25	24%	20%	28%	28%
2-13 weeks	79	13	25	47	15
14-52 weeks	65	9	29	34	28
More than 1 year	33	6	3	42	49
Alcohol/Marijuana or Minimal Users (n=164)					
1 week or less	17	12%	18%	53%	17%
2-13 weeks	80	23	19	38	20
14-52 weeks	38	13	11	37	39
More than 1 year	29	3	21	31	45

Note: Rows sum to 100%.

Conclusions and Recommendations

The results of these analyses of multiple drug use among individuals entering publicly funded drug treatment suggest three general conclusions:

1. Multiple use is complex, and it is increasing. In addition to the TOPS data for drug treatment clients, studies of youth in high schools (Johnston et al. 1984; Rachal et al. 1980) show that marijuana and alcohol are now commonly used together.

2. The pattern or configuration of use is the most empirically and clinically useful approach to multiple drug use assessment.

3. The results strongly suggest that multiple use requires consideration of factors in addition to the pharmacological interactions.

The complex, often pharmacologically incompatible patterns of use suggest that many users often do not know or care what they use. The complex and rapidly changing array of substances used may confound any statistical or biochemical approach. A consideration of psychosocial factors, coupled with more detailed understanding of pharmacological effects, is needed to disentangle the epidemiology of multiple use and to design more effective treatment approaches.

After considering all of the evidence concerning measures of drug use, several recommendations seem warranted for further research on this critical issue of multiple drug use. First, it is clear that there are a number of options available for measuring drug use, each of which has strengths and weaknesses. Second, it is also clear that the choice of a measure can be greatly influenced by the clinician's, researcher's, and policymaker's purposes, the population sampled, and the questions under consideration. Third, basic and complex measures of multiple use are available, depending on the level of specificity needed in research.

Recommended Measures

The simplest measures of drug use are the single use measures, which are appropriate when the study focus is on one specific drug. For treatment clients, heroin use and primary drug appear to be the best single use measures. Heroin use is the focus of a major proportion of the treatment effort and is still the most serious problem treated in terms of social cost and personal suffering. A measure of primary drug use can be calculated for all clients. Since the use of the primary drug is likely to be the focus of treatment, it may be an appropriate indicator of treatment effectiveness. However, single use measures are not able to reflect the broad spectrum of drug use.

The multiple drug use indices are somewhat more complex and attempt to reflect the full range of drug-taking behavior along a single dimension. Such measures can provide a broad overview of drug use. The Severity Index was judged to be the best unidimensional multiple use index for the treatment population. While such an index is helpful in indicating a general level of drug use, it may be insensitive to patterns of use and drug substitution.

The most complex measures are those that attempt to reflect the multiple dimensions of drug use behavior. A Multidimensional Index was constructed using principal components analysis of drug use among TOPS treatment clients. It indicated three factors underlying clients' drug use: a polydrug factor, a heroin-cocaine factor, and an alcohol-marijuana factor. The Multidimensional Index provides a more detailed picture of drug use than is possible with a single index, but it has limited clinical utility.

Clearly, multiple drug use is more common among clients entering treatment today than it was when the DARP studies were initiated or, even later, when the CODAP system was developed. The CODAP system and much of drug treatment research has focused on the primary drug of abuse as a descriptor of use patterns. Although useful, classification by primary drug does not capture the full scope of drug use. Based on the original work of Simpson (1974, 1976), the seven drug patterns developed for TOPS provide a hierarchical classification of use patterns that can be readily understood and used by clinicians, policymakers, and researchers.

Treatment Implications

Compared to drug use patterns observed in treatment populations in the late 1960s and early 1970s, the increased use of multiple drugs by current clientele indicates a need for careful consideration of treatment approaches. The seven patterns provide a framework for the design, conduct, and evaluation of current treatment efforts. The patterns were chosen and defined with treatment needs in mind and clearly separate heroin and narcotic users from clients who abuse nonnarcotic drugs. Use of these patterns can help answer such questions as:

1. Do clients with various patterns of use require different treatment approaches?

2. What types of users benefit most or least from particular modalities and environments?

3. Are different types of ancillary services required by various types of users?

4. How do patterns of use change after a client enters treatment?

Given the prevalence of multiple drug use, descriptions based on a single or a limited number of drugs would provide insufficient information to address the more complex issues now facing treatment programs. The patterns, in combination with information on the severity of use and primary drug of abuse, could certainly provide a more complete assessment of the nature and extent of total drug use. Consequently, the increased information should help treatment programs design and deliver services more effectively.

Research Directions

In the TOPS analyses, drug use measures developed in prior research have been examined and refined, and new measures have been constructed, both for quantitative measures (e.g., Severity Index) and for classification measures (e.g., the seven patterns). The result has been a set of recommended measures to be used in the further analyses of the TOPS data and in other research. Major questions on the epidemiology of multiple drug abuse and the association of multiple drug abuse with other factors can now be examined more comprehensively with these measures in the TOPS and other data sets. Epidemiological questions for general and treatment population include:

1. How do patterns of use develop?

2. Are patterns of use episodic, persisting, or random?

3. What are the demographic characteristics of different types of users?

4. Has and will the prevalence of patterns change over time?

The association of these measures with other variables should provide important information on the causes and consequences of multiple drug use.

Questions that are in need of careful examination include the following:

1. What is the relationship between pattern classes and drug-related problems?

2. Do such factors as depression, criminal behavior, and employment vary systematically with drug use severity or the pattern classes?

3. What individual characteristics or environmental conditions are associated with patterns of use?

4. How are community and treatment factors related to changes in the patterns of use over time?

Further TOPS research has taken the next logical step of using the drug use measures developed to address many of the questions posed above for the drug treatment population. We would strongly recommend the use of these measures in other appropriate studies where multiple drug use is common. The use of these measures in a variety of studies should significantly increase our understanding of the dynamics and nature of multiple drug abuse.

Coordination of Pharmacological, Epidemiological, and Psychosocial Research

To advance the understanding of the complex nature of multiple drug use, a multidisciplinary approach is needed. Increased interaction of epidemiological, psychosocial, clinical, and preclinical researchers should provide a stronger foundation for research design and interpretation of study results. As a first step, we suggest a focus on three areas for collaboration:

1. Identification of patterns of use and potential combinations of drugs in the field and in the laboratory;

2. Confirmation of research findings in field, clinical, and preclinical studies; and

3. Assessment of effect of patterns of multiple use on dependency.

More specifically, we would suggest a series of meetings with epidemiologists, clinicians, and pharmacologists. The objective would be the development of known and potential patterns of multiple drug use. Specific patterns could be identified for monitoring in epidemiological or treatment studies and/or pharmacological analysis in the laboratory. Known and potential correlates and consequences, particularly dependencies, of the patterns could also be investigated across the multidisciplinary settings. Such initial collaborative efforts should lead to research that will expand our knowledge of both the basic mechanisms and multiple drug use and efficacy of therapies to ameliorate adverse effects of multiple use patterns.

FOOTNOTES

[1]The weights developed for the Lu Index and the T-scores of the Douglass/Khavari Index reflect both the importance of each drug and the frequency of use of each drug by clients. Thus, these values were used in computing the final index for these measures (i.e., these weights were not multiplied by frequencies prior to combining them).

[2]The term "other narcotics or opiates" is used in TOPS. The term "other opiates" that was used in DARP generally describes the same class of drugs.

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Statistical Analysis of Drug Interactions

Clifford L. Mitchell, Ph.D.

INTRODUCTION

The study of drug interactions poses the problem of how best to characterize the effects observed when two or more agents are administered together. As with other types of experiments, the experimental designs and statistical techniques used depend on the questions asked. Clearly, any reasonable evaluation of a drug interaction presupposes that a precise question is being asked.

This article deals only with the question of whether to characterize an interaction as one of addition, antagonism, synergism or potentiation. In this discussion the following definitions are used for these terms: (1) ADDITION - the situation in which, within the limits of the dose-response curve, the effect produced by the agents is the algebraic sum of their independent actions; (2) ANTAGONISM - the situation in which the effect is less than the algebraic sun of their independent action; (3) SYNERGISM - the situation in which for drugs exhibiting the same observable response, the effect produced is greater than the algebraic sum of their independent actions, (4) POTENTIATION - the enhancement of action of one drug by a second drug that exerts no detectable response on the variable measured when it is administered alone. In practice, the terms synergism and potentiation are often used interchangeably, The terms underadditive and overadditive have been used in place of antagonism, synergism and potentiation (Pöch and Holzmann 1980). Also, other definitions of addition are sometimes used (cf. Pöch 1981). The procedures discussed require the definition of addition given above.

Much of the material in this article has been presented previously (Mitchell 1976). That article also contains a discussion of experimental design and its statistical basis which is not presented here.

NOTE : Portions of the text of this article and figures and tables as noted were originally publlshed in Mitchell, C.L. The design and analysis of experiments for the assessment of drug interactions. Ann NY Acad Sci 281:118-135.

IMPORTANCE OF CHARACTERIZING DRUG INTERACTIONS

Characterizing drug interactions as to addition, antagonism, syngergism and potentiation is merely a descriptive exercise; it does not yield information concerning the mechanism for the interaction. Since one is presumably more interested in the mechanism, why spend time and effort in characterizing the interaction? Loewe (1957) answered this question succinctly when he stated "the 'why?' of a phenomenon cannot be studied without adequate knowledge of the 'what?', the phenomenon itself."

Defining a drug interaction as addition, antagonism, syngergism, or potentiation is a problem of determining the quantitative relationship between the doses of the combinations and the effect observed. Since the nature of the interaction may change depending on the doses and time intervals studied (cf. Gessner 1974) it behooves one to have dose-effect and time-effect data for the combinations in order to have a rationale for the doses and times to be utilized in mechanistic studies. This is no different than what is expected in single drug studies. Unfortunately, much of the drug interaction literature suffers from a lack of quantitative evidence for the type of interaction (cf. Mediphor 1984, for listing of unsubstantiated cases of drug interactions) . Obviously the extent to which dose-effect and time-effect studies are done should vary according to the question(s) asked and the (perceived) importance of the interaction.

It is also important to obtain both dose-effect and time-effect information about the substances individually on the responses to be measured before designing the drug interaction experiment. This is necessary for two reasons. First, this information provides a rationale for the doses used in the interaction studies and the time after dosing at which the effect is to be measured. Second, it aids in determining the statistical procedures to be used in the interaction studies. These procedures depend on whether only one or both of the substances affect the response when given alone and whether the measurements are quantitative or quantal in nature.

PROCEDURES WHICH MAY BE USED WHEN BOTH SUBSTANCES GIVEN ALONE AFFECT ME MEASURED RESPONSE

Quantitative Data

The first step is to determine the potency of one substance relative to the other in affecting the response. The purpose of this is to provide a rational basis for the doses used in subsequent studies. The most simple method assumes that the two compounds yield dose-effect responses which are linear and parallel. The most commonly used parallel line bioassays are 4 point (two dose levels of each substance) and 6 point (three dose levels of each substance) assays (Finney 1952). The ad-

vantage of the latter is that it provides a test for non-linearity. Both, however, encompass a test for deviation from parallelism. This is important because if the dose-response curves are not parallel, then the relative potency will change, depending on the doses used. If this is the case, then the methods described in the paper are of limited value.

If the onset and duration of action of the compounds are different (a likely case), then obviously different relative potencies will be obtained depending upon when the measurements are taken. The two most common procedures utilize either the time of peak effect or the area under the time-effect curve. For drug interaction studies, the former is generally preferred since it avoids some of the complications that can arise if the compounds have grossly different time-effect curves. Better yet might be to determine relative potencies at more than one time interval. Most important, though, is to have a reason for the time(s) examined, based on previous experiments or published information.

Once the relative potency has been determined, subsequent studies involve combining fractional doses of the substances and comparing the responses observed against those obtained using standard doses of each substance individually. The hypothesis to be tested is that, as far as the response being measured is concerned, the two compounds behave as though they were different forms of the same substance. Thus, doses of the combination and single substance(s) are picked such that equivalent responses should be obtained if the effect of the two together is additive. For example, given two compounds (A and B) in which A is four times as potent as B, a mixture of one part A and four parts B should yield a response equivalent to two parts A or eight parts B when each is administered alone if the effect of the two together is additive. If the effect of the mixture is significantly greater than this, synergism is indicated; if it is significantly less, one infers antagonism. The statistical procedures used depend upon the design of the experiment. The Student's t-test can be used if one is only comparing two means. If more than two means are being compared, a one or two way analysis of variance(depending on the design) followed by designated comparisons of means (i.e., multiple comparison procedures) is more proper. If one has reason to believe that certain requirements of parametric tests are not met (e.g., equality of population variances and/or normal distribution of data), non-parametric equivalents may be used (e.g., Mann-Whitney U test instead of Student's t, Kruskal-Wallis one-way analysis of variance instead of analysis of variance, the Cochran Q Test, or Friedman two-way analysis of variance).

An example of this technique is presented in Figures 1 and 2. The experiment involved determining the effect of morphine and chlorpromazine alone and in combination on the escape response elicited by tooth-pulp stimulation in cats (Mitchell 1966).

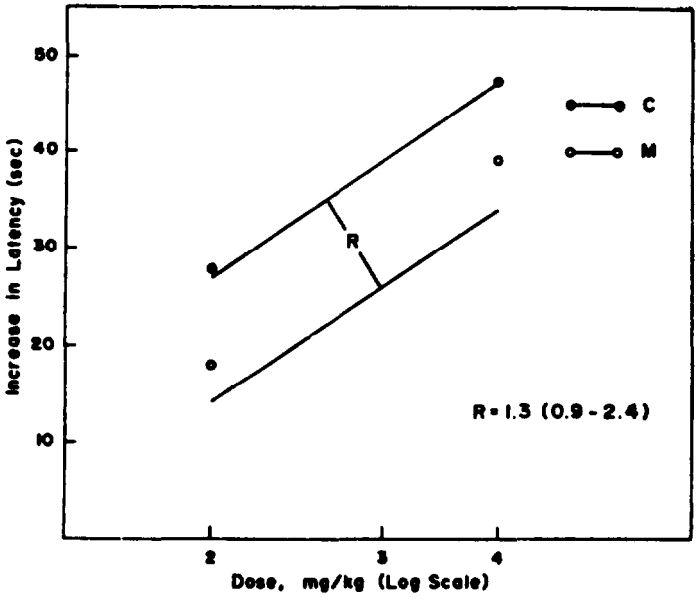

FIGURE 1

Dose-Response Curves for Chlorpromazine Hydrochloride and Morphine Sulfate as Determined in the 4 point bioassay.

C = chlorpromazine, M = morphine, and R = relative potency. (Modified from Mitchell 1966).

Figure 1 shows the potency of morphine sulfate relative to chlorpromazine hydrochloride when the measurements were taken at the time of peak effect for both compounds. Since the two drugs were virtually equipotent in this test, the combination of one part morphine and one part chlorpromazine was compared against two parts morphine and two parts chlorpromazine, each separately, as shown in figure 2. An analysis of variance was performed on these data, following which the means were compared using one of the multiple comparison procedures, Duncan's new multiple range test (Steel and Torrie 1960). No significant difference ($p>0.05$) was obtained between the effect of morphine, 4 mg/kg, chlorpromazine, 4 mg/kg, and the mixture of 2 mg/kg of each. Moreover, morphine, 2 mg/kg, chlorpromazine, 2 mg/kg, and the mixture of 1 mg/kg of each were not significantly different ($p>0.05$). Thus, it is inferred that the effects of morphine and chlorpromazine are additive in this model under the conditions of the experiment.

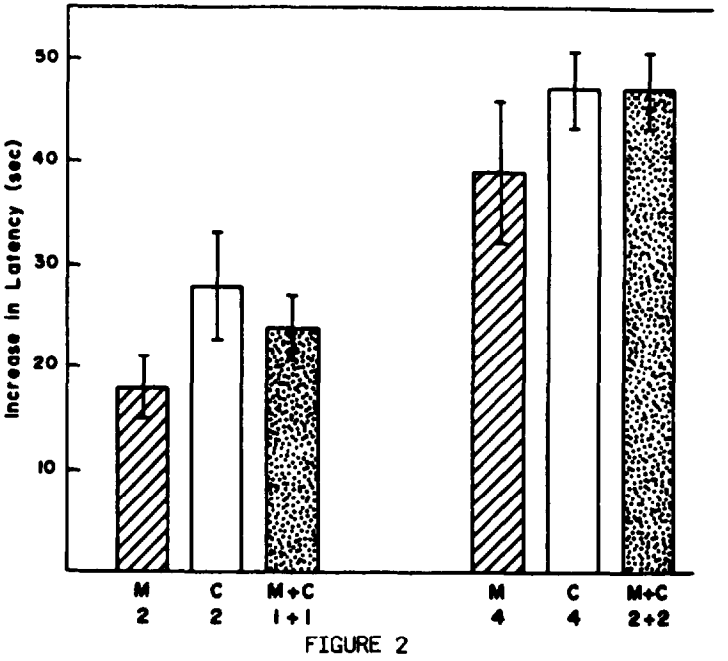

FIGURE 2

Effect of Morphine Sulfate, Chlorpromazine Hydrochloride, and Their Canbination on the Latency for an Escape Response to Tooth-Pulp Stimulation in the Cat.

Bars represent mean change (± standard error) in the average latency for 10 trials after drug and the average latency for 10 control determinations. The observations were made 45 minutes following the administration of morphine and 60 minutes following the administration of chlorpromazine. In all instances, the number of animals was 8. The doses were 2 and 4 mg/kg of morphine (M) and chlorpromazine (C) and 1 and 2 mg/kg of each for the combination (WC) (modified from Mitchell 1966).

Quantal Data

These data are first analyzed by probit or logit analysis, with the relative potency determined by the ratio of one ED_{50} versus the other (Finney 1952). This second step is sometimes neglected in practice, but it should not be since it encompasses a test for deviation from parallelism. The methods outlined below illustrate probit analysis and, like that for quantitative data, assume parallel dose-effect curves. Again different ED_{50}s may be obtained, depending on when the effect is measured. Thus, the comments made above are also relevant here. Once the ED_{50}s (and, hopefully, the potency ratio) have been determined, subsequent studies are conducted in a manner similar to that

described for quantitative data except that the statistical procedures are different owing to the nature of the data. Specifically, one might use either the chi-square or Fisher's exact probability tests, depending on the sample size and the expected frequencies.

Tables 1 and 2 show an example of this technique. In this experiment the effects of ethanol alone and in combination with chlorpromazine or chlordiazepoxide on the ability of mice to remain on an inclined screen were examined. Table 1 shows the ED_{50}s and the potency ratios. Table 2 shows that when one-half of the ED_{50}s for ethanol and chlorprormazine were combined. additive effects were obtained. Potentiation was observed when one-half of the ED_{50}s for ethanol and chlordiazepoxide were combined. This was determined by comparing the frequency of mice falling from the inclined screen for the ethanol drug combination versus the ED_{50}s of ethanol alone. For the combination, each drug was administered such that their time of peak effect coincided. It should be emphasized that the findings of addition with the combination of ethanol and chlorpromazine does not mean that under other conditions potentiation might occur. Indeed, in the same article Gebhart et al. (1969) did demonstrate potentiation using another endpoint (see below). Also, the study would have been more complete if other fractional doses had been combined and compared with their predicted equivalent doses of the substances alone.

PROCEDURES WHICH MAY BE USED WHEN ONLY ONE OF THE SUBSTANCES GIVEN ALONE AFFECTS THE MEASURED RESPONSE

The condition in which one of the substances is inactive when given alone results, on the one hand, in a simpler situation and on the other in a more complex situation than when both are active. It is simpler because the potency of one substance relative to the other need not (indeed, cannot) be determined. It is more complex because the investigator must now search for another rationale for the doses and times of measurement to be used in the experiment. Once these parameters have been chosen, the procedure is simply to compare the effects of the combinations with those for the active agent alone. The hypothesis to be tested is that, as far as the response being measured is concerned, the "inactive" substance exerts no influence on the other when the two are given in combination. The statistical procedures used depend upon the experimental design and whether the data are quantitative or quantal in nature. In general, any of those mentioned above may be used. It must be remembered, however, that it is mandatory to demonstrate that the one substance is inactive in the dose used unless it is known a priori that it is.

TABLE 1

Effect of Drugs on the Ability of Mice to Remain on an Inclined Screen*

Drug	50% Effective Dose † (mg/kg)	Potency Ratio+
Ethanol	1820 (1436-2043)§	--
Chlorpromazine	11 (9-14)	(121-205)
Chlordiazepoxide	65 (57-78)	28 (21-34)

* After Gebhart et al. 1969. Mice were placed on a 60° inclined screen at the following times after drug administration: ethanol(50% v/v), immediately; chlordiazepoxide, 30 min. and chlorpromazine, 60 min. All drug injections were given intraperitoneally.
† The dose causing 50% of the mice to fall from the inclined screen as determined by the probit method. For each agent, at least 3 doses were used.
+ The potency ratios were calculated relative to ethanol.
§ 95% Confidence interval.

TABLE 2

Effect of Drugs in Combination with Ethanol on the Ability of Mice to Remain on an Inclined Screen*

Drug-Ethanol Combination	Nunber of Mice Tested	Nunber of Mice Respondingf	p+
50% effective dose of ethanol	20	13	
1/2 50% effective doses, ethanol + chlorpromazine	20	10	>0.30
1/2 50% effective doses, ethanol + chlordiazepoxide	20	19	<0.05

* After Gebhart et al. 1969. Chlorpromazine was given 60 min. before ethanol: chlordiazepoxide 30 min before ethanol. Mice were placed on the 60° inclined screen immediately after ethanol administration.
† The number of mice falling from the 60° inclined screen.
+ Probability of X^2 (ethanol-drug combinations versus ethanol alone): $p<0.05$ is considered significant.

TABLE 3

Sleeping Time of Mice Treated with Saline or Iproniazid 1 Hour Before Injection of Hexobarbital*

Drug	N	Sleeping Time (in min)+
Saline + hexobarbital	18	24 + 0.65
Iproniazid + hexobarbital	15	65 ± 4.78†

* The iproniazid dose was 100 mg/kg the hexobarbital dose, 80 mg/kg; all injections were administered i.p.
+ Defined as length of time between losing and regaining righting reflex. Figures represent mean ± standard error.
† Significant difference at $p < 0.05$, t' test.
From Mitchell 1976. Copyright (1976), New York Academy of Sciences.

An example using quantitative data is illustrated in Table 3, above, which shows the effect on the sleeping time of mice of pretreatment with iproniazid or saline 1 hour prior to the injection of hexobarbital. Iproniazed is a monoamine oxidase inhibitor which, by itself does not produce sleep. Since the data are quantitative in nature and only two groups are involved, the first impression might be to analyze the data using the Student's t-test. One of the assumptions of the Student's t-test is that the samples are drawn from populations having equal variances. There is a simple test for this assumption which, unfortunately, is too often ignored by biologists. For the data shown in Table 3 the assumption of equality of variance is rejected at $p<0.0005$. In such a case either the t'-test or a non-parametric method (in this instance, the Mann-Whitney U test) might be used. Another option is to use an appropriate transformation (logarithmic, square root or other) which "normalizes" the data and meets the criteria for parametric tests. The purpose of this illustration was twofold; first, to show how a simple statistical method can be used to study drug interactions; and second, to caution you about inequality of variance. Inequality of variance occurs more often than recognized in biological data. Situations in which one compound inhibits the metabolism of the other frequently present such a case.

The results of an experiment using quantal data and the Fisher's exact probability test are shown in Table 4. An ED_{50} for ethanol producing a loss of righting reflex (LRR_{50}) in mice was determined and found to be 4.3 g/kg (95% Confidence interval of 3.9 to 5.2 g/kg; Gebhart et al, 1969). LRR_{50}s for chlorpromazine and chlordiazepoxide could not be determined that did not

also produce Varying degrees of lethality. The ED_{50s} for the three agents which caused mice to fall from an inclined screen could be determined and were called PD_{50}s (see above). One-half of the LRR_{50} of ethanol was then given in combination with one-half the PD_{50} for ethanol, chlorpromazine, or chlordiazepoxide. Singly, these doses produced no LLR. Statistical comparisons were made using Fisher's exact probability test because the expected frequency in the cell number of mice losing the righting reflex" was less than five. Otherwise a chi-square test could have been used. Potentiation of the effect of ethanol by both chlorpromazine and chlordiazepoxide was concluded. It should be emphasized that doses of both chlorpromazine and chlordiazepoxide much larger than those used here are required to produce loss of righting reflex in mice.

TABLE 4

Ability of Drugs in Combination with Ethanol to Produce a Loss of Righting Reflex (LRR)*

Treatment	Number of Mice		p+
	Tested	Respondngt	
1/2 LRR_{50} of ethanol plus:			
1/2 PD_{50} § of ethanol	20	0	
1/2 PD_{50} of chlorpromazine	20	7	<0.004
1/2 PD_{50} of chlordiazepoxide	20	13	<0.001

* After Gebhart et al. 1969. Chlorpromazine was given 60 min. before ethanol; chlordiazepoxide 30 min. before-ethanol. The mice were tested immediately after ethanol administration.
The number of mice losing righting reflex.
† Fisher's exact probability (1/2 LRR_{50} ethanol + PD_{50} of ethanol versus 1/2 LRR_{50} of ethanol + 1/2 PD_{50} of drug): $p<0.005$ is considered significant.
§ One-half the dose causing 50% of the mice to fall from a 60° inclined screen.

Probit analysis may also be used for studying drug interactions where one of the compounds is inactive. One approach using this method is shown in Table 5. These data from Chau et al. 1973, illustrate the enhancement, by vasopression, of pentazocine lethality.

TABLE 5

Lethal Effect of Pentazocine and Vasopressin in Unanesthetized Rats

Compounds	i.m LD_{50} of Pentazocine*
	mg/kg
Pentazocine	153 (131-177)
Pentazocine and vasopressin (5 U/kg)	139 (115-168.2)
Pentazocine and vasopressin (10 U/kg)	39 (21.6-68.4)
Vasopressin alone at 100 U/kg	no lethality

* Ten animals per dose level.
From Chau et al. 1973. Copyright (1973) American Society for Pharmacology and Experimental Therapeutics.

Another example is shown in figure 3. These data, from a report by Tulunay and Takemori (1974) illustrate the enhanced efficacy of naloxone induced by pretreatment with morphine. The tail flick analgesia assay in mice was used. The animal responses were made quantal by establishing an end-point at the mean peak effect which represented an increase in the reaction of an individual animal of greater than three standard deviations of the control mean reaction time for all animals used in the group. In control animals, the ED_{50} ± 95% confidence intervals of morphine sulfate, subcutaneously, 30 minutes after administration, were 4.1 (3.2-5.3) mg/kg without naloxone and 35.3 (28.2-41.0) mg/kg with concomitant administration of naloxone, 0.16 mg/kg. In animals pretreated 3 hours earlier with 30 mg/kg of morphine sulfate the ED_{50}s were 4.8 (3.7-6.2) mg/kg and 82.8 (65.1-108.4) mg/kg, respectively. Thus, pretreatment with a single dose of morphine did not change the ED_{50} of morphine alone but significantly altered the ED_{50} for the morphine plus naloxone combination, demonstrating an increase in the antagonistic potency of naloxone.

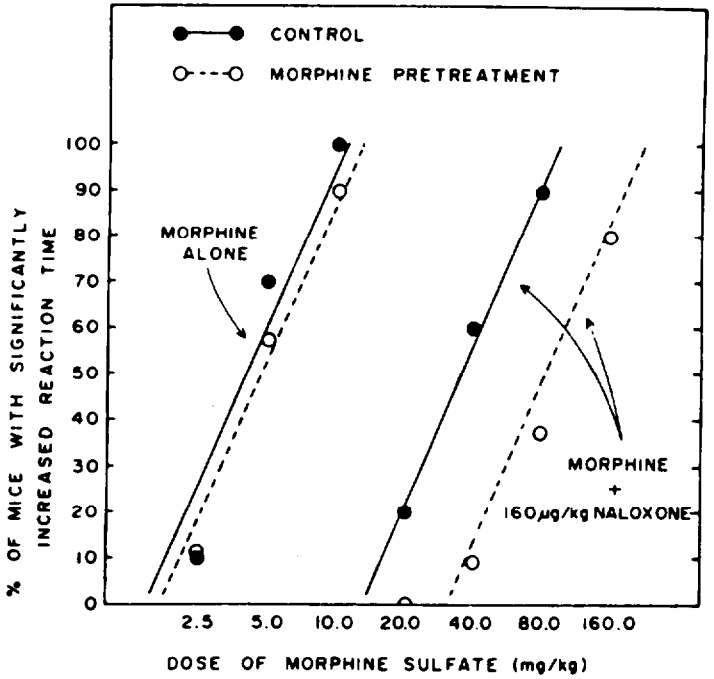

FIGURE 3

The Enhanced Efficacy of Naloxone Induced by Pretreatment with Morphine

See text for details. From Tulunay and Takemori (1974). Copyright (1974) American Society for Pharmacology and Experimental Therapeutics.

Had either Chau et al. (1973) or Tulunay and Takemori (1974) desired, they could have quantified the degree of enhancement by obtaining the ratio of the ED_{50}s for the two naloxone groups. Figure 4 illustrates this type of approach just mentioned. Although the data concern the efficacy of morphine in adrenalectomized versus nonadrenalectomized animals, the analogy to the study of drug interactions is apparent. Analgesia was determined 30 minutes after the s.c. administration of morphine in rats using the hot plate method. The 50% analgesic dose (AD_{50}) was defined as that dose permitting 50% of the animals to remain on the heated plate for 30 seconds. As can be seen in figure 4, under the condition of the experiment, adrenalectomized rats are more sensitive to the analgesic effect of morphine than sham operated animals. This is demonstrated by the fact that in sham operated rats 1.7 (1.2-2.3) mg/kg of morphine is equivalent to 1 mg/kg in adrenalectomized animals.

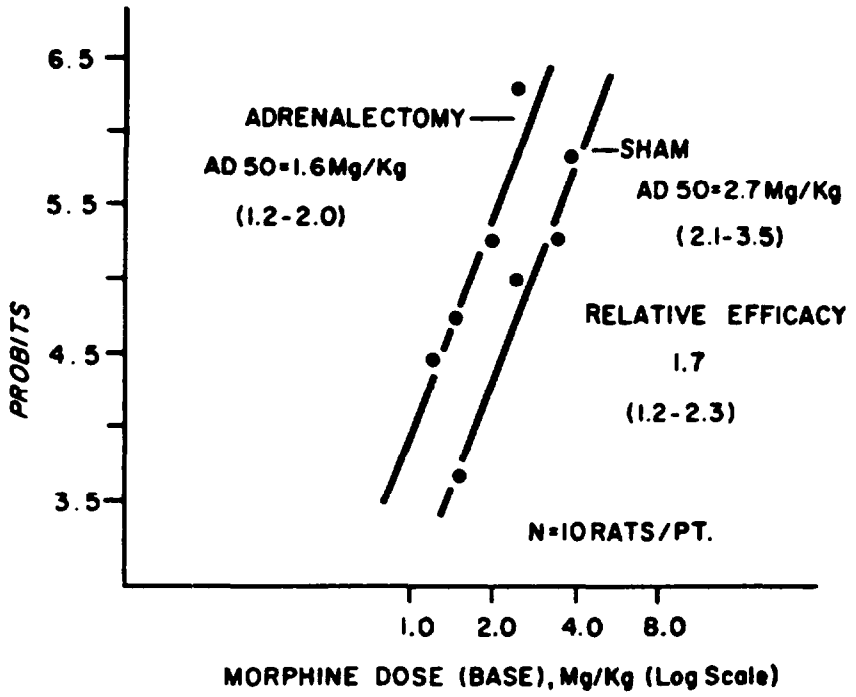

FIGURE 4

Dose-Response Curves Generated While Determining Equi-analgesic Morphine Doses on the Hot Plate.

AD_{50} morphine analgesic &se in 50% of the animals. See text for further details. From Gebhart and Mitchell 1972. Copyright (1972) European Journal of Pharmacology.

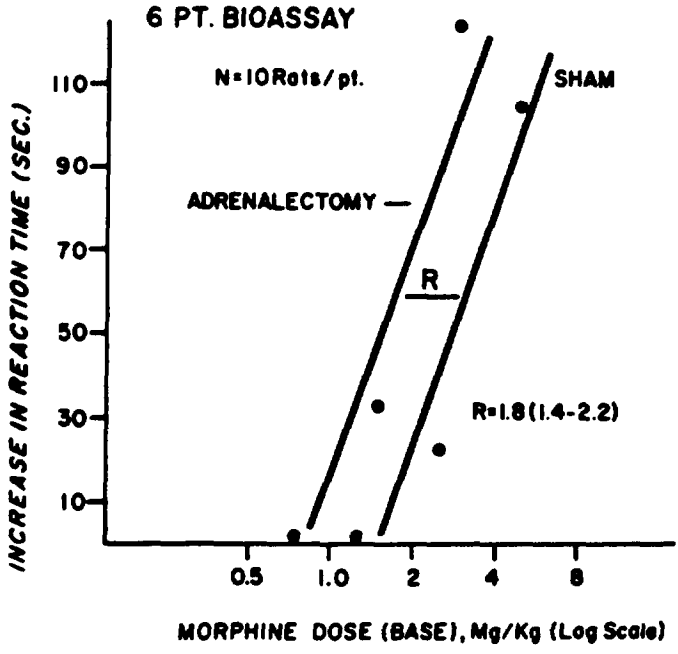

FIGURE 5

Dose-Response Curves as Determined in the 6 Point Bioassay. R; Relative Efficacy.

See text for further details. From Gebhart and Mitchell 1972. Copyright (1972) European Journal of Pharmacology.

The bioassay technique may also be used for quantitative data as shown in figure 5, from the same article by Gebhart and Mitchell (1972) as cited above. The experimental procedure was the same as that already described except that no cutoff time was used. Before proceeding with the analysis it was verified that adrenalectomy alone did not alter the control reaction times. Thus the data analyzed were the actual increases in reaction times from the control determinations. Results similar to those seen using quantal data were obtained. The utility of this technique for drug interaction studies where one of the compounds is inactive in the test procedure is, I trust, obvious. One advantage of this method lies in the fact that it is possible to quantify the potency of one agent relative to another in enhancing or antagonizing the effects of the compound of central interest (i.e., the one which is active in the model when given alone).

ISOBOLOGRAHIC METHOD

Loewe and Muischnek (1926) introduced the isobolographic method several years before the statistical methods in biological assay were formulated (Bliss 1939; Finney 1952). Until recently, the method has never been widely accepted for a variety of reasons. Among these are the complex and exotic terminology associated with it; the tedious nature of the method; and the fact that, as introduced by Loewe, it was never truly quantitative. Recent drug interaction literature, however, indicates an increase in its use (cf. Fircio et al. 1978; Yeung and Rudy 1980; Masuda et al. 19811 Foltin et al. 1983; Marshall et al. 1983; Kissin et al. 1984) . The material which follows will point out the similarities and differences between this approach and those presented above. The reader interested in examining the method in more detail should consult the articles by De Jongh (1960) and Gessner (1974) for more complete discussions of the method and for additional references to Loewe's work.

An isobole (from the Greek, isos [equal] and bolos [effect]) is a line connecting equi-effective doses. To determine an isobole, one first must choose an effect to be measured. This can be any measurable effect, as for example, a decrease in blood pressure of 20 mm mercury, sleeping time of 25 minutes, or the incidence of oeath in 50% of the animals. Most uses of the method have focused on quantal responses (e.g. determining ED_{50}s or LD_{50}s). The amount of different mixtures of the two substances necessary to produce the specified effect is then determined. A graph is prepared using doses of one component as the abscissa and doses of the other as the ordinate. Points representing the various combinations tested and found to produce the specified effect are placed on the graph. The line drawn to connect these points is called an isobole: its points represent combinations which cause identical effects. A series of such lines is called an isobologram (Loewe 1953). There are several types of isoboles, of which only two will be presented in this article.

The first type (Type I) is represented by those situations in which the desired effect can be produced by both substances alone. Figure 6 shows a theoretical isobologram illustrating addition, potentiation, and antagonism. If the effect of substances A and B together is additive, the isobole is a straight line connecting the two points obtained for each agent alone (Figure 6a). In such a case the specified effect is reached with three-quarters the effective dose of A in combination with one-quarter the effective dose of B, or one-half of each or one-quarter of A and three-quarters of B, and so on. In other words, so far as the effect measured is concerned, one compound is acting as an analytical concentration (or dilution) of the other one. (N.B., This does not imply the same mechanism of action for both substances, however.) If the substances enhance each other's effect, one needs less of both substances in combination to produce the specified effect; hence, this isobole is a curved line situated below the line for addition (Figure 6b). If the substances have antagonistic effects, one needs more of both in combination to produce the specified effect; thus this isobole is a curved line situated above the line for addition. One might also obtain isoboles which indicate mixed effects. One example might be potentiation for a certain range of combinations and addition over the remainder (see below).

A second type (Type II) of isobole occurs when only one of two substances given alone produces the desired effect. A theoretical isobologram illustrating potentiation, antagonism, and no effect for one substance on the other is shown in Figure 7. When substance B has no influence on A, the isobole will run parallel to the abscissa (Figure 7a). If substance B potentiates A, then less of substance A is needed, and this isobole will lie below the neutral isobole (Figure 7b). Antagonism (Figure 7c) is indicated by an upward shift in the line.

Gessner (1974) has modified Loewe's method in order to apply a quasi-statistical treatment to the data. He determines the ED_{50} and its 95% confidence interval for each substance alone (if both are active), constructs the expected isobole assuming additivity, and places a confidence interval on it by connecting the lower and upper confidence limits for the two compounds with dotted lines (see Figure 9). ED_{50}s and their confidence intervals for different doses of the combination are then determined using either (1) different doses of both compounds combined in various mixed ratios, or (2) different doses of one compound in the presence of a fixed dose of the other. Additivity or non-additivity is determined by comparing the observed versus expected ED_{50}s and the 95% confidence intervals.

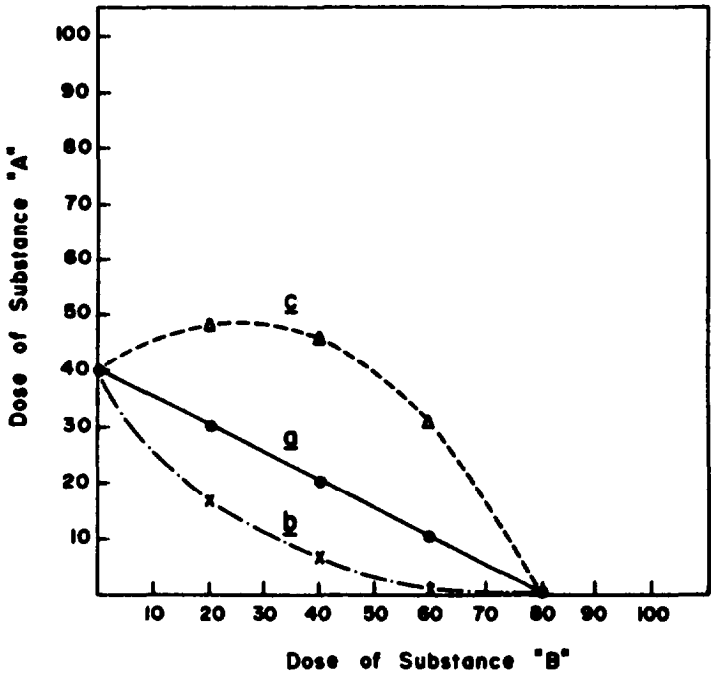

FIGURE 6

Type I Isoboles Illustrating Addition (a). Potentiation (b). Antagonism (c).

The numbers for the doses are in arbitrary units. See text for further details. From Mitchell 1976. Copyright (1976) New York Academy of Sciences.

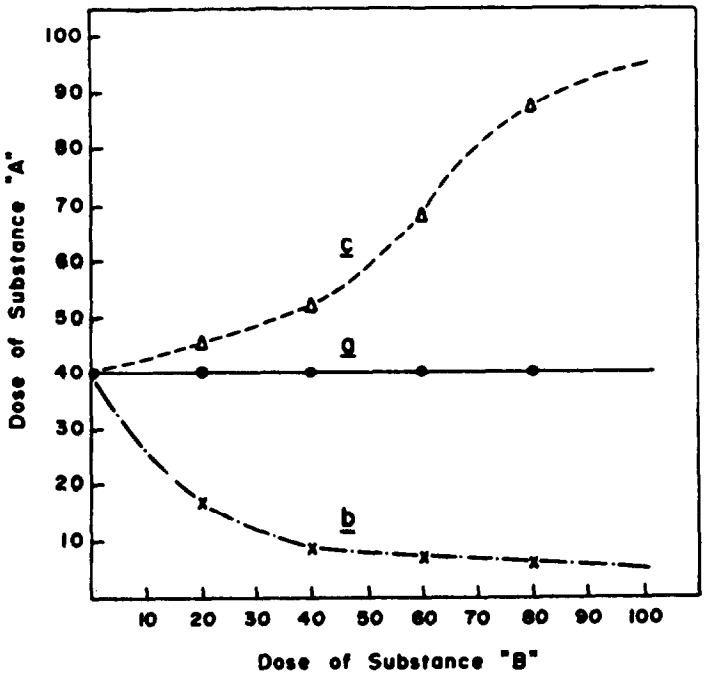

FIGURE 7

Type II Isoboles Illustrating No Effect of Substance B (a), Potantiation (b), and Antagonism (c).

The numbers for the doses are in arbitrary units. See text for further details.

Actual examples of Gessner's approach with Type I isoboles illustrating addition only and both potentiation and addition are shown in Figures 8 and 9, respectively. These data are from Gessner and Cabana (1970). Figure 8 shows the isobole for the interaction of the hypnotic effect of trichloroethanol and ethanol in mice. Each of the points represents the ED_{50} (± 95% confidence interval) for trichloroethanol in producing loss of righting reflex in the presence of a fixed dose of ethanol. It is apparent from this graph that the experimental points do not depart from simple additivity. The isobole for the interaction of the hypnotic effects of chloral hydrate and ethanol in mice is shown in Figure 9. The points represent the ED_{50} (± 95% confidence interval) for either chloral hydrate (vertical confidence interval lines) or ethanol (horizontal confidence interval lines) in the presence of a fixed dose of the other agent. Potentiation was concluded for all mixtures having a chloral hydrate/ethanol ratio greater than 1:7. Addition was concluded for ratios less than this value. The conclusions were based upon a comparison of the observed versus expected ED_{50}s and their 95% confidence intervals.

The primary disadvantage of the isobolometric approach as modified by Gessner is its tediousness. This arises due to the requirement of determining the exact amounts of a series of mixtures needed to produce a specified effect. It is much easier to measure the effects of given quantities of a mixture. This latter approach is the one utilized in the methods described earlier. It has an advantage, I suppose, in that it forces one to examine numerous different concentrations of the mixtures. This is not excluded in the other methods, however. Indeed, the prudent investigator would do this anyway.

Conceptually, both approaches are similar. When the experimental substances, each alone, are active in the test preparation, the working hypothesis is that the two compounds behave as though they were different forms of the same substance, one of which is possibly (depending on the potency ratio) diluted with an inert substance. This is tested in one case by comparing the responses of different portions of the mixtures to the. responses obtained with certain doses of the compounds alone. In the other (isobolometric) case, it is tested by determining the dose of the mixture necessary to produce a response equivalent to that for certain doses of the compounds alone. In either case, the doses of both the mixtures and the compounds separately which should give equal effects if the null hypothesis is true, are specified by the potency of one compound relative to the other in the test procedure. One infers additivity if the null hypothesis is accepted. One infers either potentiation or antagonism if the null hypothesis is rejected, depending upon the direction of the deviation from additivity. When one substance is inactive when given alone in the test situation, the null hypothesis for both approaches is that it has no effect when given with the other.

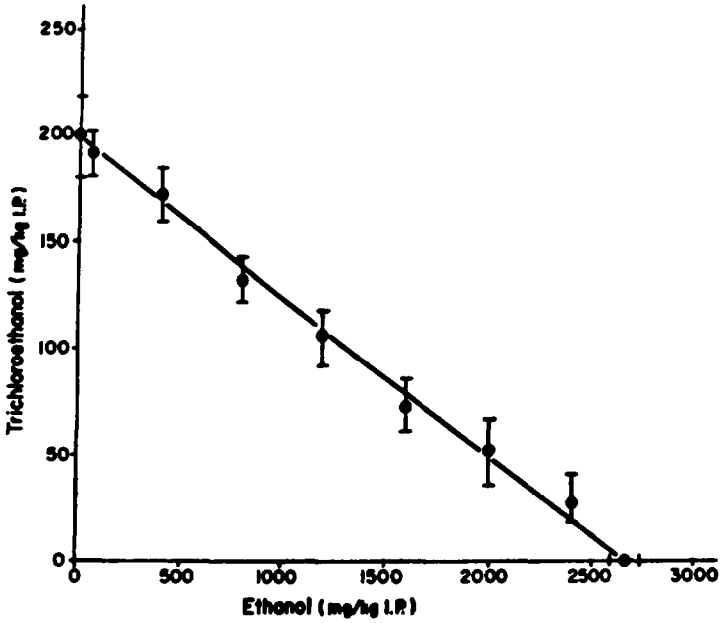

FIGURE 8

Isobole for the Interaction of the Hypnotic Effect of Trichloroethanol and Ethanol in Mice.

The ED_{50} points are plotted with their 95% confidence limits. The expected location of the ED_{50} points, given the occurrence of a simple additive synergism, s given by the solid diagonal. See text for further details. From Gessner and Cabana (1970). Copyright (1970) American Society for Pharmacology and Experimental Therapeutics.

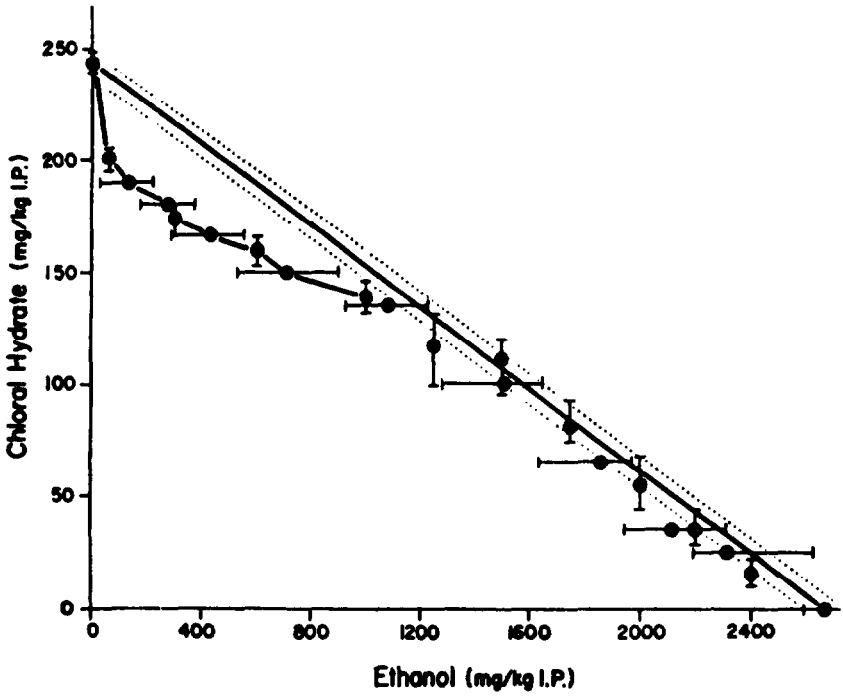

FIGURE 9

Isobole for the Interaction of the Hypnotic Effects of Chloral Hydrate and Ethanol in Mice.

ED_{50} points are plotted with their 95% confidence limits. The expected location of the ED_{50} points, given the occurrence of a simple additive synergism,is given together with the 95% confidence limits by the solid and dotted straight line diagonals, respectively. In the area of significant pdtentiation, the ED_{50} isobol has been generated by connecting adjacent points. See text for further details. From Gessner and Cabana (1970). Copyright (1970) American Society for Pharmacology and Experimental Therapeutics.

From the statistical point of view there is, however, a major difference between Gessner's modification of Loewe's isobolometric technique and the more conventional methods. With conventional techniques& both the expected response (assuming additivity) and the real" response can be determined experimentally. This is done by comparing the response of a given dose of the mixture with the responses obtained for the appropriate doses of the substances alone, the latter constitute the expected response. (Of course, the experiment should be designed such that possible differences due to the time of day in which the three responses are measured are minimized.) With the isobolometric technique, the expected dose cannot be-determined exoerimentallv. It can onlv be inferred from the line drawn connecting the ED_{50}s for the two compounds. Moreover, because of the time-consumina nature of the method. this line is generally based on historicai data rather than data obtained on the same dav as that for the experimental ooints. From a practical point-of view, this may not matter in most cases, since the evidence for potentiation or antagonism may be striking enough that this is of no consequence.

Whatever approach one uses, it is important to be aware of the underlying assumptions. Two specific problems deserve comment. First, great day to day variation can exist in the determination of 50% effective doses (LD_{50}, ED_{50}, etc.). Thus, the precision with which these parameters are known may not be great (the 95% confidence limits give some indication of this, however). Second, dose response curves for 2 agents can appear to deviate considerably from parallelism before one has statistical evidence to reject the null hypothesis of parallelism. Thus, deviation from parallelism may, in fact, be true even though the data are treated as supporting parallelism of the two dose response curves. Either of these conditions can result in artifacts interpreted as "significant interactions" due to the misestimation of the parameters used in determining the interactions. It is likewise important that all possible precautions be taken before, during, and after the experiment to ensure that the reported results are meaningful. This responsibility rests squarely upon the shoulders of the investigator.

SUMMARY

The design of drug interaction experiments focusing on whether to characterize the interaction as addition, antagonism, synergism or potentiation is based, in part, on whether or not both substances when given alone affect the response. If both substances are active, one determines the potency of one substance relative to the other in affecting the response. This can be done for either quantitative or quantal data. Once the relative potency has been determined, subsequent studies involve combining fractional doses of the substances and comparing the results against those obtained using standard doses of the

substances individually. Doses of the combination and the single substances are picked such that equivalent responses should be obtained if the effect of the two together is additive. The null hypothesis is that the two compounds behave as though they were different forms of the same substance, one of which is possibly (depending on the potency ratio) diluted with an inert substance. Equivalence of response can be tested using such parametric tests as Student's t or analysis of variance (or their nonparametric equivalents) for quantitative data. The chi-square or Fisher's exact probability test may be used for quantal data. Additivity is inferred if the null hypothesis is accepted. One infers either antagonism or synergism (depending upon the direction of the diviation from additivity) if the null hypothesis is rejected. If one substance is inactive when given alone the null hypothesis is that it has no effect when given with the other. This is tested using the same techniques as mentioned above, except that there is no need, obviously, to determine relative potency.

The isobolographic method for studying drug interactions was compared with those mentioned above. Both approaches have the same conceptual basis. The isobolographic method is more tedious, however, since it entails determination of doses required to cause a specific response, whereas the other methods focus on the responses caused by specific doses.

It was cautioned that, whatever the approach, it is the investigator's responsibility to know what assumptions are being made and to take all possible precautions before, during, and after the experiment to ensure that the reported results are meaningful.

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Problems of Pharmacodynamic Measurement Related to Psychoactive Drug Interactions in Humans

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INTRODUCTION

In measuring the effects of psychoactive drugs, a large number of factors need to be taken into account. These relate to properties of the drug itself (Netter 1983; Oates and Shand 1972), to the organism upon which it is acting (Crooks 1983; Munte et al. 1984), and to the measurement strategy being employed. In situations where more than one active agent is present, a number of special problems exist with respect to experimental design and the interpretation of data (Vesell 1984; Oates and Shand 1972). These arise fran both pharmacokinetic and phannacodynamic sources (Brodie and Mitchell 1972; Ellinwood et al. 1984; Netter and Netter 1983). The organism itself is constantly changing in response to both its internal and external environments, and it is adapting to the presence of exogenous substances which alter arousal and a variety of processes serving physiological and psychological equilibrium (Netter 1983; Vesell 1984; Munte et al. 1984). In these circumstances, sensitive and selective drug-effect detection as well as inmunity fran measurement noise are difficult to achieve.

This paper looks at some critical elements of the man-machine interface as they relate to drug-effect measurement, and it comments on problems which may arise because of the highly adaptive nature of many biological control systems. Current models of central neural processes still lack sufficient accuracy to permit a genuine mechanistic interpretation of the measured effects of psychoactive agents on human information processing, affect, and cognition. An integrated, neurotransmitter-based understanding of systems affected by mood-altering substances is comnonly lacking.

Modern instrumentation techniques are becoming available which have great temporal precision and high sensitivity to changes in central nervous system (CNS) function--whether these perturbations are produced by rhythmic biological activity, disease states, or

the introduct ion of exogenous, pharmacologically active chemicals (Aufdenbrinke 1982; Bigler 1977; Fink 1978; Grunberger et al. 1982; Itil 1978; Linnoila et al. 1978; Young and Sheena 1975). A persistent problem is the difficulty of separating the effects of concanitantly active drugs which act at related receptor sites, and through similar basic mechanisms. This is especially so when the drugs are pharmacokinetically interactive, share a cannon time course of action, and act on processes which have poorly characterized fluctuations in endogenous activity.

The author will identify sane critical elements of the man-machine interface as they relate to drug-effect measurement and will suggest what he considers to be the attributes of an "ideal" pharmacodynamic measurement technique. From this will arise a consideration of characteristics which render dependent variables suitable for use as pharmacodynamic probes. A brief concluding comment will be made concerning the special problems which arise in drug-effect measurement when drugs interact.

PHARMACOKIKETICS versus PHARMACODYNAMICS

This paper is mainly about pharmacodynamics, but it would be neither wise nor accurate to imagine that these two aspects of pharmacology are functionally distinct or independent. To avoid the possibility of confusion, the following definitions will govern the sense in which these terms are used in this paper:

> Pharmacokinetics is the study of the movement of drugs into, through, and from an organism or system, including analysis of data related to the absorption, distribution, metabolism, and excretion of drugs and their metabolites, and to the time course of drug effects. That is, pharmacokinetics is the study of the effects of organisms on drugs.
>
> Pharmacodynamics is the study of the mechanism of drug action, and of the responses of an organism or system to the administration of drugs, including analysis of the relationship between drug concentration and effect. That is, pharmacodynamics is the study of drugs on organisms.

THE MAN-MACHINE INTERFACE AND DRUG-EFFECT MEASUREMENT

Man and other animal forms are canplex biological entities which contain many control systems which are highly integrated with each other, and which are autoregulatory within certain limits. Pharmacodynamic studies seek to measure drug-induced perturbations in this complex of adaptive control. However, control is frequently nonlinear, and input/output relations are frequently incanpletely understood, and, in quantitative terms, poorly modeled. Control parameters change over time, for a variety of reasons, and the integrated system, and its functional sub-systems, are subjected to a multitude of internal and external sources of noise.

Therefore, it is difficult to separate system responses which result from "drug perturbation" from other forms of system disturbance. Further, biological organisms (even unicellular ones possessing irritability) do not "like" being probed. Engineered physical systems, while they may "respond", are indifferent to the various sensing systems which are used to measure their performance (even if, in so doing, they are either disrupted or destroyed). [It is unlikely that one can measure any process without taking "something" from it, even if only a few electrons or photons.]

The various interfaces, and associated transducers, which are established to permit the noninvasive acquisition of physiological information can be unstable over time. In sane senses, the less invasive the technique the more prone to degradation is the information-containing signal , and the more information extraction relies on inferential and probabilistic processes. An additional cunplication is that in the clinical and clinical research environments ergonanic considerations are often paramount. They may dictate further reduction in the "direct coupling" which one might logically seek between event, transducer, and data acquisition system. It is not hard to imagine that in sane circumstances an adequate level of "ecological validity" may be difficult to secure.

SOME ATTRIBUTES OF THE MEASUREMENT TECHNIQUE

What then might be the attributes of an "ideal" pharmacodynamic measurement technique? Perhaps the most obvious consideration is that the detection technique ought not to pervert the response unacceptably. An example of such "perversion" might occur in a system for measuring finger tremor which employs a heavy accelerometer attached to the finger. The alteration in mass of the tremoring digit would be likely to lower artificially the frequency or amplitude of the measured tremor.

While there may be a basis for argument about the importance or relative importance of the following in particular circumstances, it is necessary to consider the implications of whether or not sensing the dependent variable is:

a. Without subject constraint;
b. Without attachment to the subject;
c. Without subject awareness;
d. Objective, autanatic, and rapid;
e. Accurate, and sufficiently precise; and
f. Immune to extraneous "environmental" influences.

The impact on experimental design and the validity of experimental data will vary fran circumstance to circumstance, depending on the care, attention, and relative weighting the above factors receive, and on the robustness of the dependent variable. A lively debate on the above would not be beyond the realm of possibility, but it is beyond the scope of this paper.

CHARACTERISTICS OF THE DEPENDENT VARIABLE

Less debatable, perhaps, would be the assertion that the following characteristics of the dependent variable are highly desirable:

a. Low complexity for ease of extraction of single response elements;
b. High sensitivity and selectivity for the drug(s) being studied;
c. Appropriate differential sensitivity to such influences as heat, humidity, pressure, light, sound, diet, exercise, sleep, arousal, and other factors which may themselves be components of the evoking stimulus or of the response;
d. Low between- and within-day random variability ("random" noise) ;
e. Infradian, circadian, and ultradian rhythms (where present) which have been adequately characterized ("periodic" noise); and
f. Derivation directly from the relevant behavior, and presentation in an ecologically valid manner.

Where it is not possible to achieve "f" (above), the dependent variable should probably be derivative of involuntary responses requiring little, if any, subject participation; and in turn, would ideally have been shown on an empirical basis to be sensitive to the drug(s) being investigated in a dose-response manner . Of all the characteristics listed above, "b" and "c" appear to be the most difficult to achieve in reality.

DATA ACQUISITION AND ANALYTICAL GENERALITIES

Much useful pharmacodynamic data can be collected by the use of such instruments as questionnaires, visual analog scales, and a variety of observational techniques using the usual sensory modalities of the observer (vision, hearing, touch, etc.). While, in sane senses, the following comments could be generalized to cover that sort of data collection, they are more specifically focused on data acquired using electronic, optoelectronic, mechanical, and other sorts of transducers. In general, the term "output signal" may be taken to mean a tine-varying electrical event bearing a known or calibrated relationship to changes in the dependent variable. It is not intended in this context to examine the physical characteristics of various transducers; whether they are resistive or capacitive devices; or whether the primary transduction yields current, voltage, or a change in resistance. The “output signal" may be thought of simply as the electrical analog of information which indicates the state of the dependent variable. It is usually a voltage, varying within a range acceptable to the monitoring device.

However generated, output signals should be readily amendable to available signal reduction and analysis techniques. Where copious

information is made available by a particular measurement system, it may need to be "reduced" in quantity by intermittent sampling over time, by electronic preprocessing, or by other techniques--to yield a set of "raw" data which can be accatmwdated by the investigator. "Accommodated" may mean direct analog or digital recording on magnetic tape, temporary residence in a computer's main memory, long-term storage on one of a variety of mass media, or even being directly recorded onto paper as a pen trace or a series of nunbers.

Whenever possible, the raw data should be entered onto/into the storage medium of choice as the experiment proceeds. This will serve to minimize later translational errors, and immediately will create a permanent record of the raw data. It may be desirable to create a "back-up" copy of the original data set, or to copy it in whole or in part to a medium which will facilitate later analysis or re-analysis. While it is often desirable to perform parameter extraction and to produce numerical or graphical sumnaries of results within the time frame of the experiment, a number of precautions need to be observed. Within the limits of the available data storage and retrieval systems, the data should be permanently stored in that state closest to "raw data" which is practical. This facilitates subsequent re-analysis, and may, in the future, permit the use of an analysis technique which was not previously thought of or available. However, in instances where parameter extraction is analytically trivial, proven, and robust, it may be sufficient to store the parameters themselves, or even their summary statistics.

The time frame in which graphical and statistical sumnaries are made available, and the persons who will have access to these data, will depend very much on local circumstances, system capacity, the need for "real-tine" results, and both ethical and scientific propriety.

CHANGES OBSERVED IN THE DEPENDENT VARIABLE

Generally, it should be possible to correlate observed changes in the dependent variable with known indicators of a particular drug's effects, at least for purposes of calibration. A problem arises when there are no other known or accepted indicators. When a new measure of drug effect has been developed which is either more sensitive or selective, this may be ill-advised other than as a means of pointing out differences. Further, the fact that a given measure of drug effect is both well known and well accepted does not *per se* make it valid.

If one is monitoring drug concentrations in the course of a pharmacodynamic experiment, it should be possible to correlate observed changes in drug effect over time with changes in the relevant effective drug concentration. The key word is relevant. The relevant concentration/time profile (corrected for distributional time lags) is that of the compound thought to elicit the particular drug effect (whether receptor-mediated or

not). It may be total plasma concentration of the parent drug whch is in simple and rapid equilibrium with a known site of action. On the other hand, it may be the "unbound" (free) drug concentration distributed across a number of transporting membranes (differentially distributed)-a minute portion of which is actually in dynamic, time-varying equilibrium with a poorly identified, but specific, receptor, which is, in turn, distributed unequally among a variety of sites. A myriad of states of intermediate complexity came to mind. Pharmacodynamic measures of sufficient sensitivity and selectivity would be clearly preferable in the more complex case; and what one would seek is a measure which might be repeated sufficiently often to resolve, in time, the drug's effect (however rapid).

TABLE 1

Examples of Pharmacodynamic Dependent Variables

A) COMPLEX VOLUNTARY
- Autanobile Driving (real)
- Various Task Simulators
- Maze-following Equivalents
- Cognitive Psychometrics
- Affective Psychometrics

B) ENCEPHALOGRAPHIC
- Spontaneous EEG
- Evoked Potentials
  - Cortical
  - Brainstem

C) VISUAL SYSTEM
- Flicker sensitivity
- Pursuit movements
- Vergence movements
- Nystagmus (various)
- Miniature movements
  - Microsaccades
  - Tremor
  - Drift

D) AUDITORY SYSTEM
- Pitch discrimination
- Threshold detection
- Flutter fusion
- Acoustic impedance

E) VOICE ANALYSIS
- Vocal Tremor
- Feature extraction

F) NEUROMUSCULAR
- Tremor measurements
- Standing steadiness
- Reflex kinetics

G) REACTION TIMES
- Various

H) CARDIOVASCULAR
- Heart rate
- Blood pressure
- Photoplythysmography

I) RESPIRATORY
- Respiratory rates
- Carbon dioxide drive
- Respiratory volumes

J) SKIN CHANGES
- Color
- Temperature
- Impedance (GSR)

K) GASTROINTESTINAL
- Bowel sounds

For further discussion of sane of the above variables, the interested reader is referred to Aufdembrinke (1982), Bigler (1977), Grunberger et al. (1982), Itil (1978), Linnoila et al. (1978), and Young and Sheena (1975).

In the real world of the intact human being, one has a limited number of biological fluids in which to measure drug levels (blood, urine, saliva, cerebrospinal fluid, bile, etc.). It is, generally, not possible to measure drug concentration over time in the micro-envirotxnent of the receptor, and the ideal pharmaco-dynamic dependent variable awaits discovery. In the meantime, available samples are taken, and corrections in timing are made to accomodate known pharmacokinetic behavior. Newer nuclear medicine techniques such as positron emission tomography and nuclear magnetic resonance imaging will afford better distributional information; and the search continues for more accurate and more precise noninvasive measures of drug effect with which to correlate this new information. Sane examples of currently available pharmacodynamic dependent variables are listed in table 1.

WHEN PSYCHOACTIVE DRUGS INTERACT

The situation which exists when more than one drug OK substance is active concurrently is somewhat more complex. If no kinetic interaction occurs, and the drugs have distinct and different mechanisms, sites, or time courses of action .(the simplest case), the above principles apply in a fairly straightforward manner. In the slightly more complex case of drugs with similar mechanisms of action, but distinctly different time courses, it is sometimes possible to separate their effects on a pharmacodynamic basis if good kinetic data are also available. Due consideration must be given to the difference between simple additive effects and those which are produced by synergistic drug interaction. The phenomena of cross-tolerance and inhibition further complicate the situation.

Given these complexities, one is, perhaps, well advised to select for investigation drugs whose dynamic and kinetic interaction are particularly illustrative from a mechanistic perspective, or drugs whose interactions pose special hazards for the exposed population. It seems likely that the time is not too far distant when the technical advances of modern noninvasive imaging will greatly increase our ability to produce accurate kinetic models of drug behavior within the CNS. Presently, there are pharmacodynamic probes being developed which have greater precision, speed, and selectivity. Given this convergence, one may reasonably expect that increasing knowledge of the relationship of psychoactive drug kinetics and dynamics will lead to a more perceptive and mechanistically based view of psychoactive drug interactions in general.

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Pharmacokinetic Mechanisms of Ethanol-Psychotropic Drug Interactions

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Given the ubiquitous nature of alcoholic beverages in our culture, ethanol-drug interactions have substantial social importance, With 29% of women and 13% of men in the United States taking prescribed psychotropic drugs (Parry et al. 1973), and a large number of others taking nonprescribed psychotropics. the interaction of ethanol* with psychoactive agents is particularly important. Yet, the different kinds of interactions, their frequency, and the clinical and social impact are not easily studied.

Although the problems of experimental investigatjon are somewhat simplified by a pharmacokinetic/pharmacodynamic division of ethanol-drug interactions, the patterns of alcohol and psychotropic drug intake may confound the findings of even the most carefully designed studies. In designing or evaluating clinical research protocols, it is necessary to consider several factors which have the potential to affect the results and applicability to real life situations. Drug use or alcohol intake may be acute or chronic, and may interact in the clinical situation in any of several ways. An occasional social drinker with the acute onset of stress may be prescribed a bentodiazepine and decide to take it with a cocktail at a social gathering (acute ethanol/acute drug). An alcoholic who has been hiding the severity of the problem from his physician may be prescribed a benzodiazepine for "anxiety" or an antidepressant for "depression" (chronic ethanol/acute drug). Another example is the occasional drinker who is maintained on an antidepressant and after having a cocktail finds the enhanced effects impair his driving ability (acute ethanol/chronic drug). Another common clinical situation is that of the polysubstance abuser with pharmacodynamic and pharmacokinetic interactions'of alcohol and a variety of abused drugs (chronic ethanol/chronic drug).

In addition to duration of drug or ethanol ingestion, other factors such as the types of drugs taken, dosage combinations, routes of administration, pharmacokinetic and pharmacodynamic characteristics of the particular psychoactive agent and ethanol, and the presence of coexisting organic or psychiatric illness also influence the nature and importance of the interaction.

There are several excellent reviews on ethanol-drug interactions (Sellers and Holloway 1978; Linnoila et al. 1979; Weller and Preskorn 1984), and this chapter will not be a repetition of those efforts. Instead, the pharmacokinetic mechanisms of psychotropic drug-ethanol interactions will be discussed and relevant examples cited. It is hoped that this conceptualization will provide a framework for understanding and evaluating the pharmacokinetic mechanisms and clinical significance of ethanol-psychotropicdrug interactions. Although the following discussion will be limited to the effect of alcohol on pharmacokinetic processes, it should be kept in mind that psychotropic medications may in turn alter the metabolism and pharmacologic action of ethanol (Sellers et al. 1972; Mezey 19761.

Pharmacokinetic interactions arise from drug-induced alterations in absorption, distribution, biotransformation, or excretion of another drug. Acute alcohol intake inhibits gastric emptying (Nimmo 1976), resulting in a lag in onset and decreased rate of absorption (MacLeod et al. 1977; Greenblatt et al. 1978). The clinical significance of these findings may not be as great as the acute metabolic effects. Inhibition of "first-pass" effects can result in greater systemic availability.

All orally administered drugs must pass first through the liver before reaching the systemic circulation, so that inhibition of metabolism by acute alcohol would produce greater systemic availability of the drug dose. Acute alcohol intake inhibits demethylation and/or hydroxylation of benzodiazepines, increasing peak plasma levels of most drugs of this class (MacLeod et al. 1977; Laisi et al. 19791. Similar effects are seen when ethanol and amitriptyline are given concurrently (Preskorn and Hughes 1983). Acute alcohol intake increases splanchnic blood flow, irritates the gastric mucosa, and increases motility in the duodenum (Magnussen 1968). Chronic intake results in structural defects in the gastrointestinal tract and changes in enzymatic activity (Findlay et al. 1976). Despite this, there is little evidence to suggest that altered oral absorption is an important mechanism of alcohol-drug interactions, particularly since acute alcohol has been shown to decrease the clearance of intravenously administered drugs, such as diazepam (Sellers et al. 1980a) and lorazepam (Hoyumpa et al. 1981).

Drug distribution is another potential process that can be altered by ethanol. After absorption, a drug is distributed to tissues with high blood flow, such as brain, liver, and kidney, and then to tissues with lower blood flow but higher affinity, such as muscle or fat. Distribution factors are important in terminating clinical action of single doses of such drugs as benzodiazepines or thiopental. For example, despite a shorter elimination half-life, the duration of action of intravenous lorazepam is greater than that of diazepam because of the greater lipid solubility of the latter drug (Arendt et al. 1982).

Ethanol may potentially affect drug distribution by altering membrane permeability, cardiac output, and protein or tissue

binding. Modification of albumin binding sites or alterations in other binding substances (e.g., $alpha_1$-acid glycoprotein), intermediary metabolism, or endogenous substances are potential areas of binding interactions (Sellers and Holloway 1978).

Before discussing any of these problems in any further detail, some basic principles of pharmacokinetics require review.

One of the basic and most important concepts of clinical pharmacokinetics is clearance. It is that pharmacokinetic parameter that relates concentration to the rate of drug elimination. It is expressed as volume per unit time and indicates the volume of blood completely removed of drug per unit time. Total systemic clearance (Cl) is the sum of hepatic clearance (Cl_H) and extrahepatic clearance (Cl_{EH}) (Wilkinson and Shand 1975).

$$Cl = Cl_H + Cl_{EH} \quad (1)$$

When a drug is only eliminated through hepatic metabolism, which is the case for a majority of the psychotropic drugs, then total systemic clearance equals hepatic clearance.

Total systemic clearance can be calculated by one of the following formulas:

$$Cl = \frac{0.693 \cdot V}{t_{1/2}} \quad (2)$$

or

$$Cl = \frac{FD}{AUC} \quad (3)$$

V is the volume of distribution, and t½ is the half-life of elimination determined from the elimination rate constant, K_{el}. FD represents the fraction of the drug dose reaching the systemic circulation and AUC is the area under the drug concentration-time curve. Clearance may also represent loss of a drug across an eliminating organ (i.e., liver) and the equation describing it can be of value in understanding the effects of altered blood flow, plasma protein binding, enzyme activity, and secretory activity on drug clearance.

$$Cl_H = Q_H \cdot E_H \quad (4)$$

Equation 4 demonstrates that hepatic clearance is a function of hepatic blood flow (QH) and the hepatic extraction ratio (EH). The extraction ratio relates the rate of drug extraction to the rate at which a drug is presented to the liver. It can be expressed as:

$$E_H = \frac{^{Cl}int}{Q_H + {}^{Cl}int} \quad (5)$$

where Cl_{int} is the intrinsic clearance, defined as the maximum ability of the eliminating organ (liver) to remove the drug from the blood when there are no flow limitations. Substituting equation 5 into equation 4 gives:

$$Cl_H = \frac{Q_H\ (Cl_{int})}{Q_H + Cl_{int}} \tag{6}$$

Since it is the unbound drug which is available for hepatic elimination, the intrinsic clearance of unbound drug (equation 7) can be substituted into equation 6 to give the hepatic clearance of unbound drug:

$$Cl_{u_{int}} = Cl_{int} / f_B \tag{7}$$

where f_B equals the unbound fraction in the blood.

$$\text{Hepatic Clearance of unbound drug} = \frac{Q_H\ (f_B\ Cl_{u_{int}})}{Q_H + (f_B\ Cl_{u_{int}})} \tag{8}$$

For a drug with a high intrinsic clearance in the liver, the extraction ratio is high and approaches unity, and hepatic clearance approaches organ blood flow (equation 9).

$$Cl_H \approx Q_H \tag{9}$$

These drugs are therefore flow-limited in their clearance. Some psychotropics with high E (>0.7) include desipramine, morphine, meperidine, propoxyphene, and propranolol (Williams and Benet 1982).

For drugs with intrinsic clearance much smaller than liver blood flow, the extraction ratio is low (<0.3) and clearance is considered capacity-limited (equation 10).

$$Cl_H \approx f_B\ Cl_{u_{int}} \tag{10}$$

Low E drugs include amobarbital, phenobarbital, diazepam, chlordiazepoxide, and phenytoin (Williams and Benet 1982).

The effect that alterations in protein binding will have on clearance is dependent on extraction ratio. hanges in protein binding are most important in low E (<0.3) drugs since the clearance of these drugs is dependent on unbound concentration (equation 10). Changes in the protein binding of drugs with in E>0.7 should have little to no effect on clearance since clearance is dependent on blood flow (equation 9). For these high intrinsic clearance drugs, the unbound drug is very rapidly removed from the blood, but the instantaneous association/dissociation of the drug from its binding sites provides a constant source of unbound drug while passing through the liver.

Displacement from binding sites in the bloodcan result in increases in the volume of distribution (V). This can be seen by the following relationship (Wilkinson andShand 1975).

$$V = V_B + V_T = \frac{f_B}{f_T} \tag{11}$$

Where VB equals the volume of the blood, VT equals the tissue volume, f_B is the fraction unbound in the blood, and f_T is the fraction unbound in the tissue. If the unbound fraction in the blood increased, then the volume of distribution would increase. For a drug with an E>0.7, this increase in the volume of distribution will cause an increase in the half-life for elimination of the drug, since:

$$t_{\frac{1}{2}} = \frac{0.693 \cdot V}{Cl} \tag{12}$$

This lengthens the time that the drug stays in the body as well as the amount of time required for achievement of steady state, although time averaged steady-state levels of total drug (bound plus unbound) (Css) should be unchanged (Gibaldi and Koup 1981). Average steady-state levels of unbound drug in blood (Cuss) will be elevated, as can be seen by equation 13.

$$Cu_{ss} = C_{ss} \cdot f_B \tag{13}$$

On single dosing, there will be a longer elimination half-life with lower peak levels of total drug.

On the other hand, an increase in the volume of distribution for a drug with an E<0.3 could be offset by the increase in clearance and have no significant effect on elimination half-life. The increase in volume of distribution and clearance will cause a decrease in average steady-state blood levels of total drug. The average steady-state levels of unbound drug will be unchanged, although within a dose interval there will be fluctuations, including an initial, transient, higher than normal unbound concentration.

Diazepam can be used to illustrate these points. Diazepam has a low E and is highly bound, and changes in protein binding affect its systemic clearance as well as steady-state concentration of total drug (bound plus unbound), but steady-state concentration of unbound drug is relatively unaffected (Sellers et al. 1979; Sandor et al. 1983). For a highly bound, low E drug, alterations in unbound fraction have two important clinical implications (Sandor et al. 1983). First, total drug concentration at steady state may not correlate well with clinical effect. Second, an increase in unbound drug in plasma is associated with a decrease in total drug concentration in plasma as unbound drug enters tissue. There is a transient rise in unbound concentration but a more rapid distribution of drug. The clinical consequences are

the possibility of increased therapeutic or toxic effects early in the dosing interval and diminished therapeutic effect late in the dosing interval. There is no change in the time averaged unbound concentration over the dosing interval, although greater fluctuations are seen.

An increase in the average steady-state concentrations of unbound drug for a drug with E>0.7 could have a greater clinical significance since larger concentrations of the unbound species are available at sites of pharmacological action. Total drug concentration in the blood could, once again, not correlate with the observed clinical effect.

There are relatively few studies of protein binding changes with acute and chronic ethanol administration. In vitro work has shown that chronic ethanol administration can impair synthesis and secretion of proteins and glycoproteins in the liver (Sorrell et al. 1983). Acute ethanol administration in perfused rat liver studies has demonstrated a depression of albumin production (Rothschild et al. 1983). Malnutrition, often found in chronic alcoholics, can also cause hypoalbuminemia (Rothschild et al. 1983). It is known that disease, stress, and trauma can increase levels of $alpha_1$-acid glycoprotein (AGP) (Edwards et al. 1982; Piafsky 1980) which has a strong affinity for basic drugs, but whether it increases with acute ethanol is not known, symptomatic withdrawal from chronic ethanol administration may be stressful enough to cause increases. In a recent study of 15 alcoholics in withdrawal, the unbound fractions of diazepam and propranolol were determined on each of the first 3 days of withdrawal and again between 5 and 7 days postadmission (Sandor et al. 1983). Unbound diazepam fraction was elevated and propranolol unbound fraction was decreased relative to normal values during the first day of withdrawal. Over the 7-day withdrawal period.the diazepam unbound fraction decreased and the fraction of unbound propranolol increased. The mechanism of diazepam binding changes is uncertain, although altered liver metabolism and/or nutritional status may be involved. Levels of free fatty acids, which increase during chronic alcohol consumption (Shaw and Lieber 1976) and are known to displace drugs from binding sites (Sellers et al. 1980b), were only weakly associated with diazepam binding changes. There was an elevation of AGP levels durinq the symptomatic phase of withdrawal and this correlated well with a decreased unbound fraction of the basic drug propranolol (pka = 9.45).

We have examined the protein binding of desipramine and imipramine, two basic drugs that bind to albumin and $alpha_1$-acid glycoprotein. The decreased unbound fraction seen in alcoholics compared to normal controls correlated with increased $alpha_1$-acid glycoprotein (table 1). We did not find hypoalbuminemia in our alcoholics, although it has been observed in alcoholics with liver disease.

TABLE 1

Comparison of Desipramine Protein Binding
in Alcoholics and Normal Controls

	Alcoholics (n=4)		Normals (n=4)	
Free Fraction, %	14.07	1.62	17.15	1.29
Total Protein, g/dl	6.87	0.33	6.98	0.34
Albumin, g/dl	4.63	0.57	4.66	0.14
α_1 -Acid Glycoprotein, mg/dl	107.60	14.66	84.80	2.82

The acute effects of low-dose ethanol are to increase hepatic blood flow by increasing cardiac output, vessel dilation, and splanchnic blood flow (Stein et al. 19631, while acute high-dose ethanol can lower hepatic blood flow by decreasing cardiac output. The effects of chronic alcoholism on liver blood flow are unknown. Although intrahepatic shunting of blood flow has been found in cirrhosis (Groszman et al. 1972), the effects of chronic alcoholism, short of alcoholic liver disease, has not been documented. For drugs with E>0.7, increases in hepatic blood flow result in increased hepatic clearance, while decreases in hepatic blood flow decrease hepatic clearance. Acute low doses of ethanol would be expected to increase hepatic clearance of these drugs, while acute high doses might be expected to reduce clearance. Blood flow changes should not have a significant effect on the clearance of low E (<0.3) drugs.

Alcohol alters drug metabolism through its effects on hepatic biotransformations. The purpose of drug metabolism by the liver is to render lipid soluble (nonpolar) substances into water soluble (polar) derivatives for renal excretion (Hoyumpa and Schenker 1982). Acute alcohol intake usually decreases (by inhibition or competition) drug metabolizing enzymes (i.e., decreases Cl int) (Rubin et al. 1970; Cinti et al. 1973). Barbiturates, benzodiazepines, methadone, and meprobamate are so affected (Hoyumpa and Schenker 1982; Williams and Benet 1982). Chronic alcohol intake increases the activity of a variety of microsomal enzymes, the content of cytochrome P-450, and the activity of NADPH-cytochrome P-450 reductase (Ishii et al. 1973). As a result, in the absence of severe liver damage, metabolism of drugs (Clint) is usually enhanced. Without liver biopsies or pharmacokinetic assessments, it is difficult to predict whether enzyme induction or liver damage will predominate. Chronic.

ethanol consumption enhances the metabolism of chlordiazepoxide, diazepam, phenytoin, imipramine, meprobamate, barbiturates, and others (Sellman et al. 1975; Sandor et al. 1981; Ciraulo et al. 1982; Misra et al. 1971). Chronic ethanol consumption may cause an increase in glucuronidation by inducing glucuronyltransferase (Ideo et al. 1971). On the other hand, acute ethanol consumption was shown to decrease the clearance of lorazepam (a drug eliminated by glucuronidation) by inhibitin UDP-glucuronic acid synthesis (Hoyumpa and Schenker 1982 , In general, cirrhosis tends to impair oxidative metabolism, while it spares or only slightly impairs glucuronidation (Williams and Benet 1982).

The concept of hepatic extraction ratio is important in predicting the effects of metabolism interactions. For a drug with a high extraction ratio, such as propranolol, induction does not affect clearance or half-life, although oral availability is decreased, due to a larger portion of drug being removed in the first pass through the liver before it reaches the systemic circulation. For a drug with a low extraction ratio (e.g., diazepam), enzyme induction results in enhanced clearance and decreased half-life. The extraction ratio of imipramine is intermediate (about 0.65). Enzyme induction, as occurs with chronic alcoholism, enhances metabolism of imipramine. Figures 1 and 2 show the semilogarithmic plots of plasma concentration versus time in a representative alcoholic and a normal control given single intravenous and oral doses of imipramine (Ciraulo et al., unpublished data). Oral availability was lower for the alcoholic subject. The alcoholic had enhanced clearance and a shorter elimination half-life (table 2).

TABLE 2

Pharmacokinetic Parameters for Imipramine in a Representative Alcoholic and Normal Control

Parameters	Imipramine			
	50 mg P.O.		12.5 mg IV	
	Alcoholic	Normal	Alcoholic	Normal
Clearance, L/hr/kg	2.28	1.26	0.94	0.65
Elimination Half-life, hr^{-1}	7.79	15.64	12.00	16.81
AUC, ng · hr/ml	261.00	446.00	156.00	206.00
Vol. of Distribution, L/kg	25.60	28.44	15.40	15.69
Free Fraction, %	16.40	16.11	17.41	17.06

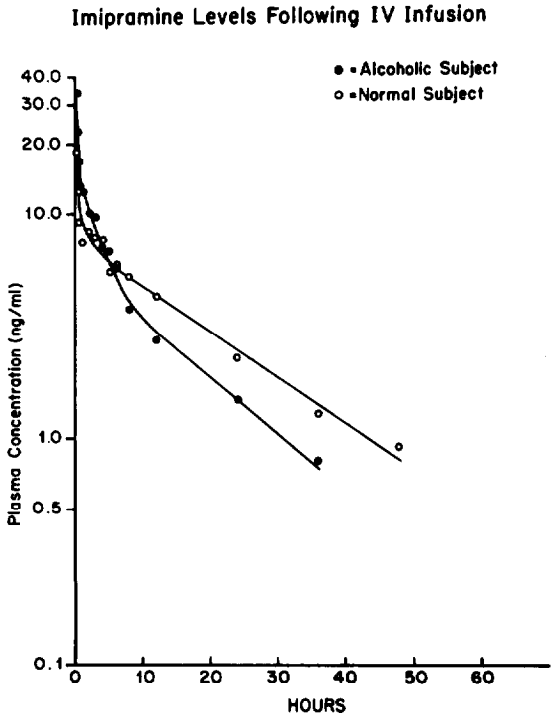

FIGURE 1

Plot of imipramine plasma concentrations following an IV infusion of a 12.5 mg dose. The solid line represents the computer generated curve.

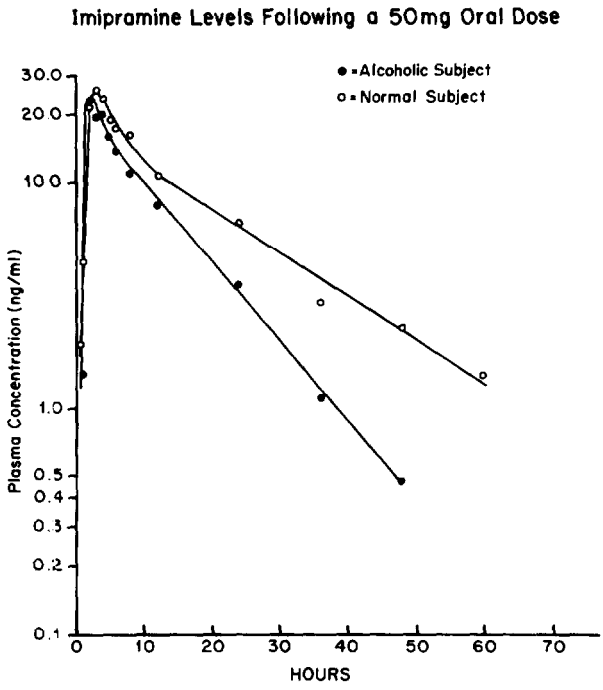

FIGURE 2

Plot of imipramine plasma concentrations following a 50 mg oral dose. The solid line represents the computer generated curve.

Chronic dosing studies show that steady-state levels of imipramine and its metabolites are lower in depressed alcoholics compared to nonalcoholic depressed patients (Ciraulo et al. 1982) (table 3). A standard 150 mg dose of imipramine given to alcoholics yields a mean steady-state concentration well below what many consider to be a minimum effective therapeutic level (Ciraulo and Jaffe 1981). Clearance of desipramine is enhanced in alcoholics when given intravenously (Ciraulo et al., unpublished data). Although there is also a trend for enhanced clearance of oral and intravenous desipramine (Ciraulo et al., unpublished data), there is such great variability that differences are not statistically significant. The reasons for this are unclear, although such factors as enterohepatic recycling and genetic variability in hydroxylation capacity may be involved.

Contrary to our findings with antidepressants, we have preliminary evidence that hydroxylation of alprazolam, a triazolobenzodiazepine, is inhibited in acute alcohol withdrawal. Figure 3 presents data from a multiple dose study in which panic disorder patients, two of whom were alcoholics, received three different dosing regimens of the drug. The alcoholic patients had impaired clearance, higher steady-state plasma concentrations, and more drug-related side effects as compared to nonalcoholics. The

TABLE 3

Plasma Levels (ng/ml) of Imipramine and Its Metabolites 8 Hours After the Last Dose[a]

	IMI	% free	DMI	% free	2-OH-IMI	2-OH-DMI	Total Tricyclic Species
Alcoholics							
Mean	50*	11.0	84	13.1	12.8**	15.9	156***
SD	41	2.7	75	1.0	7.5	9.1	76
N	11	10	11	10	11	11	11
Controls							
Mean	106	10.8	93	12.1	22.6	24	234
SD	46	1.1	53	1.1	9.8	12.6	96
N	12	11	12	9	10	11	10

[a]IMI=imipramine; DMI=desipramine; 2-OH-IMI=2-hydroxyimipramine; 2-OH-DMI=2-hydroxydesipramine; SD=standard deviation. *$p<0.005$, **$p<0.01$, ***$p<0.05$ (significance level using unpaired *t* test).

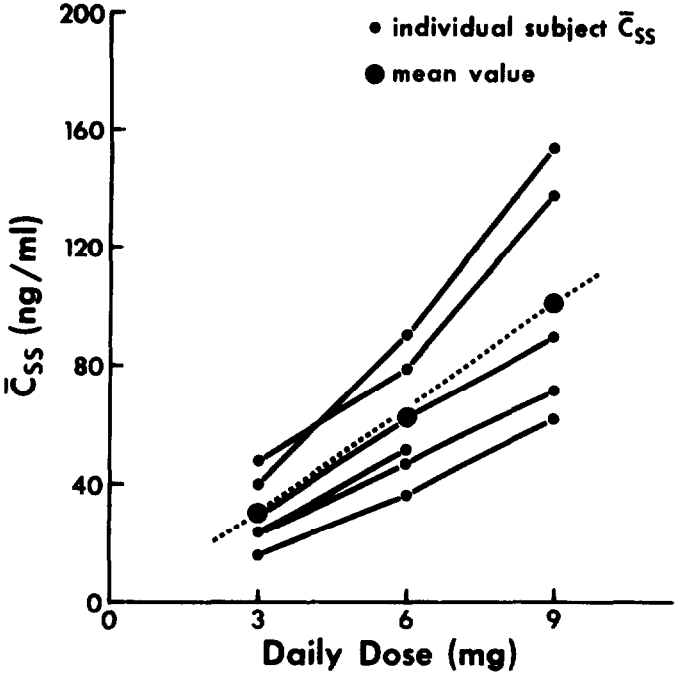

FIGURE 3

Mean steady-state alprazolam plasma concentration versus daily dose of alprazolam for six subjects. The two uppermost lines represent data from two chronic alcoholics (nondrinking). The four lower lines represent data from nonalcoholic subjects.

number of subjects is too small for meaningful statistical comparisons, but the clinical differences were dramatic. If these findings are substantiated in a larger number of subjects, it would suggest that not only are different oxidative processes (e.g., demethylation, hydroxylation) altered differentially as a result of chronic alcoholism, but also that drugs metabolized by the same biotransformation reaction (i.e., hydroxylation) may be affected differently by chronic ethanol consumption. Both desipramine and alprazolam are hydroxylated, yet in chronic alcoholics,clearance of the former drug is slightly enhanced or unchanged while that of the latter is impaired.

For those drugs with an intermediate extraction ratio, there will be a combination of effects caused by blood flow changes, intrinsic clearance changes, and alterations in protein binding. Only careful experimentation can show which change or combination of changes will predominate.

SUMMARY

Acute and chronic ethanol consumption alters psychotropic drug pharmacokinetics. An understanding of the processes of drug absorption, distribution, biotransformation, and elimination provide a rational basis for predicting and evaluating drug interactions. Careful application of clinical pharmacokinetic models describing these physiological processes are particularly appropriate for the task of understanding drug and alcohol interactions.

(1) Absorption. (a) Acute alcohol inhibits first-pass effect increasing systemic bioavailability. (b) Ethanol inhibits gastric emptying and may delay drug absorption (increase lag time of absorption) and decrease the rate of absorption. (c) The effects of chronic alcohol intake are unknown.

(2) Distribution. (a) Hypoalbuminemia may be present in alcoholics with liver disease. (b) Fluctuations in free fractions of drugs may occur in the alcohol withdrawal period. The clinical effects of protein binding changes are dependent on degree of binding, hepatic extraction ratio, and binding protein. (c) Acute low-dose ethanoi increases hepatic blood flow while high doses decrease it. The effects of chronic alcohol intake on liver blood flow are unknown. Hepatic blood flow changes show the greatest effects on drugs with high extraction ratios.

(3) Metabolism. (a) Acute alcohol ingestion usually inhibits drug metabolism and chronic intake (in the absence of severe liver disease) enhances metabolism. (b) Cirrhosis impairs oxidative metabolism, but spares glucuronidation.

Although these generalizations may serve as useful guidelines for predicting alcohol and psychotropic drug interactions, they should be applied with caution as exceptions do exist.

FOOTNOTE

[1]The terms alcohol and ethanol are used interchangeably.

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Complex Interactions Between Drugs and Dietary Factors

Elliot S. Vesell, M.D.

Multiple dynamic interactions occur among host factors that affect drug response (figure 1); these host factors and their interactions are responsible for large interindividual variations in drug disposition (Vesell 1982, 1984b). The critical role in drug disposition played by host factors depicted in figure 1, and by dynamic interactions among them, is insufficiently appreciated. Too often, patients are incorrectly treated as being equivalent to one another and unchanging with respect to their dosage requirements. Too few physicians recognize that a particular patient's dosage requirements can change with an alteration in even one of the host factors shown in figure 1. Thus, in a given patient, a dose of a particular drug that is therapeutic at one time may become either toxic or ineffective at another time. As more active drugs with lower therapeutic indices are marketed, physicians must individualize drug dosage according to the special and changing requirements of each patient.

Diet is a multifaceted, complex host factor that can alter drug response by changing several pharmaookinetic parameters (figure 1). The human diet is highly heterogeneous in its preparation, chemical composition, volume, and times of consumption (figure 2). Accordingly, dietary effects on drug kinetics vary widely in subjects of different age, sex, socioeconomic status, ethnic background, and geographic region. Indeed, these effects can vary in the same subject over time and seasons as changes occur in his or her dietary habits. Now, as a result of numerous studies on food-drug interactions, several fundamental principles have emerged, as well as certain problems whose resolution requires more investigation and fresh insight. This review identifies several of these problems and offers approaches to their solution.

MAGNITUDE OF INTERINDIVIDUAL VARIATION IN DRUG RESPONSE

Normal subjects exhibit large interindividual variations in pharmacokinetic values when the same drug in the same dose is administered by the same route to different normal adult male or

female subjects under similar environmental conditions. Table 1 shows that the magnitude of these interindividual pharmacokinetic variations commonly ranges from threefold to elevenfold, depending both on the drug and the population studied. Figure 1 identifies 27 different host factors that can cause large variations among subjects in rates of drug elimination. Since some of these host factors--including genetic constitution, diet, exposure to numerous drugs, and other environmental chemicals--are broad in scope, many additional specific items could be listed under each factor. These and other host factors shown in figure 1 primarily influence hepatic drug-metabolizing enzyme activity (HDMEA), although effects on drug absorption, distribution, and excretion can also occur. Since large interindividual pharmacokinetic variations persist even when the other factors shown in the outer circle of figure 1 are held constant, these large interindividual variations, existing in normal subjects maintained under similar environmental conditions, arise mainly from genetically controlled differences in HDMEA (Vesell and Penno 1983).

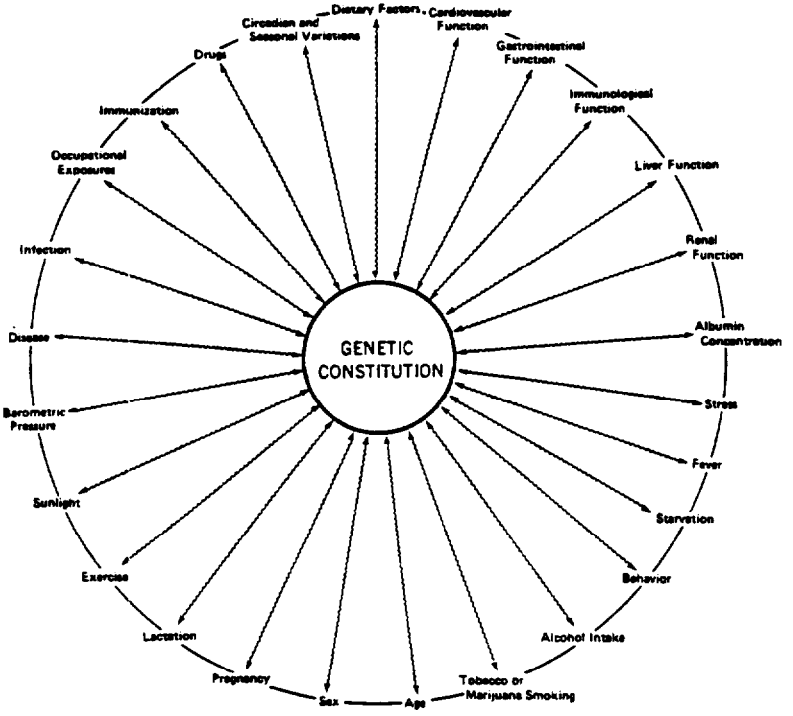

FIGURE 1

This circular design suggests the multiplicity of either well-established or suspected host factors that may influence drug response in man. A line joins all such factors in the outer circle to indicate their close interrelationship. Arrows from each factor in the outer circle are wavy to indicate that effects of each host factor on drug response may occur at multiple sites and through different processes, including drug absorption, distribution, metabolism, excretion, receptor action, and combinations thereof.

DIETARY FACTORS THAT AFFECT DRUG RESPONSE

This review focuses on complex, multifaceted effects of dietary factors on drug response. Most studies designed to identify the influence of dietary factors have had to explore each dietary factor in isolation from additional dietary factors and from other host factors shown in figure 1. However, in the real world, many of these dietary factors can and do interact with each other. The extent and nature of such interactions among dietary factors and also between dietary factors and other host factors need to be explored and defined. Figure 2 suggests the extensive potential for dynamic interactions among dietary factors.

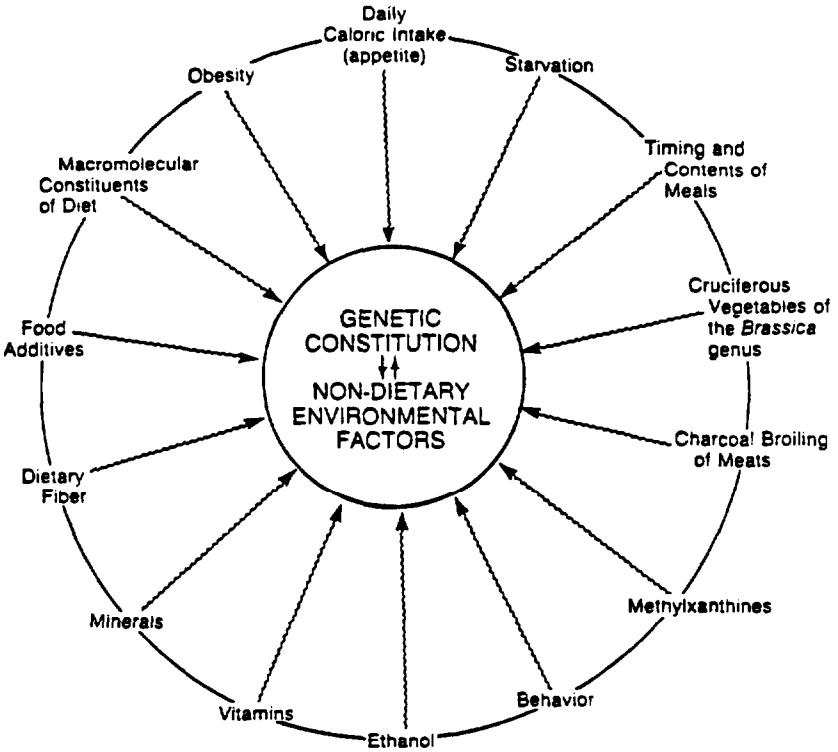

FIGURE 2

This circular design suggests the possibility of dynamic interactions among the several well-established or suspected dietary factors that may influence drug response in humans. Arrows from each factor in the outer circle are wavy to indicate that effects of each dietary factor on drug response may occur at multiple sites and through different processes. The inner circle suggests that effects of dietary factors may be modified by many other environmental factors, as well as by genetic factors.

Table 1. lnterindividual variations in plasma half-lives of drugs metabolised by hepatic detoxifying enzymes

Drug	Plasma half-life (hours)	Factor of variation	No. of individuals investigated
Aminopynne	1.1-4.5	4	12
Amylobarbitone	1.4-6.4	5	14 pairs of twins
Antipyrine	5-35	7	33
Carbamazepine	18-55	3	6
Diazepam	9-53	6	22
Dicoumarol	7-74	11	14 pairs of twins
lndomethacin	4-12	3	15
Nonripryline	15-90	6	25
Phenylbutazone	1.2-7.3 days	6	14 pairs of twins
Phenytoin	10-42	4	86
Primidone	3.3-l6.2	5	46
Theophylline	4-18	5	45
Tolbutamide	3-27	9	50
Wartarin	15-70	5	40

As documented abundantly for such drugs of abuse as alcohol, marijuana, cocaine, and heroin (DuPont 1976), drugs of abuse are rarely used singly; rather, they are taken in various combinations. Such multiple drug use by an individual enhances opportunities for pharmacokinetic and pharmacodynamic interactions between these drugs and numerous host factors shown in figure 1 (Braude and Vesell 1976). The role of dietary factors in affecting potential interactions among drugs of abuse themselves and other host factors has been neither widely recognized nor Investigated. Hopefully, this review (Vesell 1984b) will serve to focus attention on such interactions.

EFFECT OF FOOD ON ABSORPTION OF ORAL DRUGS

Figure 2 suggests not only that many dietary factors can interact with each other to lnfluence drug disposition, but that each can also affect drug disposition at several discrete sites, including sites of drug absorption, distribution, metabolism, and excretion. This section deals mainly with effects of food on absorption of drugs taken by mouth. For decades, eating has been recognized to of fact drug response, and patients have long been aware that taking some medications with meals reduces gastrointestinal side effects.

The general outcome of taking medication with meals is a retarded rate rather than an altered total amount of gastrointestinal drug absorption. Retardation of the gastrointestinal absorption rate of drugs occurs mainly because meals slow gastric emptying. Meals can increase, decrease, or be without effect on the absolute systemic availability of a drug (Welling 1977). For the relatively few drugs whose gastrointestinal absorption increases after meals--griseofulvin (Crounse 1961; Kabasakallan et al. 1970), lithium (Jeppson and Sjogren 1975), nitrofurantoin (Bates et al. 1974; Reidenberg and Vesell 1975), diazepam (Korttila and Kangas 1977; Korttila et al. 1976), and riboflavin (Jusko and Levy 1967; Levy and Jusko 1966)--explanation is offered "in terms of delayed gastric emptying and gastrointestinal transit which allows more complete dissolution or prolonged residence at a site in the intestine from which absorption is optimum" (McLean et al. 1978).

Divergent effects of meals on drug disposition depend on the pharmacologic profile of the drug, its formulation, and the composition and size of the meal. Excellent reviews (Melander and McLean 1983; Welling et al. 1975) of the effeots of meals on drug absorption obviate detailed discussion here. Only the pharmacologic principles that determine the results of these food-drug interactions will be described. Application of these principles requires recognition that food-drug interactions may be markedly modified by numerous host factors, such as age and general condition of the patient; cardiovascular, hepatic, and renal function; intercurrent diseases; and whether the patient is ambulatory or bedridden (Welling et al. 1975). The appreciable influence of numerous host factors (rarely defined adequately in individual studies on this subject) may explain frequent inconsistencies in the literature.

Two pharmacologic principles determine how food affects drug absorption from the gut. Food enhances gastric blood flow but retards gastric emptying. Since the rate of diffusion of a chemical across a capillary is a function of its concentration gradient across the capillary membrane, meal-induced increases in splanchnic blood flow should accelerate drug absorption from the gut lumen to the capillary. Complexity in practical application of this seemingly simple principle arises from the fact that the effect on blood flow depends greatly on meal content, i.e., chemical composition of the food. Blood flow can be doubled by a high-protein liquid meal and slightly reduced by a liquid glucose meal (Brandt et al. 1955). Effects of meal-induced enhancement of splanchnic blood flow on drugs with high hepatic extraction are of special significance and are discussed separately below.

The second fundamental principle is that meals slow the rate of gastric emptying, thereby delaying rate of drug absorption from the gastrointestinal tract. The influence of this factor on rate of drug absorption is more complicated than might be suspected. Changes in gastric emptying depend not only on the type of drug, but also on the type of meal, as different foods have different effects on gastric emptying. Delayed emptying is caused by hot

meals (Davenport 1961), solutions of high viscosity (Levy and Jusko 1965), fat, and, to lesser extents, by proteins and carbohydrates (Bachrach 1959). Compared to liquid meals, solid meals almost double emptying time of the stomach (Marcus and Lengemann 1962).

Complexity is further increased because the nature of the drug under consideration can modify this effect. Pharmacologic properties of drugs that influence absorption from the gut and, thus, cause variable effects on gastric emptying include solubility and stability in the highly acidic gastric juices as well as the llpophilic character of the dissolved drug molecules, e.g., whether the drug is ionized (thus, relatively resistant to passage) or not ionized (hence, readily traversing lipid membranes) at gastric pH. The Important role of pH in drug absorption is illustrated by the effect of antacids in altering rate but not extent of diazepam absorption (Greenblatt et al. 1978).

After passage from the stomach to the small intestine, food stimulates intestinal motility, thereby accelerating dissolution of solid particles. Food also simultaneously decreases passage of drugs from diffusion across intestinal mucosa by accelerating their motion through the intestine. Further complication arises from the fact that some foods, especially fat, stimulate bile flow and secretion. As surface-active agents, bile salts enhance dissolution of poorly soluble drugs, thereby accelerating drug absorption (Gibaldi and Feldman 1970). On the other hand, bile salts can impede absorption by forming insoluble complexes with other drugs (Bates and Gibaldi 1970).

The pharmacologic character of the drug determines the precise proportion absorbed in the stomach and in the small intestine. In general, relatively little drug absorption occurs in the stomach as compared to that in the small intestine, because of greater surface area in the latter. By retarding stomach emptying, food delays drug absorption, which takes place mainly in the small intestine. Particular pharmacologic properties, such as weak basicity or transportation by active carrier mechanisms, render some drugs more likely than others to be absorbed in the small intestine. Thus, complex characteristics of the patient, drug, food, and physiologic mechanisms of gastrointestinal absorption render difficult predictions and interpretations of how meals ultimately influence drug absorption in a given patient at a given time.

This section concludes with an illustration of a problem associated with literal interpretation of principles governing the influence of enhanced gastric blood flow on drug absorption. Let us consider model drugs with high intrinsic clearance. Several investigators have reported that meals elevated plasma concentrations of such drugs subject to extensive first-pass effect, including propranolol (McLean et al. 1981; Melander et al. 1977), metoprolol (Melander et al. 1977), and lidocaine (Elvin et al. 1981). After high protein meals, the increase in oral

bioavailability of drugs subject to large first-pass effect has been attributed to the enhanced hepatic blood flow associated with such meals. The area under the curve (AUC) after intravenous (i.v.) dosing is decreased for such drugs, while it is increased after oral dosing; the kinetic basis for this difference has been reported (Elvin et al. 1981).

Enhanced blood flow presumably serves to allow such high-extraction drugs to pass rapidly through the liver, thereby escaping hepatic removal and causing higher drug concentrations in systemic circulation. Lidocaine kinetics were evaluated thoroughly before and after a meal; enhanced systemic bioavailability of oral lidocaine after a meal was attributed entirely to transient food-induced elevations in rate of perfusion of the splanchnic vascular bed (Elvin et al. 1981). Whereas alterations in rates of hepatic lidocalne metabolism or of protein binding of lidocaine could hypothetically have induced similar results, Investigation of these possibilities indicated that these measures did not ohange after meals. Thus, alteration in hepatic blood flow was induced by food alone (Elvin et al. 1981). Several recent studies, however, offered a different view. A thorough computerized simulation performed to predict the magnitude of change that meals produce in apparent oral bioavallability of propranolol revealed that the meal-induced increase in hepatic blood flow was of too short a duration to explain the extent to which the bioavailability of an oral dose of propranolol rose (Svensson et al. 1983). The authors concluded that "the effect of food on drug metabolism appears to be a complex and time-dependent process requiring further investigation." In another investigation, they tested their conclusion by measuring clearance of indocyanine green given i.v. before and after a high carbohydrate meal in six normal subjects (Svensson et al. 1984). Again, they concluded that the meal-induced Increase In hepatic blood flow probably made only a very small aontribution to the increase in propranolol bioavailability (Svensson et al. 1984). Related observations on altered aminopyrine disposition after meals have been reported by Shively et al. (1981). In normal men, aminopyrine t 1/2 was 34% longer acting and apparent volume of disposition was 33% larger 3 hours after meals than during fasting. Plasma protein binding of aminopyrine was reduced by meals, explaining in part the meal-induced increase in aminopyrine apparent volume of disposition. Melander and McLean (1983) thoroughly and critically reviewed the influence of food on the presystemic clearance of drugs. Meals commonly accelerate presystemic clearance of lipophilic bases (such as propranolol and amitriptyline), but rarely alter that of lipophylic acids (such as sallcyllc acid and penicillin), although esters of such acids (acetylsallcylic acid and pivampicillin) are subject to this meal-induced effect (Melander and McLean 1983). See Helling (1984) for the most recent review on effects of meals on gastrointestinal absorption of drugs.

DIETARY FACTORS THAT AFFECT DRUG METABOLISM

Pioneering experiments demonstrated that several discrete dietary factors could alter the rate of drug metabolism and produce clear results that have frequently been reviewed (Anderson et al. 1982; Conney et al. 1977, 1980; Kappas et al. 1977; Vesell 1980). They need only be summarized here. Antipyrine, theophylline, phenacetin, and acetaminophen served as model drugs in these studies. Carefully selected normal subjects received an oral dose of one of these drugs before, during, and after a single dietary manipulation lasting 3 to 14 days. All other environmental factors during the studies were controlled as rigidly as possible. The present inquiry will focus on the question of how much these and related dietary factors contribute to large interindividual variations in rates of drug metabolism.

Results of these studies showed that: 1) On a dally diet of 2,500 calories, a high ratio of protein (44%) to carbohydrate (35%) content enhanced antipyrine and theophylline metabolism, whereas a high ratio of carbohydrate (70%) to protein (10%) content retarded their biotransformation (Kappas et al. 1976). Substitution of fat for carbohydrate did not significantly change these results (Anderson et al. 1979), which recently were extended from an entirely oral route of dietary intake to a completely i.v. one (Vesell 1984a). 2) Ingestion of charcoal-broiled beef increased the rate of antipyrine and theophylline metabolism (Kappas et al. 1978), but not that of acetaminophen (Anderson et al. 1983). The rate of biotransformation of phenacetln was not changed, although charcoal-broiled beef induced a large first-pass effect, thereby appreciably reducing plasma phenacetin concentrations (Conney et al. 1976). 3) Cruciferous vegetables in large amounts induced the metabolism of antipyrine and theophylline (Pantuck et al. 1979) and the glucuronidation of acetamlnophen (Pantuck et al. 1984a). 4), Theobromine acetate in high concentrations retarded its rate of biotransformation (Drouillard et al. 1978). Theobromine is a major constituent of chocolate, and the same dose of theobromine taken in chocolate rather than as the salt did not alter its metabolism, presumably because of its reduced bioavailability In chocolate. 5) Starvation of obese subjects for 10 days did not alter antipyrine or tolbutamlde disposition (Reidenberg and Vesell 1975), but antipyrine metabolism was impaired in Indian (Narang et al. 1977) and Sudanese (Homeida et al. 1979) children with protein malnutrition. Nutritional rehabilitation of these children restored antipyrine kinetics to normal. A few of the factors shown in the outer circle of figure 2 have not been studied in man; but in laboratory animals, they have been shown to affect drug metabolism and disposition.

TO WHAT EXTENT DO DIETARY FACTORS CONTRIBUTE TO INTERINDIVIDUAL VARIATIONS IN DRUG METABOLISM?

The preceding studies, each performed on a different dietary factor, were carefully controlled: only a single dietary variable was altered independently of all others. Furthermore, subjects were selected so that their hepatic cytochrome P-450-dependent monooxygenases would be under stable, near-basal conditions

(neither markedly induced nor Inhibited through the potential influence of numerous environmental perturbations) (Anderson et al. 1982; Conney et al. 1977, 1980; Kappas et al. 1977; Vesell 1980, 1982). None of the subjects took any drug regularly, smoked cigarettes, or drank alcohol chronically. A single dietary manipulation could be Introduced under these well-defined, uniform environmental conditions. Any alteration in rate of metabolism of a model drug (such as antipyrine) or the theophylline aould serve as a reliable, sensitive index of the effect of that specific nutritional change on the subject's hepatic drug-metabolizing capacity. Use of each carefully selected subject as his or her own control eliminated not only all genetia but also most extraneous environmental sources of variation in drug metabolism. Therefore, alteration observed in disposition of a model drug after imposition of a single dietary manipulation could reasonably be ascribed to that nutritional change alone. Furthermore, this experimental design permitted results to be verified in several ways. The effect could be reproduoed in the same or in other subjects. Dose-response relationships could be generated between the particular dietary factor investigated and subsequent change in model drug metabolism.

How far can these well-established, verified results on dietary faators in normal subjects under near-basal aonditlons be extended to other more complicated dynamic ciraumstanaes, such as those prevailing among patients whose environments may be rapidly changing in complex ways? What portion of total interindividual variation among such patients, and among normal subjects with unrestricted lifestyles, can be attributed to dietary factors? These difficult questions cannot be answered simply. Complex interactions between numerous factors probably explain the totality of interindividual variation that occurs in rates of drug metabolism among all subjects. In some individuals, dietary considerations may play a major role, as as can smoking, age, and genetic factors; or, several factors may share equally or interact with these and additional factors to account for variability.

This discussion emphasizes the complexity of interactions that may occur when all subjects are included. Interactions can take place not only among different types of environmental factors, but also among dietary factors themselves (figure 2). Therefore, the magnitude of alteration in drug metabolism lnduaed by manipulation of only single dietary faotors in subjects under carefully controlled environmental conditions needs to be compared to the magnitude of total interindividual variation in rates of metabolism of the same model drugs before imposition of any dietary change. Since several dietary alterations can ahange a subject's rate of drug metabolism, It might be expected that these dietary factors account for a large proportion of the extensive variation among normal subjects. The latter, however, does not necessarily follow from the former well-established observations, and It remains to be determined whether such extrapolations are valid.

With respect, to changes in antipyrine and theophylline metabolism after imposition of diets high in cruciferous vegetables and charcoal-broiled beef, relatively small alterations (10% to 20% of basal) are caused by these dietary manipulations. Such changes are an order of magnitude less than those observed among normal, carefully selected subjects of the same age and sex, who use no drugs, are nonsmokers, and are not excessive users of alcohol (Penno et al. 1981; Penno and Vesell 1983). Alvan (1978) doauments 600% interindividual variation in antipyrine clearance in a representative number of subjects. Hence, these particular dietary factors might initially appear to play only a very small role in accounting for the 600% interindividual variation in antipyrine metabolism among normal subjects under basal environmental conditions. Although each factor may play a small role by itself, a much larger synergistic effect could emerge in combination with other factors. Figure 2 was designed to suggest this possibility and shows each dietary factor in dynamic interaction with other dietary as well as environmental and genetic factors.

While the magnitude of metabolic change contributed by large shifts in the proportion of protein to carbohydrate content on an isocaloric diet is larger than that of diets high In cruciferous vegetables, It is still considerably less than the 600% interindividual variation that is common when antipyrine kinetics are compared in at least 12 normal subjects (Alvan 1978; Penno et al. 1981; Penno and Vasell 1983). Here again, It might initially appear that even a very marked manipulation in the ratio of protein to carbohydrate content might be insufficient to contribute substantially to the much larger interindividual variations among normal subjects in rates of drug metabolism. Superficially, such a conclusion might seem to be supported by the observation of no change in antipyrine clearance after starvation of obese subjects.

Studies on starvation, however, are compatible with a major effect of changing the proportion of the macromolecular constituents of isocalorlc diets. This reconciliation of seemingly contradictory results offers an opportunity to stress the complex effects of several dietary factors and the possibility for interactions among them. Why doesn't starvation change antipyrine metabolism, when switching the proportion of carbohydrate to protein aontent alters antipyrine metabolism profoundly? Possibly, the body is more sensitive to the former dietary manipulation than to the latter. Through detection of the gross diet change from starvation for a limited time, the body can compensate by providing the amino acids required for protein synthesis from another source. In contrast, the body may not be able to detect and, hence, compensate for a much more subtle switch in the proportion of calories supplied as either carbohydrate or protein. If this change is uncompensated, depletion of protein could reduce rates of synthesis of hepatic drug-metabolizing enzymes, which, in turn, could induce retention of antipyrine and theophylline.

Although fasting greatly alters hepatlc metabolism of some drugs in rodents (Dixon et al. 1960; Furner and Feller 1971; Kato and Gillette 1965), no change in drug metabolism occurred in obese, but otherwise healthy, human subjects after 7 to 10 days on a diet in which total daily carbohydrate intake was under 15 g (Reidenberg and Vesell 1975). This diet induced ketoaaldosls and weight loss ranging from 4 to 15 kg. When uncorrected for body weight, the apparent volume of distribution of both antipyrine and tolbutamlde was lower after fasting than before, presumably because, during fasting, the early loss of body weight is mainly from body water rather than from fat stores or muscle mass (Reidenberg and Vesell 1975). In each subject, the extent of decrease in the apparent volume of distribution was proportional to loss of body weight; and when correction was made for body weight, fasting had no effect on apparent volume of distribution of either antipyrine or tolbutamide. These results, extended to other hepatic microsomal oxidations, Including those for sulfisoxazole, isoniazid, and procaine (Reidenberg 1977), disclosed that, when allowance was made for body weight, neither half-life values nor rates of hepatia metabolism of these drugs changed in otherwise normal obese subjects who fasted 7 to 10 days. Several reviews that describe effects of obesity on drug disposition suggest that volumes of distribution of certain drugs are increased in obesity. The extent of this increase appears to correlate with the lipid-solublllity of the drug (Abernathy and Greenblatt 1982; Abernethy et al. 1984).

General conclusions on the failure of absolute fasting to alter hepatlc drug metabolism in normal subjects or in subjects without liver dysfunction were extended by a study of seven female subjects, which confirmed classic anorexia nervosa (Bakke et al. 1978). In these subjects, prolonged refusal to eat induced differing degrees of dehydration, hyponatremia, hypoahloremia, hypokalemia, and anemia. When compared with age- and sex-matched normal nurses who served as aontrols and when values were corrected for body weight, the subjects with anorexia had normal antipyrine kinetics.

A study on Asian Indian subjects (Krishnaswamy and Naidu 1977) revealed that in 15 men suffering from nutritional edema--a severe manifestation of protein deficiency and resultant hypoalbumlnemia --the mean plasma antipyrine half-life of 12.8 hours did not differ from that of age- and sex-matched nonsmoking controls (11.2 hours), but it was higher than that of age- and sex-matched smoking controls (8.9 hours). In the same study, another group of 13 undernourished, underweight men without edema had a short mean antipyrine half-life of 8.6 hours (same range as that of smoking controls); this could be because some of these 13 subjects smoked, some drank alcohol, and some were agricultural laborers exposed to pesticides known to induce hepatic drug-metabolizing enzymes. Thus, in this study, severe malnutrition did not alter antipyrine disposition, supporting observations already described for subjects with anorexia nervosa and for obese, but otherwise normal, subjects after a fast of 7 to 10 days. Several problems, however, including chronic exposure of some subjects to inducing chemicals, render the results inconclusive.

In a significant contribution, phenylbutazone kinetics were measured in four normal male Asian Indian controls (mean age, 30 years) and in five undernourished male Asian Indian subjects with hypoalbuminemia (mean age, 36 years), none of whom smoked cigarettes or consumed alcohol for prolonged periods (Adithan et al. 1978). The malnourished group had shorter mean plasma phenylbutazone half-lives, but larger mean phenylbutazone apparent volume of distribution and metabolic clearance, than did the controls. These deviations in phenylbutazone disposition in undernutrition presumably arose as a result of reduced binding of phenylbutazone to albumin, with a corresponding increase in drug availability for metabolism and elimination.

A STATISTICAL APPROACH TO DETERMINE CAUSES OF LARGE INTER-INDIVIDUAL VARIATIONS IN DRUG METABOLISM RATES

Isolation and investigation of each environmental factor Independent of all others and under rigidly controlled conditions offer advantages enumerated above. Nevertheless, as we have also seen, this method does not permit easy extrapolation to a different circumstance and a different question: How much of total extensive interindividual variation in drug metabolism in a large population under nonbasal conditions oan be accounted for by each dietary factor alone?

Statistical approaches to this question have been attempted. In gathering 128 factory workers in London, investigators deliberately chose subjects with different environments (Fraser et al. 1979). Antipyrine was then given onoe to each of these subjects. A computerized program based on multiple regression analysis was used to relate antipyrine clearance of each subject to numerous anthropometric and biochemical indices of nutritional status. Five variables correlated independently with antipyrine clearance: race, contraceptive pill usage, smoking status, ponderal index (weight/height^2), and serum albumin concentration (Fraser et al. 1979). Because coefficients for race and diet were virtually identical, the investigators concluded that it was impossible to analyze the role of one factor independently of the other. Most of their Asian Indian subjects were vegetarians, whereas almost all of their population of white Londoners ate meat; furthermore, many were subject to such additional environmental perturbations as cigarette smoking and oral contraceptives.

Recognizing that reliable conclusions regarding the role of dietary factors in large interindividual variations in antipyrine kinetics were impossible in this mixed and, hence, hopelessly confounded experimental situation, the investigators decided to apply their statistical method to another group of less confounded subjects. The second group was considered more amenable to investigation by multiple regression analysis because it was racially homogeneous. Subjects in the second study were 36 healthy adult Indo-Pakistani immigrants to Britain. Among these subjects, antipyrine clearance was much slower in the 16 lactovegetarians (0.54 ± 0.06 ml min^{-1} kg^{-1}) than in the 20 regular

meat eaters (0.91 ± 0.07 ml min^{-1} kg^{-1}) (Mucklow et al. 1982). Since absence of meat from the diet was associated with a significantly smaller daily intake of dietary protein (which, in the 16 lactovegetarians, was abnormally low by Western standards), Mucklow and coworkers concluded that this difference in daily protein intake was the principal cause of differences in antipyrine clearance,

The investigators recognized, however, that their methods are open to criticism. For example, Mucklow et al. (1982) state: "Retrospective dietary assessments made at a single interview, even when this is conducted by an experienced dietician, are open to criticism since they rely heavily upon the memory of the subject interviewed, the estimates of quantity made by the dietician, and subsequent expression of those quantities in mass units. The opportunity for error is clearly increased when the interview is conducted through an interpreter." The 16 lactovegetarians had high standard deviations in mean antipyrine clearance. This extensive interindividual variation in antipyrine kinetics within a population uniform with respect to low protein intake clearly must arise from other factors. The investigators also attempted to identify some alternative sources for these interindividual variations: "significant correlations occurred between antipyrine clearance and age, sex, religion, smoking, hemoglobin, kilocalories, carbohydrate, and fat. No significant correlation was observed between antipyrine clearance and weight, coffee/tea index, alcohol intake or plasma albumin." But, they did not attempt to relate the socioeconomic or educational level of subjects to their dietary habits, particularly protein intake. This and additional confounding factors might have influenced results.

Even for this limited group of 36 Indo-Pakistanis, the methodology left the major conclusion open to question because, as Mucklow and coworkers (1962) state, "when non-vegetarians alone were considered, there was no significant correlation between antipyrine clearance and daily meat intake, raising the possibility that one or more other dietary factors might be of greater importance. Moreover, many of the variables correlated significantly with each other as well as with clearance. Stepwise multiple regression analysis was therefore performed and identified smoking, age and fat intake as independent correlates with clearance." Other discrepancies merit attention. Again, according to the investigators, since "daily protein intake was significantly lower amongst vegetarians, while daily fat intake was similar in the two subgroups, it was surprising that regression analysis identified fat intake as the only independent dietary correlate with antipyrine clearance." This anomaly should be considered in light of the carefully controlled dietary studies by Anderson et al. (1979) that assigned a small role to fat in antipyrine kinetics, and in connection with the inconsistency of these results on albumin with those of a previous study by Fraser et al. (1979). Collectively, these difficulties suggest that the statistical approach used here and elsewhere (Fraser et al, 1976) may yield irreproducible, erroneous results.

In an earlier study with multiple regression analysis to determine the basis of interindividual variations in antipyrine clearance among 49 Gambians (Fraser et al. 1976), the principal causative factor identified was another nutritional factor, the number of cola nuts chewed per day ($r = 0.4$). In a prospective study on an entirely different population of carefully controlled, environmentally stable normal men living in south-central Pennsylvania, chewing cola nuts did not alter antipyrine clearance (Vasell et al. 1979). Because of multiple genetic and environmental differences between the groups investigated, these apparently conflicting results are not necessarily contradictory. Nevertheless, their divergence emphasizes the crucial role played by the criteria used to select methods to analyze data and subjects to receive drugs. This group has extensively applied their statistical method to determine causation of large interindividual kinetic variations without describing strengths and weaknesses; therefore, others have attempted to critically assess this application of multiple regression analysis (Vasell 1984a; Vesell and Penno 1983). While this statistical method has great potential, it requires considerable modification beyond its initial applications in this area (Fraser et al. 1976, 1979; Mucklow et al. 1982) if that potential is to be realized (Vesell 1984a; Vesell and Penno 1983). Thus far, its applications in kinetics (Fraser et al. 1976, 1979; Mucklow et al. 1982) have been disappointing, as those who have used it neither formulated nor addressed, much less demonstrated fulfillment of, several fundamental assumptions inherent in its use (Vasell and Penno 1983). As noted above, contradictory findings emerged in different applications (Fraser et al. 1976, 1979; Mucklow et al. 1982; Vesell and Penno 1983).

Four fundamental assumptions of the particular statistical model used are dubious when applied to investigations of sources of interindividual differences in antipyrine kinetics and are described in detail elsewhere (Vesell 1982, 1984a; Vesell and Penno 1983). Briefly, too few subjects are used to be representative of the population from which they are derived; the method has, thus far, failed to account for most of the intersubject variability; the results are conflicting and they differ from much earlier work on age, sex, and genetic constitution (Vesell and Penno 1983). The potential of multiple regression analysis to resolve sources of kinetic variations is much greater than has been realized by the particular model used. The technique itself is both sensitive and powerful. For multiple regression analysis to be used appropriately, however, a model must be developed that encompasses nonlinear as well as linear relationships (Cohen and Cohen 1975). With antipyrine, only a linear model has, thus far, been used. Error terms especially need to be appropriately modeled, rather than treated in a simply additive manner as in past applications of this method. In contrast to the use of this statistical approach in the assessment of variations in antipyrine kinetics, investigators who applied this model in the assessment of factors that cause large interindividual variations in theophylline clearance clearly recognized

its limitations and the requirement that the conclusions be considered only tentative until tested by a prospective controlled experiment (Jusko et al. 1979). The investigators state that: "The factors identified as important in theophylline body clearances are associations found by retrospective statistical analysis which need not imply a cause-and-effect relationship, especially where a pathophysiological or drug interaction rationale does not exist. Often these factors need further confirmation by prospective examination of cohorts of subjects with the disease or history in question."

A THIRD APPROACH TO ASSESSMENT OF DIETARY CONTRIBUTIONS TO INTERINDIVIDUAL VARIATIONS IN DRUG DISPOSITION.

The magnitude of interindividual variation shown in table 1 for some drugs can depend on the drug selected for study, the number of subjects studied, the particular population from which the subjects are drawn, and the "condition" of the subjects, including their present and past health, genetic constitution, age, sex, diet, and exposure to environmental chemicals and drugs that induce or inhibit hepatic mixed-function oxidases. Also, the extent of interindividual variation can reflect complex interactions among these and other sources (figures 1 and 2). Even in the same subject, however, kinetic values can fluctuate markedly from one study to another if any of these factors change. As already suggested, results of previously published reports also reflect the specific method used and the degree to which the assumptions underlying each method are fulfilled. Accordingly, this review stresses the characteristics of each method and the assumptions upon which it is based.

It should be emphasized that when subjects are under basal environmental conditions with respect to the many factors that can affect hepatic drug oxidation and when, accordingly, their hepatic drug-metabolizing enzymes are relatively uninduced and uninhibited, large interindividual variations still remain (table 1). Although well established, this important fact is often ignored. Thus, under near-basal conditions, large interindividual kinetic variations cannot be attributed convincingly to any specific environmental factor. Twin and family studies have indicated that these large interindividual kinetic variations in subjects under near-basal environmental conditions arise from genetic factors (Penno et al. 1981; Penno and Vesell 1983; Vesell 1982, 1984a; Vesell and Penno 1983). Nevertheless, under other conditions in which environmental factors are permitted to exert a differential (unequal) influence, this pattern of genetic transmission can be concealed. The major portion of interindividual variation observed can then be attributed solely to environmental sources, because underlying genetic factors that are also operative become unrecognizable by conventional methods of detection. Accordingly, the answer to the difficult question of what role nutritional

factors play in maintaining large interindividual kinetic variations in normal subjects living unrestricted lifestyles depends on the specific characteristics of the subjects selected, the extent of environmental perturbation, and the particular combination of environmental factors that exert effects on these subjects at any given time. Results obtained in such studies will often reflect, in large measure, the methods used.

To elucidate these precise relationships, a slightly different approach from those thus far undertaken is recommended. This approach incorporates parts of the several methodologies described above. Selection of normal subjects with unrestricted lifestyles is adopted from studies that used multiple regression analysis. The part adopted from carefully controlled studies on subjects under uniform near-basal environmental conditions is manipulation of single nutritional factors independent of all others with repeated use of the model drug to obtain kinetic measurements before, during, and after this single dietary change. Such an experimental design should permit assessment of the influence of a single dietary change (generally, withdrawal of a particular dietary factor) on model drug kinetics. For example, in normal subjects living an unrestricted lifestyle, substitution for several weeks of a vegetarian diet for one in which meat plays a principal part could be assessed with respect to antipyrine kinetics. All other dietary and environmental conditions of the subjects in such a study should remain as constant as possible. In separate experiments, effects of cruciferous vegetables and charcoal-brolled beef could be estimated by removing each from the diet for several weeks and comparing the kinetics of a model drug before, during, and after such withdrawal.

The influence of such variables as age, sex, smoking, alcohol, oral contraceptives, total calories, relative proportion of macromolecular constitutents of the diet, exercise, and environmental exposure to certain prevalent chemicals would eventually need to be recognized and, to some extent, tested before the generality of any conclusions drawn in one group of subjects could be extended to other groups. As already emphasized, on repetition under perturbed environmental conditions, normal subjects are more variable in thin kinetic values than are subjects under near-basal environmental conditions. Therefore, the suggested experimental design needs to establish the extent of intraindividual variation in each subject; that is, kinetic values should be measured in each subject several times before dietary manipulation. In some subjects, the magnitude of intraindividual variation may possibly reach or, perhaps, exceed that obtained after imposition of a specific dietary change. Such studies are laborious, time-consuming; and technically difficult to undertake, but they may represent the next step in the extension of conclusions on dietary factors from normal subjects under near-basal environmental conditions to subjects under environmentally perturbed conditions.

In this connection, a study revealed markedly altered therapeutic responses secondary to a change in drug kinetics produced by switching the proportion of macromolecular constituents in the diet. In 14 children with asthma, theophylline kinetics were accelerated by a diet high in protein content and retarded by a diet high in carbohydrate content (Feldman et al. 1980). Of particular interest with respect to this discussion was the observation that, within each of the three dietary groups, the extent of interindividual variation was in the same range (300%) (Feldman et al. 1980). Therefore, under none of these three different dietary conditions did the proportion of the macromolecular constituents of the diet appear to account for the 300% interindividual variations in theophylline clearance. More studies of this kind should be performed to assess the proportion of total interindividual pharmacokinetic variation ascribable to dietary factors.

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Interactions of Cannabis With Other Drugs in Man

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Interactions of cannabis constituents with other drugs are of interest because cannabis is often used in the context of other drugs. Of the many constituents present in cannabis, or in marijuana smote, only a few can be studied in any systematic way. These are the cannabinoids, such as the major active component, delta-9-tetrahydrocannabinol (THC), as well as those without psychoactivity, such as cannabinol (CBN) and cannabidiol (CBD).

Many possible interactions of cannabinoids might be studied. Pharmacodynanic interactions would mainly involve THC, as the other cannabinoids have little direct evidence of pharmacological activity in man. Pharmacokinetic interactions might involve any of the cannabinoids, as well as possibly still unstudied or unidentified materials in marijuana. Interactions might be tested between THC and drugs that might be used as probes for investigating the mechanism of action of THC. Finally, some interactions may depend on characteristics of the users, such as their idiosyncratic metabolism of the drug, or the psychological effects of the setting in which the drug is taken as well as the expectations of individual subjects.

PHARMACODYNAMIC INTERACTIONS

Ethanol

This drug is commonly taken concomitantly with the use of marijuana, with the idea that it will augment the effects of the latter drug. Such an assumption is well based, as both drugs have similar actions. At low doses they tend to produce euphoria and stimulation; at higher doses, sedation. Comparison between ethanol and THC confirmed the similarities, the major distinction being the more distorted time sense and hallucinogenic action of THC (Hollister and Gillespie 1970). One might guess that their effects would be additive. Adding ethanol to both high and low doses of THC increased impairment on several measures, as well as adding to subjective experiences (Manno et al. 1971).

Sedatives

A situation similar to that of ethanol should prevail with sedatives, but studies in man are few. Numerous studies in animals support an additive effect. In man, THC given after pentobarbital pretreatment induced hallucinations and anxiety in five of seven volunteers, to the extent that four did not complete the course of five doses of THC because of the severe psychologic effects (Johnstone et al. 1975). The same investigators found that in man THC potentiated the sedative and respiratory depressant effects of the opioid oxymorphone. Cardiovascular effects of THC seemed to be unaltered by the presence of either drug. A second study in man confirmed an additive effect when THC was combined with 150 mg secobarbital/70 Kg. No such interaction was found with CBD (Lemberger et al. 1976).

Stimulants

Stimulants combined with THC have relatively little effect in man, seeming to act in a mildly additive fashion. A dose of 15 mg of dextroamphetamine in man followed by smoking an equivalent of 15 mg THC from marijuana cigarettes revealed separate effects from both drugs: marijuana caused tachycardia and conjunctival injection; dextroamphetamine increased blood pressure and respiratory rate. The impairment of performance on cognitive tests produced by marijuana may have been overcome by dextro-amphetamine, which improved performance when given alone (Zalcman et al. 1973). Similar additive effects were seen in subjects given 10 mg/70 Kg doses of dextroamphetamine and 50 ug/Kg doses of THC by smoking. In this case, dextroamphetamine did not counter the adverse effects of marijuana on motor performance (Evans et al. 1974). Instances of combined use of amphetamines and marijuana are infrequent in social practice. One would guess that when they occurred, doses of amphetamine would be considerably higher than those given experimentally. No studies have examined an interaction with cocaine in man.

Other Cannabinoids

Two other major cannabinoids, CBN and CBD, are inevitably taken with THC when marijuana is smoked. Their proportions may vary considerably from one marijuana batch to another. Experiments have been contradictory both in animals and man. Doses of from 15 to 60 mg of CBD orally were said to block the effects of 30 mg oral doses of THC (Karniol et al. 1974). A similar finding was reported from another study which showed attenuation of the psychic "high" (Lemberger et al. 1976). CBD had no effect on the action of barbiturates. On the other hand, smoked marijuana was said to produce greater subjective, congitive, and physiological effects than smoked THC in equivalent doses. Thus, the miniscule amounts of CBN and CBD in marijuana seemed to enhance rather than block effects (Galanter et al. 1973). A slight effect was seen from 40 mg oral doses of CBD combined with 20 mg oral doses of THC. Onset of THC effects was delayed, slightly prolonged, and

slightly more intense. Quite possibly some of these differences might be due to the known proclivity of CBD to impair metabolism of other drugs, but the overall effect was of no clinical consequence. Similar doses of CBN produced no appreciable alterations of THC effects (Hollister and Gillespie 1975a). In rhesus monkeys CBD decreased operant behavior produced by THC (Brady and Balster 1980).

Other Drugs

Virtually no studies of interactions with other drugs have been done-possibly because few others, as well as the sedatives and stimulants mentioned above, are used directly in combination with marijuana. A single case report of marked sinus tachycardia when marijuana was used by a patient taking nortriptyline would be expected as an additive effect (Hillard and Vieweg 1983). Alcohol is commonly used in such combination and its use for augmenting marijuana effects seems to be based on good evidence. No antidote for THC effects is known. Tamarind, reported to be such, was not found to be active in our unpublished studies. Such has also been the case with phenitrone, which revealed no antagonism when tested in a number of animal species (Spaulding et al. 1972).

PHARMACOKINETIC INTERACTIONS

Alterations of Absorption and Distribution

When given in a lipid vehicle, THC is much better absorbed than it is in a hydroalcoholic vehicle; possibly the lipid matrix also accounts for social use of the drug in the form of a cookie. Alimentary lipemia does not seem to bind IHC in blood; clinical actions were unchanged in our studies.

Alterations of Metabolism

No changes in the kinetics of THC were observed when 20 mg oral doses were given together with 40 mg oral doses of CBN and CBD (Agurell et al. 1981). Even a 1500 mg oral dose of CBD failed to alter the kinetics of an intravenous dose of THC; a minimal effect on the formation and excretion of metabolites was noted (Hunt et al. 1981). CBD decreased the metabolism of hexobarbital; maximum concentrations and bioavailability were increased; and plasma half-life and volume of distribution were decreased (Benowitz et al. 1980). No change in the disposition of cocaine was produced by THC in rats (Vadlamani et al. 1984).

EXPLORATIONS OF MECHANISM OF ACTION

Alphamethylparatyrosine (AMPT) blocks tyrosine hydroxylase and inhibits formation of new catecholamines. Its interaction with THC was not associated with any qualitative or quantitative changes in THC action (Hollister 1974). There may have been a slight additive effect due to the sedative effects produced by AMPT. Propranolol blocked the tachycardia produced by THC but

had no effect on the cognitive chanses (Drew et al. 1972). Physostigmine amplified the lethargy and somnolence produced by THC as decreased tachycardia and conjunctival injection. In many respects, physostigmine acts both similarly-to THC (lethargy and somnolence) and different from THC (bradycardia). The interactions were undoubtedly additive (Freemon et al. 1975).

INTERACTICINS BETWEEN CANNABIS AND CHARACTERISTICS OF SUBJECTS

Metabolism

Variable responses to the same dose of THC are seen not only between subjects,but in the same subject as well. (One possible explanation for between-subject variability would be different rates of hydroxylation of drugs. An active metabolite of THC is 11-hydroxy-THC; subjects with a rapid rate of hydroxylation might be expected to have a more precipitous onset and greater intensity of THC effect than slow hydroxylators. Both metabolism of antipyrine and phenylbutatone were used as indices of hydroxylation rate. It was impossible to correlate either the speed of onset, total intensity, or duration of effects with speed of hydroxylation of drugs (Hollister and Gillespie 1975b). Thus, it seems unlikely that differing rates of drug metabolism account for the widely variable responses between individuals exposed to THC.

Personality

It has become axiomatic that the setting in which psychoactive drugs are taken is a strong determinant in the effects they produce. The axiom is seldom tested. A study of marijuana and placebo cigarettes smoked under "favorable" and "unfavorable" conditions found no appreciable contribution of the extreme settings in which the drug was taken (Hollister et al. 1975). Quite possibly, the psychological expectations or "set" of subjects are the major determinant of interindividual differences. This factor has not yet been adequately studied in the case of THC (Hollister and Overall 1976).

SUMMARY

Only THC, of all cannabinoids, has a significant pharmacodynamic interaction with ethanol. Effects in man are additive as expected. THC. but not CBD. showed a similar interaction with barbiturates. Interactions with stimulants were weakly additive, but the former drugs do not reverse impairments from THC. Interactions between cannabinoids are controversial. Some evidence consistently suggests that CBD may block actions of THC, while other evidence could not show a clinically significant interaction. CBD did not alter the kinetics of THC, but it decreased metabolism of hexobarbital. Preliminary studies of interactions between THC and drugs affecting activity of neurotransmitters have not provided good tests of the mechanism of action of the drug, showing, at best, subtle effects of questionable clinical significance. The variable responses of

subjects to THC is neither explained by differences in metabolism of drugs nor by differences in the setting in which the drug is taken.

FURTHER STRATEGIES

The paucity of recent studies of interactions of cannabis with other drugs probably means that investigators no longer construe these as very important. Adverse consequences of combined use of cannabis with other drugs have been rarely reported. Of all drugs, ethanol is the only one consistently used contemporaneously. Althogh studies of this interaction are sparse, and by no means elegant, the conclusion of an additive effect seems reasonable. Whether or not this interaction needs more documentation is questionable.

One must realize that the clinical effects of smoking cannabis are rather brief. The whole course is generally run within 3 hours, as judged both by assessment of subjective responses and by measurement of plasma concentrations of THC. Thus, even though cannabis users may also use other social drugs, unless they were to use them concurrently with cannabis, significant interactions would not be expected. Thus far, no such patterns of combined use have emerged, other than for ethanol.

While it seems likely that many smokers of cannabis also use tobacco, surprisingly little study of these interactions has been done. As the potential for both a pharmacokinetic as well as a pharmacodynamic interaction exists, it might be of some interest to test these hypotheses. The clinical effects of cannabis, as well as the kinetics of THC, might be studied in subjects who are abstainers from tobacco and who are also heavy smokers. The possibility that such studies would reveal any new important interaction is remote, as this experiment has probably been done many times in nature.

The number of interactions systematically studied to develop some insight into the mechanism of action of THC have been sparse. Work thus far in man has touched upon interactions involving catecholamine neurotransmitters and acetylcholine. Clearly, more work might be of interest, looking at specific alterations of THC effect by modifying the actions of dopamine, serotonin, and gamma-amincbutyric acid. In view of the fact that a possible mode of action of THC might be one of disordering (fluidizing) cell membranes, it might be well to study interactions between THC and drugs that alter membrane lipids, such as chronic exposure to alcohol, pretreatment with lithium, or other techniques by which membranes may be made more or less rigid. Such studies might very well be done on animals rather than in man, however.

Factors influencing the variability of response to cannabis use still remain relatively unexplored. More studies of the effects of different rates of metabolism between subjects, as well as the

effects of mind-set of subjects, would be of interest but are not crucial.

Many of the concerns about the adverse effects on health of cannabis use still remain to be explored. It does not appear, at least now, that such adverse effects are likely to be associated with unexpected interactions between the active components of cannabis and other drugs.

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Alcohol and Marijuana: Concordance of Use by Men and Women

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INTRODUCTION

There is abundant evidence that many American men and women smoke marijuana. To what extent does marijuana use enhance risk for alcohol abuse and does alcohol use increase probability for marijuana abuse? There is evidence that use of substances which have abuse liability potential (for example, opiates, alcohol, and tobacco) increases probability of concurrent use and abuse of other drugs. For example, cigarette smoking increases when men drink alcohol or self-administer opiates (Mello and Mendelson, this volume). While it is reasonable to postulate that marijuana cigarette smoking may also contribute toward concurrent abuse of other substances, there are no empirical data available from controlled clinical investigations which support this notion. The studies described in this report were designed to examine the degree of covariance between marijuana and alcohol use by men and women. We will first describe our studies of alcohol and marijuana use by male subjects who participated in controlled residential research ward investigat ions. Next, we will review studies of marijuana and alcohol use by female subject volunteers assessed in a prospective, conmmity-based research paradigm.

MARIJUANA AND ALCOHOL USE BY MALES

This report describes the first attempt to examine the effects of concurrent availability of marijuana and alcohol on drug use patterns under clinical research ward conditions (Mello et al. 1978). This study was designed to explore patterns of polydrug use involving marijuana and alcohol. The following behavioral questions were examined in a situation where subjects could work at a simple operant task to acquire marijuana, alcohol, or money.

1. Does the simultaneous availability of marijuana and alcohol change the use of either or both drugs in comparison to conditions where marijuana or alcohol is available alone?

2. When both alcohol and marijuana are available, is there a tendency to use these separately or together?

NOTE: All figures and tables in this article and portions of the text were originally published in Mello, N.K.; Mendelson, J.H.; Kuehnle, J.C.; and Sellers, M.L. Human polydrug use: Marihuana and alcohol. J Phamcol Exp Ther 207:922-935.

3. Is the temporal pattern of drug acquisition behavior different under conditions of single or simultaneous availability of alcohol and marijuana?

Since most of our information about nonopiate polydrug use has been derived from survey data andfromself-report information (Benvenuto et al. 1975; Bourne 1975; Carlin and Post 1971; Fisher and Brickman 1973; Grupp 1972; Smart and Liban 1980; Wechsler et al. 1980; Johnston 1980 and 1981; Kandel 1980 and 1984; Hochhauser 1977; Einstein et al. 1975; Welte and Barnes 1982), direct observations of multiple drug use patterns and its behavioral consequences are useful for distinguishing the actual from the anecdotal.

Volunteer subjects were recruited through advertisements in local periodicals and newspapers. All subjects selected were in good health and showed no evidence of psychiatric or medical abnormalities as determined by appropriate laboratory and clinical examinations. These included a complete physical examination, mental status examination, chest x-ray, electrocardiogram, timed vital capacity, and the following laboratory assessments: lactic dehydro genase, serum glutamic oxaloacetic transaminase, bilirubin total, total protein, albumin, globulin, agglutination ratio, alkaline phosphatase, uric acid, blood urea nitrogen, creatinine, glucose, total lipids, white and red blood counts, hemoglobin, hematocrit, and differential.

Sixteen adult male volunteers who reported concurrent use of marijuana and alcohol were selected. Each subject was fully informed about the nature and duration of each phase of the study and was told he could withdraw at any time. Subjects were closely matched for age (mean = 25; range, 21-29), years of alcohol use (mean = 6.60 ± S.E. 0.77), and years of marijuana use (mean = 7.5 ± S.E. 0.61). Subjects were matched as closely as possible with regard to socioeconomic background and general intelligence and had an average of 13.2 years of formal education (range, 11-16). Subject characteristics and self-reports of the frequency of alcohol and marijuana use are summarized in table 1.

Subjects were studied in groups of 4 and lived on a hospital research ward for 34 days. The research ward contained 2 semiprivate bedrooms, a nursing station, examining and testing rooms, kitchen and lavatories, an operant equipment room, and a spacious, comfortable dayrooom with television, high fidelity equipment and other recreational materials. Physicians, nursing personnel, and ward assistants were present 24 hours each day.

Sequence of Procedures

The sequence of drug availability conditions is shown in table 2. Each subject was used as his own control during a drug-free baseline of 5 days; a 5-day exposure to either marijuana or alcohol only; a 5-day exposure to the opposite drug only; a 10-day period when both marijuana and alcohol were simultaneously'available; followed by a 5-day drug-free control period. Each 5-day exposure to alcohol only or to marijuana only was followed by 1 drug-free

day to reduce the possibility that withdrawal from one drug would influence initial acquisition of the second drug. The alcohol or marijuana only periods provided a single drug use baseline against which to compare drug use patterns during concurrent alcohol and marijuana availability. Eight subjects were given marijuana first and 8 subjects were given alcohol first during the single drug availability periods. An alternating sequence of only alcohol or only marijuana access was intended to control for the possible influence of the order of single drug conditions on concurrent drug use during the lo-day access period.

A single acute drug administration day (marijuana plus alcohol) preceded the first 5-day single drug period and followed the 10-day period when both alcohol and marijuana were available. These acute drug administration days were included to examine the effects of acute alcohol and marijuana administration on a series of biological and behavioral variables. Within a period of 1½ hours, subjects smoked 3 marijuana cigarettes (1-g marijuana cigarette; 1.8-2.3% tetrahydrocannabinol) and consumed a 43% alcohol solution in a dose of 2.5 ml/kg in fruit juice which was sufficient to produce a blood alcohol level between 100 and 120 mg/100dl.

Operant Behavioral Procedures

In order to earn purchase points for drugs or money, subjects pressed the response button on a portable operant manipulandum. Each response transmitted a discrete radiofrequency signal to the programming and recording equipment. The manipulandum could be easily held in one hand. It measured 4.5 x 9.4 x 1.6 cm and weighed about 198g. Each manipulandum was color-coded and labeled with the subject's number to permit easy identification by the ward staff and to discourage subjects from exchanging manipulanda.

Subjects worked for drugs or money on a second order fixed ratio 300, fixed interval 1 second schedule of reinforcement, an FR 300 (FI 1 sec:S). Only the first response after 1 sec elapsed was recorded by the programming circuitry as an effective response. Responses emitted at a faster rate had no programmed consequence. This schedule of reinforcement was chosen to permit comparisons with our previous studies of operant acquisition of marijuana (Mendelson et al. 1976a).

Each purchase point required 300 effective responses on an FI 1 schedule. Thirty minutes of sustained performance resulted in 1800 effective responses or the accumulation of 6 purchase points. The cost of 1 marijuana cigarette or 50 cents was 6 purchase points (i.e., 30 min of work). This equation was made on the basis of prevailing prices for marijuana in the Boston area. The cost for 1 ounce (30 ml) of alcohol was 3 purchase points (i.e., 15 min of work). The price differential between marijuana and alcohol was established after pilot studies showed that subjects did not buy as much alcohol as they usually drank at the price of 6 purchase points (Babor et al. 1978).

Subjects could work at the operant task whenever they wished as long as it did not interfere with other ward procedures or data collection routines. Subjects could only work at the operant task within the general confines of the clinical research ward.

Available Drugs

Marijuana

Cigarettes which contained approximately 1g of marijuana were obtained from the National Institute on Drug Abuse (NIDA) in lot standard dosage form. Maximal standardization and equivalent dosage "draw" characteristics of these cigarettes were ensured by machine rolling. Each 1-g cigarette contained approximately 1.8 to 2.3% tetrahydocannabinol (THC) as assayed by NIDA. Details of the Soxhlet and modified Lerner extraction procedures and the gas chromatographic assay procedure are available from NIDA. Content analysis confirmed that the THC concentration of these cigarettes remains stable over many months. Actual content analysis of the marijuana indicated the following constituents (percent ± S.D.): cannabidiol = 0.18 ± 0.04%; Δ^{8}-THC = 0.002 ± 0.002%; Δ^{9}-THC = 2.06 ± 0.08%; cannabinol = 0.08 ± 0.12%.

Alcohol

Subjects could choose their preferred type of alcohol. Gin, vodka, scotch, bourbon, beer, or wine and mixers were available. Prices were established on the basis of the absolute alcohol ccmtent of each beverage. One ounce (30 ml) of distilled spirits, one l2-ounce (360 ml) can of beer, and one glass of fortified sweet wine (2.5 ounces or 75 ml) cost 3 purchase points.

Reinforcement Choice

During the predrug baseline period, and the 2 drug-free control days, subjects could work only for money. Money earned for operant work and for other performance and cooperation tasks was paid upon completion of the study. During the two 5-day periods when only marijuana or only alcohol were available, subjects could work for the available drug or money. During the 10-day period when both marijuana and alcohol were available, subjects could work for marijuana, alcohol, or money.

Whenever a subject activated his operant instrument, he chose whether to work for a drug or for money. When the subject pressed the appropriate button on his control panel (i.e., money, alcohol, or marijuana), this infonned the programning apparatus that points earned should count towards the selected reinforcer. Once a subject chose to work for 1 reinforcer, he could not change to a second reinforcer until an interval of 5 min elapsed. This changeover delay contingency was included to prevent rapid alternation between reinforcement conditions.

Record of Earnings

A record of purchase points earned for money, alcohol, and marijuana was continuously available to each subject on his operant control panel, located on one wall of the dayroom. When a drug purchase was made, the number of points required for that purchase was automatically deducted from the subject's total points earned for that drug. Subjects were not allowed to purchase for another subject or to earn points using another subject's manipulandum.

Control of Drug Use

All alcohol consumption and/or marijuana smoking had to be done at the time of drug purchase, under observation of a staff member. Subjects were not allowed to share drugs. Unused portions of smoked marijuana cigarettes were collected by staff so that "roaches" were not accumulated and smoked without staff knowledge. Bach roach was weighed to determine the amount of marijuana actually used by each subject. Since studies were carried out on an inpatient clinical research ward, staff were able to ensure that subjects did not use drugs other than marijuana and alcohol.

Measurement of Effective Drug Levels

Blood levels of marijuana and its metabolites were not measured directly,and effective dosages were inferred from the number and amount of cigarettes smoked.

Alcohol purchase data were supplemented by blood alcohol level measurements. A breathalyzer device was used in order to avoid multiple venipunctures. It has been repeatedly shown that about 95% of all breathalyzer readings are equivalent to simultaneous blood alcohol determinations within 10% (Dubowski 1970). Subjects were required to rinse out their mouths and refrain from smoking, eating, or drinking for 10 min before each breathalyzer measurement . Measurements were taken according to standard procedures. Blood alcohol levels were measured at 8:30 a.m., 10:00 a.m., 2:00 p.m., 3:15 p.m., 8:00 p.m., 10:30 p.m., and every hour after 11:00 p.m. if subjects continued to drink. In addition, blood alcohol levels were measured immediately before and 30 min after completion of the first and fourth drink of the day.

Medical and Neurological Assessments

Vital signs were taken 3 time each day and routine physical examinations were conducted periodically throughout the study. Upon conclusion of each drug availability condition, neurological examinations were conducted daily to ascertain the occurrence of withdrawal signs and symptoms. A complete description of procedures used to evaluate marijuana withdrawal appears in Mendelson et al. (1974). A description of the alcohol withdrawal syndrome appears in Mello and Mendelson (1977).

The pattern, rate, and duration ofoperantresponses for drug and money acquisition were automatically recorded by the programming

circuitry on electromechanical counters; interresponse time counters; cumulative recorders; and running time meters. Data on individual patterns of drug use are presented graphically. T tests were used to evaluate the statistical significance of individual changes in mean alcohol and marijuana intake during periods of single and combined drug availability. Group data were evaluated with an analysis of variance.

RESULTS

Individual Drug Use Patterns by Men

There was considerable variability between individual subjects in the amount of marijuana and alcohol consumed during each drug availability period. Consequently, individual drug use patterns are described before consideration of group trends. All subjects used alcohol or marijuana during each 5-day single drug availability period. Fifteen of the 16 subjects studied used both alcohol and marijuana during the 10-day period of concurrent drug availability. The single exception (S3-MA5) used only alcohol when both marijuana and alcohol were available.

Analysis of the weight of marijuana cigarette roaches per subject per day indicated approximately 98% of each 1-g cigarette was smoked. Subjects used roach clips and consistently smoked as much as possible of each marijuana cigarette. Subjects appeared to drink all alcohol purchased, and the effective dose of alcohol, inferred from peak blood alcohol levels, was consistent with the alcohol purchase pattern.

Average daily alcohol and marijuana use by individual subjects during each drug availability period is shown in table 1. Subjects are grouped according to the volume of alcohol actually consumed during the alcohol only period, and are designated as heavy (N=5) moderate (N=4) and light drinkers (N=7). Eleven subjects were heavy marijuana users according to our previously established criteria of 4 or more marijuana cigarettes per day (Mendelson et al. 1976a). The remaining 5 subjects could be classified as casual users who smoked 3 or fewer cigarettes per day during the marijuana only period. During the single drug availability periods, heavy drinking did not necessarily predict heavy smoking or the converse. Heavy marijuana smokers accounted for 3 of the 5 heavy drinkers, 3 of the 4 moderate drinkers, and 5 of the 7 light drinkers (table 1, columns 2 + 5). No subject showed withdrawal signs or symptoms after cessation of alcohol or marijuana use.

There was a marked lack of correspondence between actual marijuana and alcohol consumption during the single drug availability periods and retrospective self-report data shown in table 1. Only 1 of the 5 heavy drinkers reported daily alcohol use and the others reported no more than 2 to 4 beers and 2 ounces of distilled spirits per week. In fact, these subjects drank between 12 and 19 drinks per day (table 1, column 2). Although 6 subjects reported using fewer than 20 marijuana cigarettes per month, 4 of those subjects smoked between 4 and 7.8 cigarettes per day (table 1, column 5). It is impossible to determine whether subjects do not remember

TABLE 1

Changes in alcohol and marihuana use during single and concurrent drug availability conditions

Subject No., Study No., (A) or (M) First	Alcohol: Drinks/Day Mean (± S.E.)			Marihuana: Cigarettes/Day Mean (± S.E.)		
	Alcohol only	Alcohol + marihuana	Change: P <*	Marihuana only	Alcohol + Marihuana	Change: P <*
Heavy drinkers						
S1-MA2 (M)	19.4 (±2.99)	5.1 (±1.68)	↓ .001	5.0 (±1.14)	6.7 (±0.65)	↑ NS
S2-MA2 (M)	19.4 (±2.56)	8.9 (±1.91)	↓ .01	1.6 (±0.40)	0.7 (±0.21)	↓ .05
S3-MA5 (M)	14.2 (±4.21)	6.2 (±2.36)	↓ NS	0.2 (±0.20)	0	↓ NS
S4-MA2 (M)	13.8 (±2.18)	3.9 (±0.92)	↓ .001	6.8 (±1.59)	9.6 (±0.92)	↑ NS
S3-MA2 (M)	12.2 (±2.48)	4.9 (±1.10)	↓ .01	9.0 (±1.38)	10.0 (±1.31)	↑ NS
Moderate drinkers						
S1-MA5 (M)	9.4 (±6.23)	3.2 (±0.80)	↓ NS	4.6 (±0.51)	6.5 (±0.91)	↑ NS
S2-MA5 (M)	9.4 (±3.50)	4.5 (±0.95)	↓ NS	2.0 (±0.45)	2.9 (±0.48)	↑ NS
S3-MA3 (A)	6.8 (±2.52)	8.9 (±0.74)	↑ NS	7.8 (±0.66)	12.6 (±0.72)	↑ .001
S1-MA3 (A)	5.2 (±1.66)	3.8 (±0.74)	↓ NS	6.4 (±1.36)	9.2 (±0.47)	↑ .05
Light Drinkers						
S4-MA5 (M)	4.6 (±2.44)	0.6 (±0.34)	↓ .05	5.2 (±0.80)	5.7 (±0.84)	↑ NS
S1-MA6 (A)	4.4 (±1.03)	1.3 (±0.54)	↓ .05	3.4 (±0.68)	3.1 (±0.18)	↓ NS
S4-MA6 (A)	4.4 (±0.68)	1.7 (±0.40)	↓ .01	4.2 (±0.58)	3.8 (±0.29)	↓ NS
S4-MA3 (A)	3.2 (±2.18)	1.3 (±0.82)	↓ NS	5.8 (±0.80)	7.5 (±1.05)	↑ NS
S3-MA6 (A)	3.2 (±0.20)	2.6 (±0.40)	↓ NS	2.2 (±0.37)	2.7 (±0.33)	↑ NS
S2-MA6 (A)	3.0 (±0.84)	2.4 (±0.34)	↓ NS	4.4 (±0.68)	5.8 (±0.42)	↑ NS
S2-MA3 (A)	1.8 (±0.80)	2.0 (±0.76)	↑ NS	5.0 (±0.84)	6.4 (±0.69)	↑ NS

* Significance of changes in drug use evaluated by *t* tests (two-tailed).

or deliberately misinform to ensure selection for the study. However, an empirical classification based on actual drug use behavior appears to be essential for analysis of these data.

Effects of Concurrent Marijuana and Alcohol Availability

Fourteen of the 16 subjects drank less alcohol during the period of combined alcohol and marijuana availability, in comparison to the 5-day alcohol only period (table 1, column 3). A reduction in alcohol consumption by this number of subjects was significant according to a nonparametric sign test ($p<.01$). Moreover, 7 subjects drank significantly less alcohol when marijuana was available, as evaluated by t tests (table 1, column 4).

Twelve of the 16 subjects smoked more marijuana during the period of concurrent alcohol and marijuana availability in comparison to the 5-day marijuana only period (table 1, column 6). An increase in marijuana use by this number of subjects was significant according to a nonparametric sign test ($p<.05$). However only 2 subjects smoked significantly more marijuana cigarettes (table 1, column 7).

Drug use was often quite variable within individuals over time. Daily drug use and earning patterns for selected individual subjects are presented in figures 1, 2, and 3. The most common pattern observed, i.e., to increase marijuana use and decrease alcohol use during the period of concurrent alcohol and marijuana availability, is shown in figure 1. This subject was a heavy marijuana user who smoked an average of 7 cigarettes per day during the baseline period of marijuana availability. He was also a heavy drinker and consumed an average of 14 drinks per day during the baseline

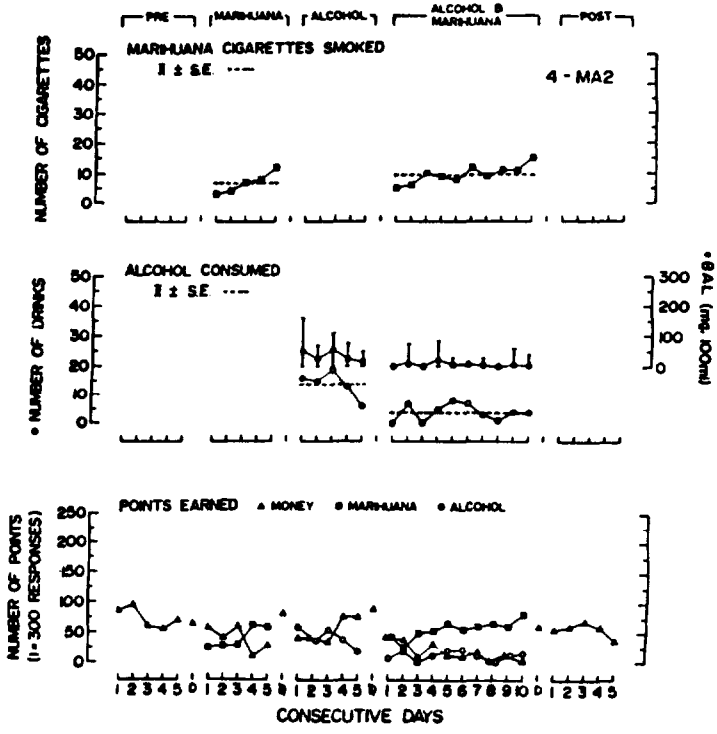

FIGURE 1

FIGURES 1, 2, and 3. *Marijuana ad alcohol use and purchase points for money and drugs earned over 34 consecutive days. The succeesive conditions of drug availability are show at the top of each figure. The first row show the numbsr of marijuana cigarettes smoked (■) each day. The dotted line and cross-hatched area (± S.E.) denotes the average number of marijuana cigarettes smoked during the entire 5 or 10 day period. The second row shows the number of alcohol drinks consumed each day (0) and the 24-h ntean and range of blood alcohol levels observed each day (●). The average number of drinks consumed during the 5 or 10 day period is shown as a dotted line and cross-hatched area (mean ± S.E.). The third row shows the number of purchase points earned for money (Δ), marijuana (■) and alcohol (0). Consecutive days of the study are shown on the abscissa. The single day (D) inmediately following and preceding the pre- and postdrug free baselines were days on which an acute combined-dose of alcohol and marijuana was given. The single day (Ø) following the 5-day period of marijuana and of alcohol availability was a day on which no drugs were available.*

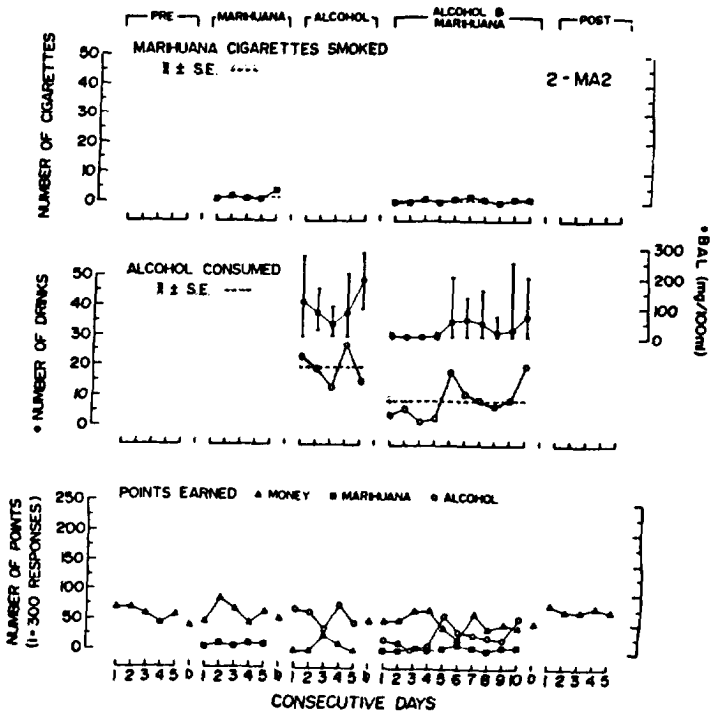

FIGURE 2 *See legend under figure 1*

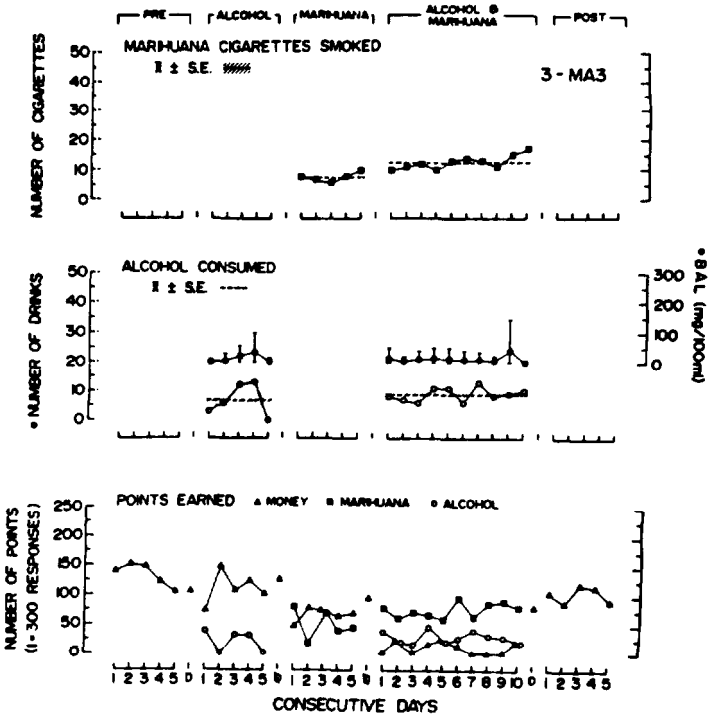

FIGURE 3 *See legend under figure 1*

period of alcohol availability. Peak blood alcohol levels ranged from 50 to 160 mg/100 ml during the hours of maximum drinking. When both alcohol and marijuana were available concurrently, marijuana smoking increased slightly to an average of 10 cigarettes per day Alcohol consumption decreased significantly to an average of 4 drinks per day ($p<.001$) and peak blood alcohol levels never exceeded 75 mg/100 ml.

A decrease in both marijuana and alcohol use during the periods of marijuana and alcohol availability is shown in figure 2. This subject was also a heavy drinker who consumed an average of 19 drinks per day during the baseline period of alcohol availability. Peak blood levels ranged between 100 and 280 mg/100 ml. This subject also showed a significant decrease in alcohol consumption during the period of concurrent alcohol and marijuana availability, despite a relatively low frequency of marijuana smoking (1.6-0.7 cigarettes per day).

Figure 3 shows data for 1 of the 2 subjects who increased both marijuana and alcohol use during the period of concurrent alcohol and marijuana availability. During the single drug baseline, this subject was a moderate drinker and a heavy marijuana smoker. During the 10 days of concurrent alcohol + marijuana availability, alcohol use increased slightly and marijuana smoking increased significantly ($p<.001$) . This subject also smoked significantly more marijuana during the final 5 days of the 10-day concurrent drug access period than during the first 5 days as determined by t tests ($p<.05$).

Group Trends in Concurrent Drug Use Patterns

Analysis of variance for repeated measures across days was done separately for alcohol and marijuana use during the 10-day period of concurrent availability. There were no significant linear trends in alcohol consumption through time. Rather, alcohol consumption decreased when marijuana became available and remained depressed in comparison to the alcohol-only baseline, throughout the period of concurrent drug availability. In contrast, there was a significant linear increase in marijuana smoking during this 10-day period ($p<.001$). A trend analysis for the entire 15 days of marijuana availability also indicated a significant progressive increase in marijuana smoking through time ($p<.001$).

The sequence of single drug conditions, alcohol, or marijuana first, did not appear to determine drug use patterns during the concurrent drug availability condition. There were no significant differences between the 2 drug sequence groups in either alcohol or marijuana consumption during the first 5 days of the concurrent drug availability period. The 8 subjects exposed to marijuana first also did not differ from the 8 subjects exposed to alcohol first in baseline marijuana smoking. However, the alcohol-first group drank significantly less alcohol than the alcohol-second group during the alcohol only baseline ($p<.001$) as evaluated by paired t tests.

In order to examine the temporal concordance of alcohol and marijuana use, the number of occasions that each subject used each drug during consecutive 4-h blocks was tabulated. Group drug use patterns during the 10-day period of concurrent alcohol and marijuana availability are compared with drug use patterns during the single drug availability periods in figure 4.

During the period of concurrent availability, alcohol and marijuana were usually used between noon and midnight (figure 4, row 1). Although alcohol and marijuana were usually used together, there were no instances of adverse reactions or other evidence of toxic drug interaction. The temporal distribution of marijuana smoking was similar during the marijuana only and concurrent drug availability periods (figure 4, rows 1 and 2). There were no significant differences in the nunber of marijuana cigarettes smoked during each 4-h time period as a function of the availability of alcohol. A comparison of the amount of alcohol consumed during each 4-h period revealed a significant decrease in drinking between 4:00 and 8:00 p.m. and between 8:00 p.m. and midnight when marijuana was concurrently available ($p<.01$). The changes in alcohol consumption during marijuana availability were not significant at any other 4-h time period as evaluated by paired t tests.

Operant Work Patterns

Although only responses emitted at a rate of 1/sec counted toward purchase points under the Fl 1 sec component of the schedule, all subjects consistently responded at a faster rate. Usually response rates were 2 or more per sec, and about 600 responses were emitted for every 300 responses required. gates of 3 or more responses per sec were not unusual. Subjects understood the schedule requirements but preferred to respond at a comfortable rate.

The temporal pattern of operant work for purchase points for alcohol (0), marijuana (■) and money (Δ, ▲) by the entire group of subjects during each drug condition is shown in figure 4. Subjects usually began operant work in the morning between 8:00 a.m. and 12:00 noon. Subjects earned the most points for money between noon and midnight in both the drug-free and drug access conditions. Operant work for alcohol and marijuana points was more equally distributed between the hours of 8:00 a.m. and 12:00 midnight in both the single and concurrent drug availability periods. Comparison of figures 4 and 5 indicate that the periods of maximum operant work usually corresponded to periods of maximum drug use.

Despite the difference in price for alcohol and marijuana (3 vs. 6 purchase points), work patterns for each drug were similar during the alcohol or marijuana only periods. When both alcohol and marijuana were available, subjects began to work for marijuana earlier than for alcohol and earned consistently more marijuana points through time. Purchase points earned for alcohol and marijuana were consistent with actual drug use. Subjects appeared to earn about as many drug purchase points as were needed for daily consumption. Subjects did not accumulate extra drug purchase

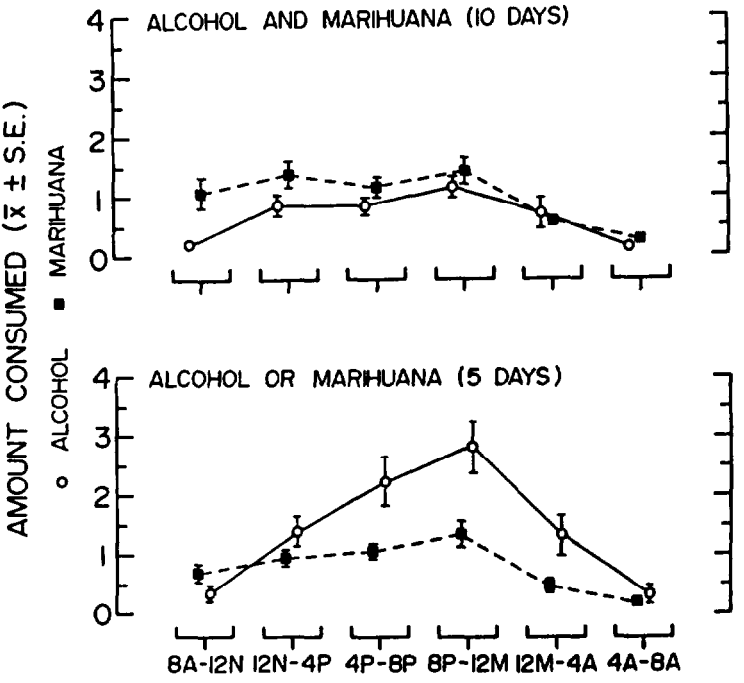

FIGURE 4 *Amount of alcohol and marijuana cigarettes used as a function of time of day, across drug availabitity conditions. Numbers of drinks or marijuana cigarettes used (mean ± S. E.) are shown on the ordinate and consecutive 4-h periods are shown on the abscissa. The top rot) shows the nwnber of alcohol drinks consumed (0) and marijuana cigarettes smoked(■) during the 10-day period of alcohol and marijuana availability. The second row shows consumption of each drug during the 5-day period of single drug availability.*

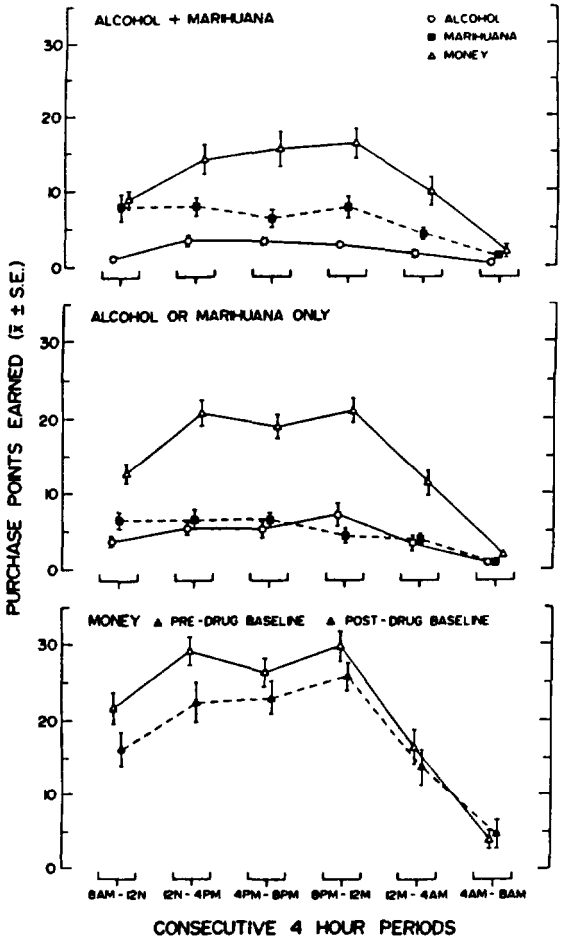

FIGURE 5 *Purchase points earned as a function of time of day across drug availability conditions. Purchase points earned (mean ± S. E.) are shown on the ordinate and consecutive 4-h periods are shown on the abscissa. The top row shows points earned for money (Δ) marijuana (■) and alcohol (0) during the 10-day period of concurrent alcohol and marijuana availability. The second row shows the purchase points earned for money, alcohol, or marijuana during the two 5-day periods when only alcohol or marijuana was available. The third row shows points earned for money during the 5-day predrug baseline and during the 5-day postdrug baseline.*

points or plan ahead for a period of work-free drug use as was previously observed in alcohol addicts (Mello and Mendelson 1972).

It is apparent that subjects earned more points for money than for either drug during both the single and combined drug availability periods (figure 3, rows 1 and 2). Subjects earned the most points for money during the drug-free baseline periods when marijuana and alcohol were not available as alternate reinforcers (figure 3, row 3). Throughout the course of the study, subjects earned an average of $257.68 (± S.E. $21.60).

The average number of total points earned per day across each successive baseline and drug access condition is summarized in table 2. The total number of points earned by the entire group tended to decrease through time as determined by a trend analysis ($p<.025$). Subjects earned fewer points during the 3 drug availability conditions than during the predrug baseline, and fewer still during the final drug-free baseline period. Differences between the pre- and postdrug baseline periods were significant as evaluated by matched pair t tests ($p<.01$).

Total points earned during the period when only alcohol was available and when alcohol and marijuana were available concurrently did not differ significantly from the predrug baseline. However, significantly fewer points were earned during the marijuana only period than during the predrug baseline ($p<.05$).

The amount of operant work and total purchase points earned remained quite consistent across the 3 drug availability conditions. There were no significant differences in total points earned during the alcohol, marijuana or concurrent drug availability periods.

Examination of total points earned as a function of alcohol consumption revealed differences in total earnings. Heavy drinkers earned significantly fewer total points than light drinkers ($p<.05$). Heavy drinkers also earned significantly less money than light drinkers ($p<.01$). Light drinkers earned an average of $8.92 per day or $303.45 for the study. Moderate drinkers earned an average of $8.18 per day or $278.13 for the study. Heavy drinkers earned an average of $5.21 per day or $177.25 for the study.

Eleven of the 16 subjects were heavy marijuana users and 3 of these were also heavy drinkers. However, if the effects of marijuana use are examined, independent of alcohol use, heavy marijuana users earned significantly more total points than light users ($p<.05$). Heavy marijuana users also earned more money than light smokers, but this difference was not significant. Heavy marijuana users earned an average of $8.13 per day or $276.42 per study, whereas light marijuana users earned an average of $6.37 per day or $216.58 per study.

Translation of average points earned per day on an FR 300 (FI 1 sec) schedule reveals that subjects worked between 8.6 and

TABLE 2

Operant purchase points earned by each subject in each condition (mean/day)

Subject	Pre-Baseline	Alcohol Only	Marihuana Only	Alcohol and Marihuana	Post-Baseline	Within Subject and Across Conditions	
						Mean	± S.E.
Heavy drinkers							
S1-MA2	86.7	96.6	75.4	86.2	76.3	84.24	±3.90
S2-MA2	57.3	66.0	71.8	80.2	68.5	68.76	±3.74
S3-MA5	113.5	95.4	109.0	91.4	82.6	98.42	±5.66
S4-MA2	73.0	95.6	82.2	85.3	57.2	78.66	±6.47
S3-MA2	109.3	121.4	114.6	123.2	90.3	111.76	±5.91
Moderate drinkers							
S1-MA5	164.8	131.4	120.0	107.3	128.3	130.36	±9.57
S2-MA5	113.0	93.0	69.6	82.4	82.8	88.16	±7.23
S3-MA3	128.8	131.4	115.4	110.2	99.2	117.0	±5.97
S1-MA3	157.7	158.8	130.0	179.4	199.7	165.12	±11.68
Light Drinkers							
S4-MA5	166.8	120.6	141.6	129.4	128.0	137.28	±8.11
S1-MA6	141.5	120.4	126.6	120.3	121.2	126.0	±4.05
S4-MA6	116.7	121.4	117.2	115.2	113.7	116.84	±1.29
S4-MA3	149.2	162.8	158.0	159.9	153.6	156.74	±2.39
S3-MA6	97.3	82.0	65.8	63.3	56.5	72.96	±7.38
S2-MA6	149.5	138.2	136.2	130.6	97.3	130.36	±8.82
S2-MA3	115.2	126.2	119.8	130.4	107.5	119.82	±4.04
Mean purchase points earned per day	121.27	116.33	109.58	112.17	103.94	112.66	±17.21
± S.E.	±6.13	±6.64	±7.06	±7.67	±9.32		

and 10.1 h per day during the pre- and postdrug baseline periods. When drugs were available, subjects worked an average of 9.7 h per day during alcohol only, 9.1 h per day during marijuana only and 9.3 h per day when both drugs were available.

DISCUSSION (Males)

Alcohol and Marijuana Use in Men

When alcohol and marijuana were concurrently available, marijuana appeared to affect alcohol use far more dramatically than alcohol influenced marijuana use. A significant nwnber of subjects reduced alcohol use in comparison to a period when only alcohol was available. The magnitude of the decrease in alcohol consumption was also significant in half of those subjects. Although marijuana smoking increased when alcohol was also available, this change cannot be attributed solely to the effects of alcohol. Marijuana smoking began to increase during the marijuana only period and this trend continued throughout the period of marijuana and alcohol availability. The progressive increase in marijuana smoking during the 10 days of concurrent alcohol and marijuana access was comparable to that previously observed during 21 days of access to only marijuana (Mendelson et al. l976a,b). These data may reflect an increased tolerance for marijuana. The development of behavioral and physiological tolerance to marijuana during chronic use has been reported by several investigators (Mendelson et al. 1974; Babor et al. 1975; Jones and Benowitz 1976).

A marijuana-related suppression of drinking was unexpected and the factors which account for this finding are unclear. There were no progressive changes in alcohol consumption comparable to changes in marijuana smoking over time. Rather, alcohol consumption decreased abruptly when marijuana became available, and remained suppressed in comparison to baseline throughout the period of concurrent drug availability (cf. figure 1). Reanalysis of drinking patterns in 18 control subjects from previous studies of casual and heavy drinkers (Babor et al. 1978) also failed to reveal any significant linear trends in alcohol consumption through time (J.H. Mendelson, unpublished observations). Therefore, it is unlikely that the observed depression of alcohol consumption reflects a time-related trend which is independent of marijuana availability.

It could also be postulated that subjects drank less alcohol during marijuana use because the level of intoxication produced was either equivalent to a higher dose of alcohol or was aversive. It is generally acknowledged that the combined effects of alcohol and marijuana are “additive” in the sense that performance impairments induced by the combined administration of both drugs are greater than those observed with either drug alone (Burford et al. 1975; Franks et al. 1975; Manno et al. 1971; Smiley et al. 1975; Smith 1976). Subjective aspects of marijuana intoxication have also been reported to be enhanced by the concurrent use of alcohol

(Hollister 1976; Manno et al. 1971). However, alcohol consumption decreased even in subjects who smoked only 1 to 3 marijuana cigarettes per day (cf. table 3), so this explanation is not compelling. The critical dose-response relationships between alcohol and marijuana which influence drug use patterns remain to be determined.

These subjects did not appear to be unusually intoxicated and did not report that the combined effects of alcohol and marijuana were aversive. We have seen no evidence for toxic interactions between marijuana and alcohol in either the chronic self-administration or the acute dose studies in which 3 marijuana cigarettes were smoked in combination with a 2.5 ml/kg dose of alcohol over a 1½-h period. Our findings are at variance with a report by Sulkowski and Vachcm (1977) in which far lower doses of alcohol (1 g/kg) and marijuana (1 cigarette containing 18 mg of Δ^9-THC) administered within a 1-h interval resulted in prolonged vomiting, headaches, and severe intoxication in 4 of 7 healthy young men with a history of alcohol and marijuana use. A lower dose of alcohol (0.5 g/kg) did not result in comparable adverse effects. Blood alcohol levels were not reported (Sulkowski and Vachon 1977).

These data indicate that the simultaneous availability of 2 recreational psychoactive drugs does not necessarily increase drug use, as has been reported for alcohol and tobacco (Griffiths et al. 1976) Rather, the availability of marijuana modulated the use of alcohol, even in heavy drinkers. Although marijuana has rarely been considered a plausible addition to the armamentarium of drugs arrayed against alcoholism, Rosenberg (1977) has proposed to use marijuana to reinforce compliance with a disulfiram maintenance program for alcoholics.

Operant Work Patterns by Men

Concurrent use of alcohol and marijuana did not change the amount or temporal pattern of operant work in comparison to periods when only alcohol. or only marijuana was available. Subjects continued to work at the operant task during the periods of maximum drug use in all 3 conditions of drug availability. Operant response rates were consistently higher than required by an FI 1 sec schedule of reinforcement. These data are consistent with our previous observations of sustained operant performance for marijuana and for money during a 21-day period of marijuana availability (Mendelson et al. 1976 a,b).

The sustained performance for drugs and money during intoxication differs from that previously observed with alcoholic subjects working at a simple operant task for alcohol or cigarettes. Alcoholic subjects alternated 2- to 3-day periods of work with 2- to 3-day periods of drinking even though periods of abstinent working resulted in alcohol withdrawal signs and symptoms (Mello and Mendelson 1972). Differences in operant task requirements do not appear to account for observed differences in drug acquisition patterns between alcohol addicts and multiple drug users. However,

the finding that heavy alcohol users earned fewer total points and less money than light drinkers is consistent with our previous observations of alcohol-related decreases in operant work by alcohol addicts (Mello and Mendelson 1932).

The tendency to earn fewer total points as the study progressed is consistent with our previous observations of both casual and heavy marijuana smokers. The total number of points earned during the postdrug baseline period were always fewer than during the predrug baseline period (Mendelson et al. 1976a). Since there was no evidence of withdrawal signs and symptoms in these 16 polydrug users, or in the 47 marijuana smokers studied previously (Mendelson et al. 1974, 1976a), this decrement may reflect boredom with the operant task.

MARIJUANA AND ALCOHOL USE BY FEMALES

We are aware of no studies with women similar to those previously described for human males. While such studies are entirely feasible for women, a number of preliminary investigations are essential prerequisites before utilizing a residential research ward design analogous to that which has been described for studies with human males. The major reason for the conduct of preliminary studies with women is due to a possible influence of menstrual cycle function on marijuana use. Clinical studies have suggested that women may use alcohol or other psychoactive substances in greater or lesser amounts as a consequence of menstrual cycle related phenomena (Belfer et al. 1971) . It has been postulated that women who experience premenstrual or menstrual related tension and dysphoria may be at higher risk for using or abusing substances when they are symptomatic (Podolsky 1963). Therefore, we have carried out a study to determine if alcohol and marijuana use vary as a function of menstrual cycle phase. This study is, to the best of our knowledge? the first major prospective investigation designed to ascertain the frequency and amount of daily alcohol and marijuana use by women during 3 consecutive menstrual cycle phases.

Thirty adult female volunteers between the ages of 21 and 36 (mean age 26.4) were recuited via newspaper advertisements and provided informed consent for participation in the study. All subjects were selected following complete physical and mental status examination and laboratory studies. No subject was pregnant, had past or current history of drug or alcohol abuse, or a recent history of amenorrhea or menstrual function disturbance. Findings reported in this study were obtained within the context of an extensive multidisciplinary investigation of behavioral and biological concomitants of marijuana use by women. Subjects were typically single women with some college education and their experience with drugs other than marijuana and alcohol was infrequent. Upon admission to the study, subjects did not differ significantly on any background variables . Table 3 summarizes general background characteristics of the subjects.

TABLE 3

FEMALE MARIJUANA SMOKERS

BACKGROUND DATA

	AGE	YEARS EDUCATION	YEARS REGULAR MARIJUANA USE	YEARS TOTAL MARIJUANA USE	MARIJUANA USE (TIMES/MONTH)	ALCOHOL USE (TIMES/MONTH)
RANGE	21-36	8-21	2-15	4-16	5-40	2-20
$\bar{X}$	26.43	14.53	7.37	9.37	15.0	7.03

30 SUBJECTS

3 CONSECUTIVE MENSTRUAL CYCLES

2701 COMPLETED QUESTIONNAIRES

95.5% OF ALL POSSIBLE DAILY USE REPORTED

Procedures

All subjects completed a detailed diary questionnaire each day. The diary was designed to monitor use of marijuana, alcohol, tobacco cigarettes, nonprescription drugs, recreational drugs (other than marijuana), occurrence of unusual events, frequency of sexual activity, morning basal body temperature, menstrual cycle status, menstrual distress symptoms, and mood states each day during 3 consecutive menstrual cycles. Subjects began diary reporting on the first day of menstruation following acceptance into the study and continued to record daily responses for 3 consecutive menstrual cycles. Subjects used an oral thermaneter to record morning basal body temperature to the nearest tenth of a degree Fahrenheit each morning before arising from bed. The remainder of diary data were recorded each evening before retiring. Completed diaries were mailed to the Harvard-McLean Alcohol and Drug Abuse Research Center every day. This study reports patterns of marijuana and alcohol consumption; mood state data and biological findings will be reported elsewhere.

During each 24-h period, subjects reported the total number of marijuana cigarettes (or other marijuana compounds) used and the 6 time periods during the day ("early morning," "late morning," "early afternoon," "late afternoon," "early evening," and "late evening") during which use occurred. Subjects also reported consumption "all day," which indicated that some amount of consumption had occurred during each of the 6 successive time periods but did not necessarily signify continuous consumption throughout the day. Subjects similarly noted the total nwnber and specific types of alcoholic beverages consumed (beer, wine, or spirits or mixed drinks) and times of alcohol use. The number of tobacco cigarettes smoked and the time of their use was recorded. Subjects further noted the quantity of other recreational or nonprescription drugs used. They also reported onset and cessation of menses and occurrence of sexual activity. Occurrence of unusual events was recorded in response to the question: "Did anything unusually good or bad happen?" during the daily reporting period.

Conclusions and Comments

Compliance of subjects for reporting daily diary events was excellent in this study. Less than 1.5% of over 2,700 questionnaires were not completed. There was a highly statistically significant correlation ($p<.0001$) between concordant use of marijuana cigarettes and alcoholic beverages during the 3 consecutive menstrual cycles. In addition, subjects tended to consistently conswne alcohol, marijuana, marijuana and alcohol, or abstain from using either substance in a similar manner across all 3 menstrual cycles.

The data obtained in this first prospective study designed to evaluate concordance of marijuana and alcohol use by women is in agreement with findings which have been obtained in previous investigations of relationships between alcohol and marijuana use (Fisher and Brickman 1973; Smart and Fejer 1973; Wechsler and Rohman 1981).

However, studies of marijuana and alcohol use by women in controlled research ward environments analogous to those described in the initial portion of this paper for men have yet to be undertaken. These studies should yield more precise information about acquisition and use patterns of marijuana and alcohol when both substances are relatively freely available for women.

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Cocaine and Other Drug Interactions: Strategy Considerations

Reese T. Jones, M.D.

THE STATE OF THINGS

Although cocaine is by most criteria an old, almost ancient drug (Van Dyke and Byck 1976), there is relatively little data on cocaine and other drug interactions collected from controlled laboratory experiments in humans. Many clinical observations, reports, and speculations about drug interactions based on uncontrolled clinical observations date back virtually to the first use of cocaine. Clinically significant cocaine interactions in humans with epinephrine and most other sympthomimetics (National Institute on Drug Abuse 1977). with opiates, and with various therapeutic drugs-lithium (Cronsow and Flemenbaum 1981), antidepressants (Rowbotham et al. 1984), local anesthetics, and virtually every class of psychoactive drug-indicate that interactions are likely tut unpredictable and complicated as to mechanisms. A vast amount of animal data illustrates numerous neurochemical, behavioral, and functional effects from cocaine's interaction with other drugs (Catravas and Waters 1981; Colpaert et al. 1978; Guinn et al. 1980; Nigro and Enero 1981; Smith et al. 1981). However, most of the published observations about humans consist of small samples in not well-controlled case reports, in surveys of operating room fatalities, in self-reports from drug users, etc. (National Institute on Drug Abuse 1977).

WHY STUDY COCAINE AND OTHER DRUG INTERACTIONS?

Information about drug interactions can be important when planning therapeutic approaches. Host of the data supporting or refuting current drug therapies for treating cocaine dependence (e.g., lithium or tricyclic antidepressants) come from patient reports and clinical observations under conditions where the dose of cocaine, the frequency of dose, the variety of adulterants that may have been added, and the variation in route of administration are completely uncontrolled and, in the usual clinical situation, uncontrollable.

Cocaine users, like most drug users, use a variety of other drugs often concurrently with cocaine or before and after. Alcohol, opiates, sedatives, anxiolytics, stimulants, cannabis, tobacco, and coffee are commonly used along with the cocaine. In addition to the drugs ingested along with the cocaine, cocaine users are exposed to a variety of adulterants commonly added to illicit cocaine Cunningham et al. 1984). Besides the usual lidocaine, lactose, or mannitol, a variety of local anesthetics are likely to be present.

I will discuss some reasons why cocaine and other drug interaction studies are so seldom done and speculate about considerations leading to useful strategies for controlled human laboratory studies or more controlled clinical studies with cocaine. The emphasis will be on considerations for human studies, even though there is a large and growing body of literature from animal studies with cocaine attempting to use drug interaction data to get at mechanisms for various effects (e.g., Knapp and Mandell 1972; Nigro and Enero 1981). This valuable literature will only be mentioned in passing where it has some specific relevance to a point being made about human psychopharmacologic studies with cocaine.

Cocaine pharmacokinetics, particularly relationships between routes of administration and relationships between kinetics and various physiological and psychological effects, have been studied in our laboratories for the past few years. In the course of these studies, we have had an opportunity to measure, in a limited way, drug interactions that may have clinical relevance, even though they don't provide much information on mechanisms of cocaine effects. A better understanding of mechanisms, of course, is one of the ideal outcomes of a drug interaction study. Our experience will illustrate potential research strategy problems and suggest a few useful considerations to partially overcome them.

WHAT NEEDS TO BE CONSIDERED IN THE PERFECT STUDY

In Adler's chapter (this volume) on critical factors in studying drug interactions, a number of basic pharmacokinetic and pharmacodynamic principles are reviewed, Research with cocaine nicely illustrates some of the problems in fully meeting those principles in human studies. Table 1 lists a few relevant methodological issues.

For example, a crucial and primary consideration is the ability of cocaine to reach its sites of action; in the brain so far as the user is concerned, but elsewhere in the body as well. The intense vasoconstriction produced by cocaine (Brodsky and Goldwyn 1977) at any but the weakest concentrations probably limits the rate of its uptake with any route of administration except, perhaps. when smoked. Thus, the time and magnitude of peak effects, duration, and, perhaps, metabolites are altered as dose/drug concentration increases.

TABLE 1

Some Methodologic Problems in Cocaine and Other Drug Interaction Studies

1.	Intense vaso (venous and arterial) constriction limits cocaine uptake.
2.	Metabolism not well understood:
	a) Both blood (pseudocholinesterase) and hepatic metabolism;
	b) Possible active metabolites--benzolecgonine and norcocaine.
3.	Brief duration of action and relatively rapid clearance.
4.	Rapid tolerance to many effects after a few repeated doses.
5.	Marked species differences in metabolism and effects; genetic differences within species.
6.	Why routes of administration in common use.
7.	Extremely wide range of doses commonly used.
8.	Extremely varied pattern of use, both frequency and other concurrent drug use.
9.	Adulterants very comnon in illicit cocaine.

After intravenous (iv.) administration in distal forearm or hand veins, we find lower peak blood cocaine levels and decreased area under the time-concentration curves, presumably because of veno-constriction in smaller veins, and a relatively longer sojourn in the venous return from the arm of injection Slower uptake and distribution leads to longer exposure to pseudocholinssterase metabolic activity when the cocaine is injected in small diameter, more peripheral veins This characteristic not only affects determination of time course of drug action, but pharmacokinetic measures as well. Surprisingly, we find no greater variability with nasal administration than with i.v., and less variability in peak levels and area under the time-concentration curve with oral administration The variability does not appear to be due to the assay (Jacob et al. 1984). Presumably, the vasoconstrictive properties of cocaine alter and generally delay absorption even more so in small animals where peripheral veins are smaller or where, after intraperitoneal administration, absorption may be erratic. Blood or tissue levels of the drug are seldom measured in animal studies, so the degree of variability is unknown

WHAT IS PROPER TIME FOR TESTING BEHAVIORAL OR PSYCHOLOGICAL EFFECTS?

The time course of most cocaine effects is relatively short when compared to a number of drugs (e.g., opiates, alcohol, some sedative hypnotics) with which one might want to study the interaction. The great discrepancy in duration of effects poses design problems when selecting the most appropriate time of testing, particularly with pyschological or cognitive tests that do not lend themselves to frequently repeated administration

Under usual laboratory conditions, the well-described euphoria or stimulated state associated with cocaine is frequently, in fact most often, followed by a sleepy, lethargic, and slightly depressed state lasting for some hours. The problems associated with studying the brief euphoria are different than the problems of studying interactions at the later state, though it's the euphoria most people are interested in Usually, because of rapidly acquired tolerance with repeated testing (Fischman and Schuster 1981; Teeters et al. 1963), it is difficult to study both phases of drug effects in the same experiment

COCAINE METABOLISM

The metabolism of cocaine is not well understood for example, most published human studies often involve only a small number of subjects (Ambre et al. 1983: Fish and Wilson 1969; Holmstedt et al. 1979; Inaba et al. 1978; Kogan et al. 1977; Javaid et al 1983; Stewart et al. 1979). Because of two major routes of metabolism-one involving pseudocholinesterase in blood and other tissue, the other by hepatic microsomal enzyme systems-one might expect relatively great variability in cocaine pharmacokinetics. Thus, data from small samples of subjects can be misleading. The question of active metabolites in humans has not been well explored. There are some suggestions from animal studies that benzoylecgonine (which is present in extremely high levels in cocaine users) and, more likely, norcocaine have biological activity (Hawks et al. 1975). Levels and activity of other metabolites and shifts in metabolic pathways when route, frequency of administration, and other concurrent drug use are varied is not well worked out in animals or in humans. Particularly in metabolic differences, the limited evidence is for great species differences in cocaine kinetics with good evidence for hepatotoxic metabolites in some strains of mouse, for example; yet, very little evidence exists for either the presence of such metabolites or hepatotoxicity in humans or, for that matter, in other genetic strains of mice (Freeman and Harbison 1981; Kloss et al. 1984).

DOSE EFFECT FUNCTIONS

Because of the very wide dose range used under illicit conditions, a proper clinically relevant and full dose-response curve is difficult to achieve with cocaine when research subject safety and selection characteristics are kept in mind as they should be (Barnett et al. 1981). Probably because of acquired tolerance,

the frequent cocaine user outside of the laboratory can achieve astronomical blood levels of cocaine and its metabolites with only minimal cardiovascular/respiratory or behavioral toxicity. Such levels cannot be safely reproduced in the laboratory under single dose conditions where subjects have been relatively drug-free just prior to testing.

The most realistic conditions for studying cocaine and other drug interactions are after repeated doses of both drugs of interest The research design issues associated with acute single doses are complex. The even more complex issues and potential research design criticisms of multiple dose subchronic cocaine studies are such that it appears difficult to convince peer reviewers that such studies are worthy of funding. For example, a relatively straightforward chronic cocaine administration project by our group has been reviewed four times by seperate peer review groups, revised each time, and still is judged to be too expensive and not important enough to support (three approvals, one disapproval). Thus, studies of full dose-response curves and of subchronic drug administration are usually either done in animals, with the resulting questions about species differences, or they are done under quite unnatural and nonrealistic ways in humans, usually with a limited dose range.

ENVIRONMENT AND TESTING SCHEDULES

Although there is no reason to think that there should not be circadian or, possibly, metaholic differences in cocaine effects, most laboratories cannot take this easily into account Our laboratory is typical in that it usually starts experiments at 8 o'clock in the morning. Many subjects comment that, in their experience, that's a rather unnatural time to be taking cocaine and that 8 p.m. or 1 a.m. would be more appropriate.

Environment is another important variable if behavior and psychological/cognitive consequences are of major interest (Post et al. 1981). With volunteer subjects drawn from the San Francisco area subject pool, it's extremely unusual for someone to take cocaine alone with no other users present As with many, if not all, psychoactive drugs, one might expect quite a different sequence of effects depending on dose and setting interactions, with interpersonal aspects of the setting being most important.

ROUTE OF ADMINISTRATION

Route of drug administration is a particularly knotty problem with cocaine, or at least one that makes for complicated designs when both the demands of controlled scientific studies and relevance to the real world are considered. Cocaine is taken by a substantial number of users via virtually every possible route--i,v., oral, and nasal, and by smoking, chewing, and, occasionally, other applications, mainly to mucous membranes (Van Dyke and Byck 1976). Proper quantitative dosimetry studies, particularly by the smoking route and by the buccal or chewing route (if swallowing is to be prevented), are particularly methodologically demanding. Despite our

laboratory's experience with quantitative tobacco smoking and marijuana smoking studies, we find that the usual style of smoking cocaine, the rapidity of onset, and the intensity of effects defy proper measures of dose actually ingested.

I have already commented on the surprisingly similar and great variability in peak blood levels and AUC when oral is compared to nasal and i.v. routes (Van Dyke et al. 1978; Wilkinson et al. 1980). Bioavailability is similar when cocaine is taken orally or nasally (about 30% to 35%). Oral administration offers many advantages for drug interaction studies, yet it would raise questions Of relevance in the minds of many. There is only a slight advantage to the nasal route in initial uptake of cocaine, at least as judged by venous blood levels. Perhaps, brain uptake is more rapid by the nasal route, but we have no evidence for this as judged by time of onset of various physiologic and subjective effects. Without radioactive-labeled cocaine and suitable instruments, brain uptake cannot be as easily measured in humans as in animals (Misra et al. 1975).

The balance between scientific precision and relevance to the real world of drug use is a tricky one to judge, particularly when planning drug interaction studies. Rapidly acquired tolerance and the likelihood of cross-tolerance to other drugs on certain (but not all) systems complicates any design involving repeated administration of a drug or involving frequent and infrequent users in a drug interaction study. Most laboratories investigating cocaine in humans find markedly diminished cocaine-induced physiologic and psychological effects after relatively few doses (Fischman and Schuster 1981). In contrast, in a repeated dose paradigm lasting more than a few days, the appearance of other and new signs and symptoms should be expected; for example, irritability, perceptual acuity increases, and, perhaps, paranoid and delusional thinking (Lesko et al. 1982; Post and Cbntel 1981). These later signs and symptoms represent cocaine effects which are just as important and real (but usually not studied) as the more commonly considered acute or early drug effects To properly study tolerance, cross-tolerance, and drug interactions with these later developing cocaine effects in humans, relatively expensive experiments done in rarely available test laboratories equipped for chronic human studies are necessary. The history of Federal support for chronic administration studies suggests that the peer review process is not particularly sympathetic to the need for such studies with cocaine, even though most individuals would agree that data associated with chronic administration is at least as important as acute, single dose administration studies.

MECHANISM OF ACTION

The ideal and, to some scientists, the major justification for drug interaction studies is to try to clarify mechanims of one or the other of the drugs involved. All indications from animal studies are that neurotransmitter systems affected by cocaine are multiple, interacting, possibly species dependent, dose dependent, and frequency-of-dose dependent Simple explanations of mechanisms

will not soon be forthcoming. Thus, if those who control research funds believe that understanding mechanisms is a major criterion or justification of interaction studies in humans, one might assume fewer such studies will be undertaken.

ROUTE OF COCAINE ADMINISTRATION: AN EXAMPLE OF ITS SIGNIFICANCE

Route of administration has important consequences. For example, we recently reported (Rowbotham et al. 1984) that a single 100 mg dose of trazodone diminished a number of the physiologic and subjective effects of a subsequent oral 2 mg/kg dose of cocaine. Cocaine-induced increases in blood pressure and pupil size and decrease in skin temperature were diminished by the trazodone pretreatment. Trazodone did not alter cocaine-induced changes in plasma epinephrine or norepinephrine levels and did not markedly alter the subjective effects of the cocaine.

We repeated the exact protocol with eight subjects but used an i.v. dose of cocaine, 0.2 mg/kg, which produced similar blood levels to the oral cocaine dose. By neither the oral nor the i.v. route was there a significant change in cocaine metabolism. As is evident in table 2, there were no significant interactions between the trazodone and the i.v. cocaine. Possible explanations include:

TABLE 2

Trazodone/Cocaine Interactions
Oral vs. Intravenous cocaine

Effect (Maximum Change Ran Precocaine Levels)	Cocaine 2mg/kg Oral		cocaine 0.2 mg/kg I.V.	
Heart Rate (BPM)		P		P
Placebo	+27.1	0.14	+21.0	0.08
Trazodone	+18.6		+17.0	
Systolic BP (mmHg)				
Placebo	+26.5	0.01	+18.3	0.55
Trazodone	+12.2		+21.0	
Skin Temperature ('C)				
Placebo	-7.3	0 .0001	-4.2	0.05
Trazodone	-3.7		-2.4	
Pupil Size (mm)				
Placebo	+1.02	0 .0001	+1.3	0.31
Trazodone	+0.80		+1.3	
Subjective High (0-100)				
Placebo	38	NS	33	0.24
Trazodone	37		29	

Conclusion : No Change after 0.2 mg/kg i.v.

a more rapid bolus of i.v. cocaine is less likely to be blocked in the central nervous system (CNS) than is the more gradual rise in CNS cocaine levels after oral cocaine, The slower absorption of cocaine orally might allow a different CNS pattern of metabolism than that reflected in the peripheral blood, A rapid change in CNS drug levels or function after i.v. doses might trigger off mechanisms which cannot be blocked or altered by the trazodone. The point is that there are route differences. Possibly, nasal administration would be different from either i.v. or oral.

In the trazodone-cocaine interaction study, our group, as often is the case in human studies, picked doses of drugs which we thought were in a reasonable range in terms of clinical use, and in some intermediate range of dose effect function. It would have been better to use two doses or three doses of both trazodone and cocaine. The single trazodone dose compared to placebo took 16 test sessions with innumerable blood samples and measures. The additional complexity from multiple doses was not practical given the money available for the study. A more serious limitation when generalizing to clinical situations is that only a single administration of trazodone was used, which would not be the case for most regular drug users

It would nave been more clinically relevant to examine not only the single administration, but the events 2 or 3 weeks after chronic trazodone and/or cocaine administration Such a study in outpatient volunteers would not be possible and probably would be viewed by the current research program peer review system as prohibitively expensive with hospitalized volunteers. Hence, the alternatives are either subchronic animal drug interaction studies or none.

TABLE 3

Caffeine-Cocaine Interactions
(Cocaine 2 mg/kg p.o.)

Peak Effects Post/Pre Cocaine	Caffeine 600 mg p.o. Before cocaine	Placebo Before Cocaine	P
Heart Rate (BPM)	42.2	28.2	0.01
Systolic BP (mmHg)	33.4	22.3	0.05
Skin Temperature (ˈC)	-7.8	-6.3	0.10
Pupil Size (mm)	1.3	0.99	0.06
Subjective High (O-100)	48.6	36.2	0.01

WHAT DRUG USE TO CONTROL? WHAT ABOUT COFFEE AND TOBACCO

A practical consideration facing any clinical investigator doing drug interaction studies is the question of what should be done about commonly used hugs like tobacco (nicotine) and coffee (caffeine). It is unusall for a frequent cocaine user not to use tobacco and coffee. It is even more common for other populations of dependent individuals, for example, heroin- or alcohol-dependent persons, to use those drugs frequently and at high dose levels. when setting up protocols, the question always arises, should such people be allowedtocontinue their tobacco use through the period of the experiment? Should they be deprived of tobacco for 12 hours prior to the experiment? Similar questions arise about coffee.

In some of our earliest pilot studies with cocaine before we were set up to measure blood levels and pharmacokinetic parameters, we measured caffeine-cocaine interactions. Table 3 lists a number of effects of a modest oral dose of cocaine, given an hour after a substantial dose of caffeine or after a caffeine placebo. Ten subjects were studied in a crossover design

The table shows peak effects after the cocaine as compared to pre-cocaine/postcaffeine levels, with heart rate, blood pressure, skin temperature, pupil size, and subjective effects all being enhanced by the caffeine pretreatment.

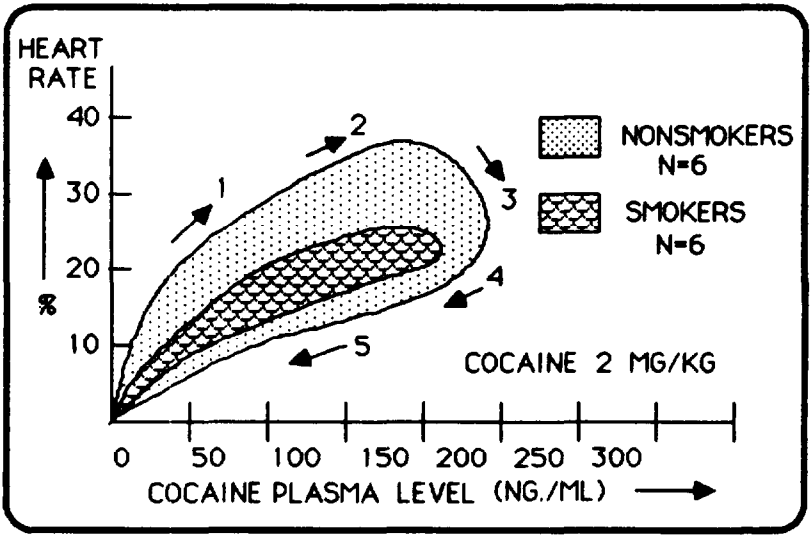

FIGURE 1

Percent Heart Rate Increase After Oral Cocaine: Tobacco Smokers vs. Nonsmokers

Whether coffee drinkers, deprived or not, are different in cocaine responses or drug interaction studies, of course, depends partially on the importance of the multiple metabolic pathways of cocaine. Since the significant metabolism of cocaine occurs in both blood and liver (Foldes 1978; Yamamoto et al. 1953), the likely predictions as contrasted with dealing with a drug that has primarily hepatic metabolism are more uncertain Whether a particular research study deprives coffee drinkers of their caffeine or not is probably less important than reporting just how this issue was handled so that future investigators can take account of it.

The problem of what to do with tobacco smokers is also relevant. Because both cocaine and nicotine have similar effects on the noradrenergic system, one might expect some degree of interaction, probably cross-tolerance. In fact, when a small group of non-smokers was contrasted to a group of smokers who regularly used at least one pack a day of cigarettes, there was some evidence of cocaine/nicotine cross-tolerance on heart rate (figure 1).

The plots of smoothed functions in figure 1 compare percent increase in heart rate over precocaine levels with plasma levels of cocaine on both the ascending and descending limbs of plasma cocaine levels If there were no difference in cocaine effects at a given plasma level on the ascending and ascending blood level functions, there would be a relatively straight and narrow line. Instead, the large, whale-shaped or balloon-shaped pattern in the figure suggests that a certain degree of acute cocaine tolerance develops even over the few hours after the single oral dose of cocaine represented in that figure. Also, the peak increase in heart rate at any given blood level was substantially greater for nonsmokers than for smokers, suggesting cross-tolerance. Clearance and t-1/2 did not vary in the two groups.

When subjects receive prolonged (2 to 3 hours) infusions of cocaine and are allowed to smoke tobacco cigarettes, we have, on each occasion, measured less cardiovascular change blood pressure and heart rate) from the tobacco cigarette smoked later in the cocaine infusion than prior to it or at the beginning, again indicating that as tolerance develops to the cocaine, there is cross-tolerance with the tobacoo. Certainly, the study of interactions between tobacco and cocaine are worthy and important in their own right But, even if other drug interactions with cocaine are the primary interest, both nicotine and caffeine consumption need to be taken into account.

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Cigarette Smoking: Interactions With Alcohol, Opiates, and Marijuana

Nancy K. Mello, Ph.D., and Jack H. Mendelson, M.D.

A number of drugs from diverse pharmacological classes have been shown to influence tobacco smoking. Alcohol, opiates, and certain stimulants increase cigarette smoking, whereas marijuana has no apparent effect on tobacco use. This chapter will describe some clinical studies of the interactions of alcohol, opiates, and marijuana with cigarette smoking. Some factors that may influence cigarette and drug interactions will be discussed.

ALCOHOL EFFECTS ON CIGARETTE SMOKING

An association between smoking and drinking was first observed in studies of alcoholics. Anecdotal observations that alcoholics tended to be heavy smokers were conflrmed by survey data and self-report studies (Dreher and Fraser 1967; Maletzky and Klotter 1974; Walton 1972). Our clinical studies of alcoholic men working for alcohol on a simple operant task (FR 1000) further strengthened the impression of concordant alcohol consumption and cigarette smoking (Mello and Mendelson 1972). Figure 1 shows the covariation between cigarette smoking and alcohol consumption by a typical subject (Subject E.S.) during 62 days of concurrent work-contingent cigarette and alcohol acquisition. There was an alternation between periods of drinking and working for alcohol and cigarettes at the operant task, even though these self-imposed abstinence periods were often associated with alcohol withdrawal signs. Cigarette acquisition declined from baseline during the alcohol availability phase but smoking was temporally correlated with episodes of drinking. Periods of abstinent working for alcohol and for cigarettes also covaried (Mello and Hendelson 1972).

The powerful association between cigarette smoking and drinking in alcoholic men was demonstrated under clinical laboratory conditions by Griffiths and coworkers (Griffiths et al. 1976). Smoking behavior of alcoholic men was measured during 6-hour sessions when alcohol or a nonalcohol vehicle control solution was available. Subjects could consume a total of 12 drinks (90 ml each containing

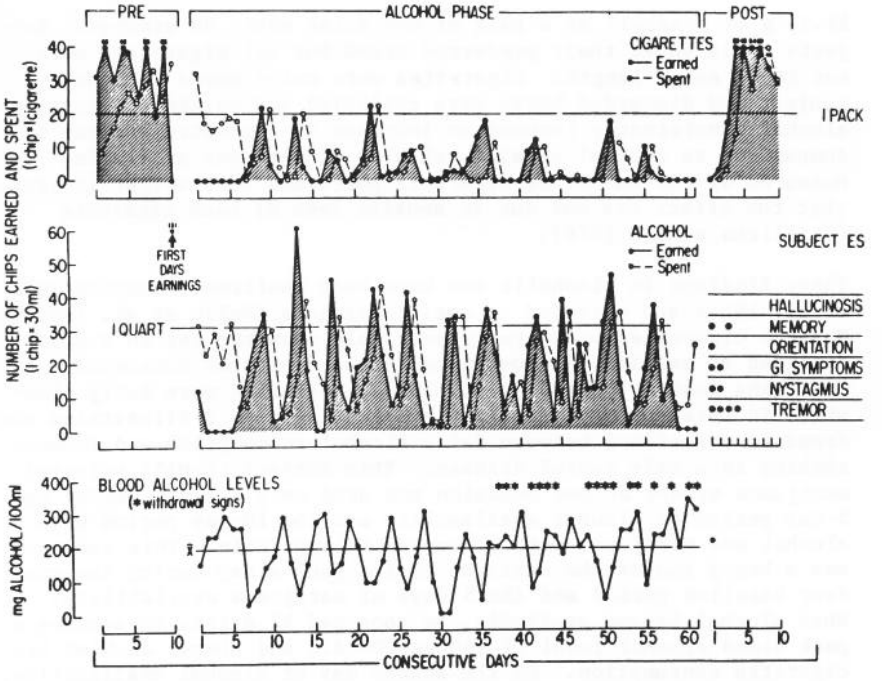

FIGURE 1

Earning and spending pattern of an alcoholic man working for cigarettes during a 10-day baseline period; for both cigarettes and alcohol during a 62-day period of alcohol availability; and for cigarettes during a 10-day withdrawal period. Tokens to purchase alcohol and cigarettes were acquired by working at a simple operant task on an FR 1000. Tokens earned for alcohol were not interchangeable with tokens earned for cigarettes. Patterns of earning (closed circles, shaded area) and spending (open circles, dotted line) for cigarettes and for alcohol are shown in the top two rows. Subjects wre allowed to work for alcohol tokens during the last 24 hours of the 10-day baseline period end these tokens could be spent after 8:00 a.m. on the first day of drinking. Tokens earned that day are shown at the arrow as first day earnings. Average daily blood alcohol levels are shown in the third row and the occurrence of measurable withdrawal signs during drinking are indicated as asterisks. The type and duration of withdrawal signs and symptoms after the subject stopped drinking are shown at the right of figure 1. Reprinted with permission from Mello and Mendelson 1972.

11.14 g of ethanol) at a rate of one drink every 30 minutes. Subjects could smoke their preferred brand but all cigarettes were cut to an equal length. Cigarettes were color coded for each subject and dlscarded butts were collected and weighed. Access to alcohol consistently induced an increase in cigarette smoking in comparison to control sessions when no alcohol was available. Measures of the number of cigarette puffs and butt weight indicated that the effect was not due to smoking less of each cigarette (Griffiths et al. 1976).

These findings in alcoholic men have been confirmed (Henningfield et al. 1984) and extended to social drinkers (Mello et al. 1980a). Tobacco cigarettes were freely available upon request in a study designed to examine the covariance between alcohol consumption and marijuana smoking (Mello et al. 1978), described more fully elsewhere in this volume (Mendelson et al.). Figure 2 illustrates the dramatic covariance between dally alcohol consumption and tobacco smoking in a male social drinker. This subject (3-MA5) rejected marijuana except on one occasion and used only alcohol during the 5-day period of alcohol availability and the 10-day period when alcohol and marijuana were concurrently available. This subject was a heavy smoker who averaged over a pack a day during the predrug baseline period and the 5 days of marijuana availability. When alcohol became available, he consumed 22 drinks to achieve a peak blood alcohol level of 160 mg/100 dl, and almost doubled his cigarette consumption. On the second day of alcohol availability, he drank very little and cigarette consumption returned to baseline levels. When alcohol consumption increased on the third day, tobacco smoking also increased. This pattern of parallel fluctuations in smoking and drinking continued throughout the 15 days of alcohol availability.

Pretreatment with a single dose of alcohol did not consistently influence smoking in social drinkers. Henningf ield and coworkers (1984) compared the effects of a single alcohol dose (0.125 to 1.8 g/kg) on cigarette smoking in social drinkers and alcoholic men. Alcohol given 30 minutes before smoking sessions had inconsistent effects on smoking by social drinkers, Two subjects increased cigarette smoking, two subjects decreased cigarette smoking and smoking was unchanged in a fifth subject. Differences in the usual pattern of alcohol consumption may have contributed to these inconsistent results in social drinkers. Subjects who increased smoking after alcohol reported consuming about one drink each day. The subject whose smoking did not change reported drinking three to four times per week whereas the subjects whose smoking decreased after alcohol usually drank once a month. However, in the alcoholic group, alcohol pretreatment was associated with significant increases in cigarette smoking (Henningfield et al. 1984).

In summary, an association between cigarette smoking and alcohol consmption by alcoholics has been shown consistently In clinical studies with a variety of techniques (Mello and Mendelson 1971; Griffiths et al. 1976; Henningfield et al. 1983, 1984). When social drinkers were given unrestricted access to alcohol over

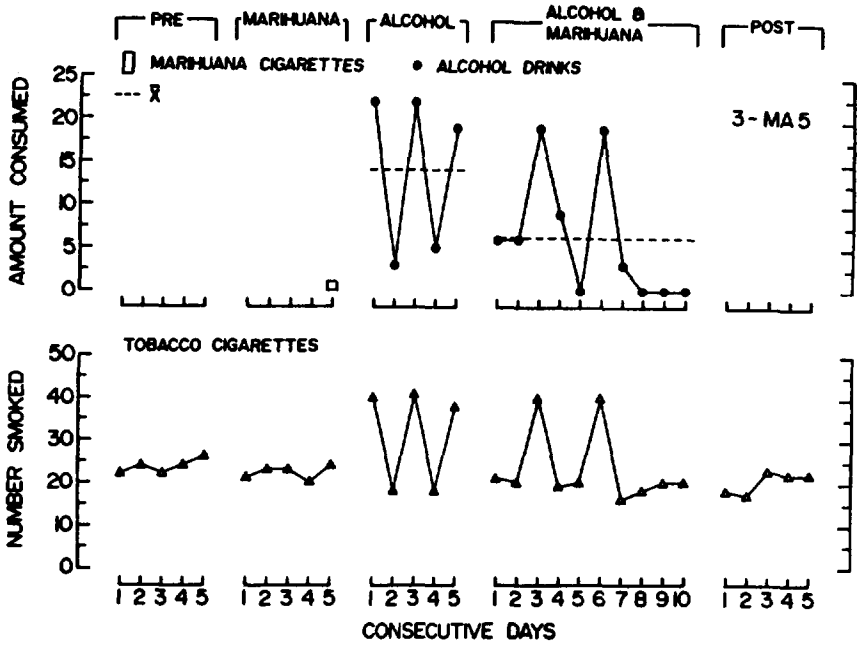

FIGURE 2

Tobacco, alcohol, and marijuana use by a male subject over 30 days. The successive drug free and drug availability conditions are shown at the top of the figure. The first row shows the number of alcohol drinks (closed circle) and marijuana cigarettes (open square) used each day. The dotted line denotes the average number of alcohol drinks consumed or marijuana cigarettes smoked during the 5- or 10-day period of drug availability. The number of tobacco cigarettes smoked each day in each condition is shown in the second row. Reprinted with permission from Mello et al. 1980a.

several days, there also was a striking covariation between alcohol consumption and cigarette smoking (Mello et al. 1978).

The mechanisms by which alcohol influences tobacco use are unknown. In a series of behavioral studies, Griffiths and coworkers (1976) presented data showing that increased cigarette smoking by alcoholic men was not adjunctively maintained by patterns of drinking and socializing. Moreover, increased cigarette smoking could not be accounted for by alterations in number of puffs per cigarette or amount of cigarettes smoked. Since increased smoklng occurred both during ethanol sessions and during the remainder of ethanol days (but not vehicle control days), sequence effects or instructions probably did not influence the phenomenon (Griffiths et al. 1976). In social drinkers, daily alcohol consumption (Mello et al. 1980a) or admfnfstratfon of a single dose of alcohol to individuals reporting a history of daily drinking (Henningfield et al. 1984) appears to be an important determinant of the facilitatory effect of alcohol on cigarette smoking. It is interesting that a history of sedative abuse appeared necessary for acute pentobarbital administratfon to increase cigarette smoking in alcoholic men (Henningfield et al. 1983).

Metabolic hypotheses include the possfbflity that alcohol may change the rate of nicotine metabolism. Since chronic alcohol consumption stimulates the activity of mfcrosomal enzymes which regulate drug metabolism (Lieber and DeCarli 1968; Rubin et al. 1970), and induction of hepatic mitochondrial activity is associated with an increased rate of nicotine metabolism (Russell 1976), smoking during drinking could be less reinforcing. However, an alcohol-related change in nicotine metabolism could account for only one dimension of the reinforcing properties of cigarettes since many complex interacting factors, including expectancy, affect drug use.

OPIATE EFFECTS ON CIGARETTE SMOKING

The opiate agonists, heroin and methadone, also have been shown to be associated with increased cigarette smoking by opiate addicts during intoxication (Mello et al. 1980b; Chait and Griffiths 1984). It appears that heroin addicts, like alcoholics, are often heavy cigarette smokers (Gritz 1980). There has been recent speculation that endogenous opioids may mediate the reinforcing effects of cigarette smoking (Karras and Kane 1980; Chernick 1983; Tobin et al. 1983; Pomerleau et al. 1983). Studies of the interactions between cigarette smoking, opioid agonists, opioid antagonists, and an opioid mixed agonist-antagonist, buprenorphine, will be reviewed in this section.

Opioid Agonist Interactions with Cigarette Smoking

The effects of heroin self-administration on cigarette smoking were studied in 12 adult male volunteers with a history of heroin addiction and cigarette smoking (Mello et al. 1980b). Each volunteer gave informed consent for participation in studies of the effects of new pharmacotherapies on heroin self-administration in a

clinical research ward setting . Naltrexone (50 mg/day p.o.), a long-acting narcotic antagonist, was compared with naltrexone placebo under double-blind conditions. Nine of the subjects in the nal trexone study were cigarette smokers. Three other subjects were involved in studies of buprenorphine, a new partial-agonist antagonist (cf. Jaslnski et al. 1978; Lewis et al. 1983). The effects of buprenorphfne and buprenorphine placebo on heroin self-administration also were compared under double-blind conditions. Naltrexone and buprenorphine each significantly suppressed heroin self-administration by heroin addicts under research ward conditions (Mello et al. 1981, 1982; Mello and Mendelson 1980; Meyer and Mirin 1979). The effects of heroin and methadone on cigarette smoking by eight subjects assigned to the placebo naltrexone condition, one subject assigned to active naltrexone, and three subjects assigned in the placebo buprenorphine conditions are described below.

Buprenorphine- and naltrexone-maintained subjects were closely matched in age (X = 27 years, range 22 to31) and social and educational background. Subjects were fully informed about the nature and duration of each phase of the study, and vere free to withdraw at any time. All subjects were in good health and showed no evidence of psychiatric or medical abnormalities as determined by appropriate clinical and laboratory examinations. Subjects lived on a clinical research ward throughout the study. Each subject served as his own control during a drug-free baseline and each successive drug condition. Consequently, it was possible to compare the effect of heroin, methadone, and control conditions on cigarette smoking by each subject.

Naltrexone subjects were studied over 34 consecutive days in groups of four. The sequence of conditions was as follows: A 9-day drug-free baseline, a 10-day period of heroin availability during which naltrexone or naltrexone placebo was given; a 5-day detoxification phase during which methadone was given to subjects on naltrexone placebo; 7 drug-free days, followed by 3 days of inpatient maintenance on nal trexone. Subjects given naltrexone during heroin availability continued to receive naltrexone throughout the study.

The eight cigarette smokers assigned to naltrexone placebo conditions each self-administered heroin. The one cigarette smoker who was given active naltrexone did not self-administer heroin.

Buprenorphine subjects were studied over 39 consecutive days. The sequence of conditions for the buprenorhine subjects was as follows : A 5-day drug-free baseline; a 14-day period during which buprenorphine (or buprenorphfne placebo) vas administered in ascending doses; 10 days of maintenance with buprenorphine (8 mg/day) or placebo when heroin was also available; 5 days during which methadone was given to subjects on buprenorphine placebo and buprenorphine in decreasing doses was continued for subjects given active buprenorphine; 3 drug-free days were followed by 2 days on nal trexone prior to discharge. Three cigarette smokers were assigned to the buprenorphine placebo condition and each self-administered heroin.

Tobacco and Heroin Acquisition. Tobacco cigarettes were available during all phases of the study. Each subject purchased his preferred brand of cigarettes. However, the nursing staff retained the cigarettes and distributed them upon request. The time of each cigarette request was recorded. Cigarette puff volume and puff duration were not measured In these ambulatory subjects (cf. Jarvik et al. 1977).

Subjects worked for heroin or for money at a simple operant task on a second order fixed ratio 300, fixed interval 1-second schedule of reinforcement FR 300 (FI 1-sec:S). Only the first response after a 1-second interval had elapsed counted as an effective response and 300 responses were required to earn one purchase point. Approximately 90 minutes of sustained performance on an PI 1-sec schedule earned 18 purchase points which could be used to buy one dose of heroin or exchanged for $1.50 in cash upon completion of the study. Subjects could work for money throughout the study but points earned for money could not be exchanged for points for heroin. When both heroin and money mere available, subjects chose to work for one or the other each time they activated the operant instrument. Details of the operant apparatus and procedures are presented elsewhere (Hello et al. 1981).

Subjects self-administered a fixed dose of heroin intravenously under the supervision of a physician. Subjects could omit any heroin injection but could not receive doses larger or smaller than specified in the protocol. Medical considerations preclude unlimited access to heroin. Naltrexone subjects could take a maximum of 40 mg of heroin each day in four 10 mg doses (at 8:00 a.m., 1:00 p.m., 8:00 p.m., and 2:00 a.m.). Buprenorphine subjects could take a maximum of 21 mg of heroin in three doses during the first 5 days of buprenorphine (or placebo) maintenance (7 mg at 9:00 a.m., 5:00 p.m., and 1:00 a.m.); and a maximum of 41.5 mg of heroin (13.5 mg per dose at the same times) during the second 5 days of buprenorphine maintenance.

Effect of Drug Conditions on Smoking. Ten of the twelve heroin addicts were heavy smokers. One subject smoked 1 1/2 packs of cigarettes or more per day and nine subjects smoked one pack or more a day during the drug-free baseline period. The other two subjects smoked less than a pack per day. The naltrexone placebo group smoked significantly ($p < .01$) more cigarettes per day during the 10 days of heroin self-administration than during the drug-free baseline as evaluated by t tests. Average cigarette smoking during the period of heroin availability was also significantly greater than during methadone detoxification ($p < .001$). There were no significant differences in cigarette smoking during the drug-free baseline periods which preceded and followed heroin and methadone. Cigarette smoking during methadone detoxification also did not differ from the drug-free baseline periods. Consequently, the significant increase in cigarette smoking appeared to be specific to the heroin condition.

The one subject given naltrexone, rather than naltrexone placebo, did not self-administer heroin since naltrexone effectively blocked heroin's subjective and physiological effects. Although this subject lived on the research ward with other subjects who were taking heroin and smoking more, there were no significant differences in his smoking behavior across conditions. This subject smoked an average of 25 cigarettes per day over the entire study. This suggests that heroin, rather than any nonspecific social interaction factors, accounted for the increase in cigarette smoking seen in the nal trexone placebo group.

Illustrative data for six individual naltrexone placebo subjects are shown in figures 3 and 4. Heavy smokers who smoked an average of over one pack of cigarettes per day during baseline are shown in figure 3. Moderate smokers who smoked a pack a day or less during baseline are shown in figure 4.

Each of the heavy smokers smoked significantly more cigarettes during heroin use than during the drug-free baseline ($p < .01$). Two subjects (4-HG-1, 1-HT-1) took all or almost all of the four heroin doses available each day. Therefore, variations in cigarette smoking observed during heroin self-administration were not related to the specific daily dose of heroin. Although subject 2-HA-1 tended to smoke least on the days that he took the fewest heroin doses, the fluctuations in cigarette smoking did not appear to vary consistently with the heroin dose. An increase in smoking to three packs a day during the final naltrexone period immediately before discharge was unusual and has not been observed in other heroin addicts studied under these conditions. Since the subject who was maintained on active naltrexone throughout the study did not show comparable elevations in smoking, it is difficult to attribute this finding to the effect of naltrexone per se.

Among the moderate smokers shown in figure 4, the subject (3-HT-1) who smoked least during baseline (an average of 15 cigarettes per day), increased smoking most dramatically when heroin became available, to an average of 32 cigarettes per day ($p < .001$). This subject took all the available doses of heroin. Subject 1-HG-1 smoked an average of 20 cigarettes per day during baseline. During the period of heroin availability, he took most of the heroin available and increased smoking by an average of seven cigarettes per day ($p < .01$). Subject 4-HA-2 smoked an average of four cigarettes more per day during the period of heroin availabillty ($p < .05$) and also took most of the heroin available.

The number of cigarettes smoked per day across the successive conditions of the study by the three buprenorphine placebo subjects is shown In figure 5. Since there were only three cigarette smokers in the buprenorphine placebo group, changes in cigarette smoking as a function of drug conditions were analyzed for Individual subjects with t tests. The introduction of buprenorphine placebo did not result in significant changes in cigarette smoking by any subject in comparison with baseline. Heroin self-administration was associated with an abrupt increase in cigarette smoking by

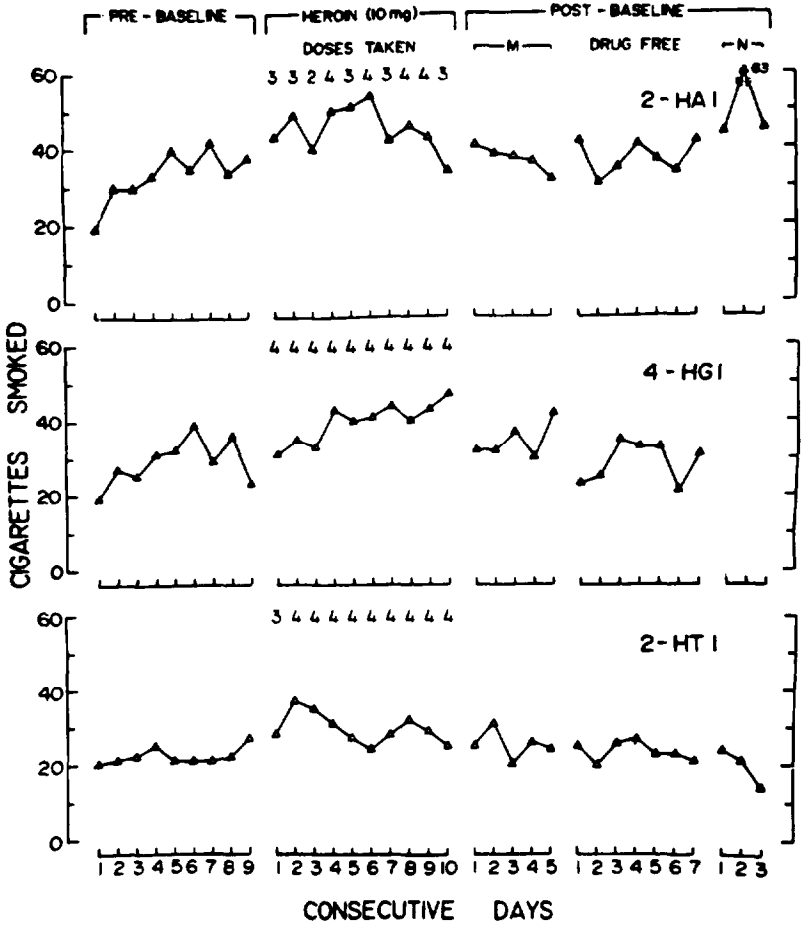

FIGURE 3

Cigarette smoking across successive drug conditions. Cigarette smoking over 34 consecutive days is shown for three individuals who were heavy tobacco smokers. Each subject was given naltrexone placebo durlng heroin availability. The successive drug conditions (drug free baseline, heroin plus naltrexone placebo, methadone detoxification, drug free baseline, and naltrexone availability) are shown across the top of the figure. Consecutive days in each condition are shown on the abscissa. The number of heroin doses taken each day by each subject is shown at the top of each row. The number of cigarettes smoked each day is shown on the ordinate. Reprinted with permission from Mello et al. 1980b. Copyright 1980, Springer-Verlag, Heidelberg.

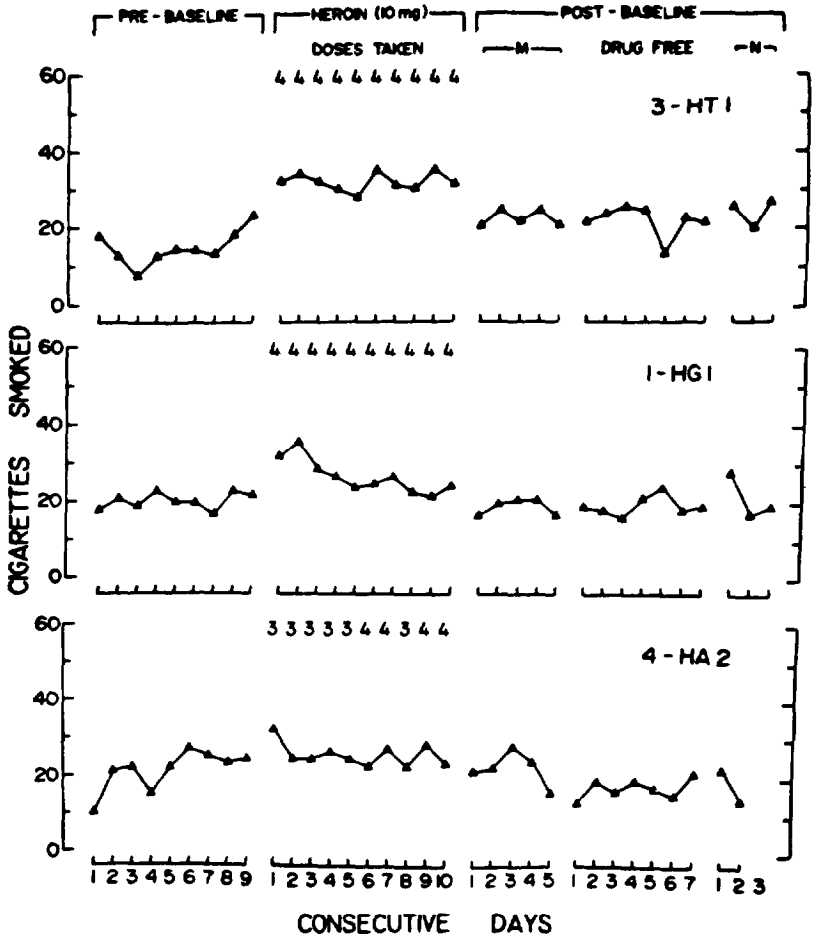

FIGURE 4

Cigarette smoking across successive drug conditions. Cigarette smoking over 34 consecutive days is shown for three individuals who were moderate tobacco smokers. Each subject was given naltrexone placebo during heroin availability. The successive drug conditions (drug free baseline, heroin plus naltrexone placebo, methadone detoxification, drug-free baseline, and naltrexone availability) are shown across the top of the figure. Consecutive days in each condition are shown on the abscissa. The number of heroin doses taken each day by each subject is shown at the top of each row. The number of cigarettes smoked each day is shown on the ordinate. Reprinted with permission from Mello et al. 1980b. Copyright 1980, Springer-Verlag, Heidelberg.

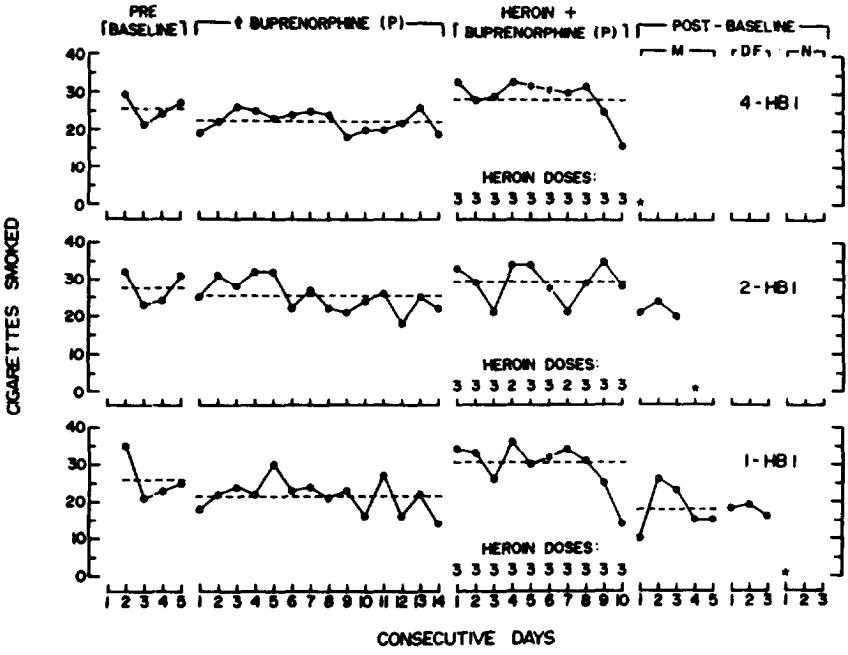

FIGURE 5

Cigarette smoking across successive drug conditions. Cigarette smoking by three individual subjects is shown over 39 consecutive days. Each subject was given buprenorphine placebo prior to and during heroin availability. The succcssive drug conditions (drug-free baseline, buprenorphine placebo, heroin plus buprenorphine placebo, and methadone detoxification) are shown at the top of the figure. Consecutive days in each condition are shown on the abscissa. The number of heroin injections taken each day by each subject is shown at the top of each row. The number of cigarettes smoked each day are shown on the ordinate. Missing data are indicated by an asterisk. The day on which each subject left the study is indicated by a star. Reprinted with permission from Mello et al. 1980b. Copyright 1980, Springer-Verlag, Heidelberg.

all subjects. Each subject smoked more cigarettes on the average during heroin self-administration than during the drug-free baseline or during buprenorphine placebo. However, only one subject

(1-HB-1) smoked significantly more during heroin use than during the immediately preceding buprenorphine placebo conditions ($p < .001$). Two subjects (1-HB-1, 2-HB-1) smoked significantly more cigarettes ($p < .01$) during the period of heroin self-administration than during the subsequent methadone detoxification period. The other subject (4-HB-1) left the study before the methadone detoxification period.

Temporal Patterns of Cigarette Smoking as a Function of Heroin Use. In an effort to determine if the significant increases in cigarette smoking by the naltrexone placebo subjects during heroin availability were generalized increases or were temporally associated with each heroin injection, two types of analyses were done. The number of cigarettes smoked before and after each heroin injection was compared and the temporal distribution of cigarette smoking during bastline, heroin, and methadone conditions was examined.

The number of cigarettes smoked during the hour preceding and the hour following each heroin injection was tabulated and the differences in cigarette smoking before and after heroin were evaluated for individual subjects. An analysis of variance showed that the time of day of the heroin injection did not result in significant differences in cigarette smoking. Therefore, it was possible to pool all pre- and post-heroin injection cigarette smoking data for each subject for matched t test analysis.

Five of the eight subjects smoked significantly more cigarettes during the hour immediately following heroin injection than during the hour preceding heroin self-administration ($p < .01$ to $.001$). The other three subjects smoked fewer cigarettes immediately following a heroin injection and this decrease in smoking was significant for two subjects ($p < .05$).

The average number of cigarettes smoked by the naltrexone placebo group during consecutive 6-hour periods was tabulated for each of three conditions: drug-free baseline, heroin availability, and methadone detoxification. The temporal distribution of group cigarette smoking during each of these conditions is shown in figure 6. There were no significant differences in number of cigarettes smoked as a function of the drug condition during the morning to early afternoon (8:00 a.m. to 2:00 p.m.) and during the afternoon to early evening (2:00 p.m. to 8:00 p.m.) periods. However, significantly more cigarettes ($p < .01$) were smoked in the evening and at night (8:00 p.m. to 2:00 a.m. and 2:00 a.m. to 8:00 a.m.) during heroin use than during baseline. Subjects smoked significantly more cigarettes in the morning ($p < .05$) and at night ($p < .01$) during heroin self-administration than during methadone detoxification. Since heroin was given once every 6 hours (at 8:00 a.m., 1:00 p.m., 8:00 p.m., and 2:00 a.m.), this shift in the temporal distribution of smoking could reflect the fact that subjects were awake longer and therefore smoked more. However,

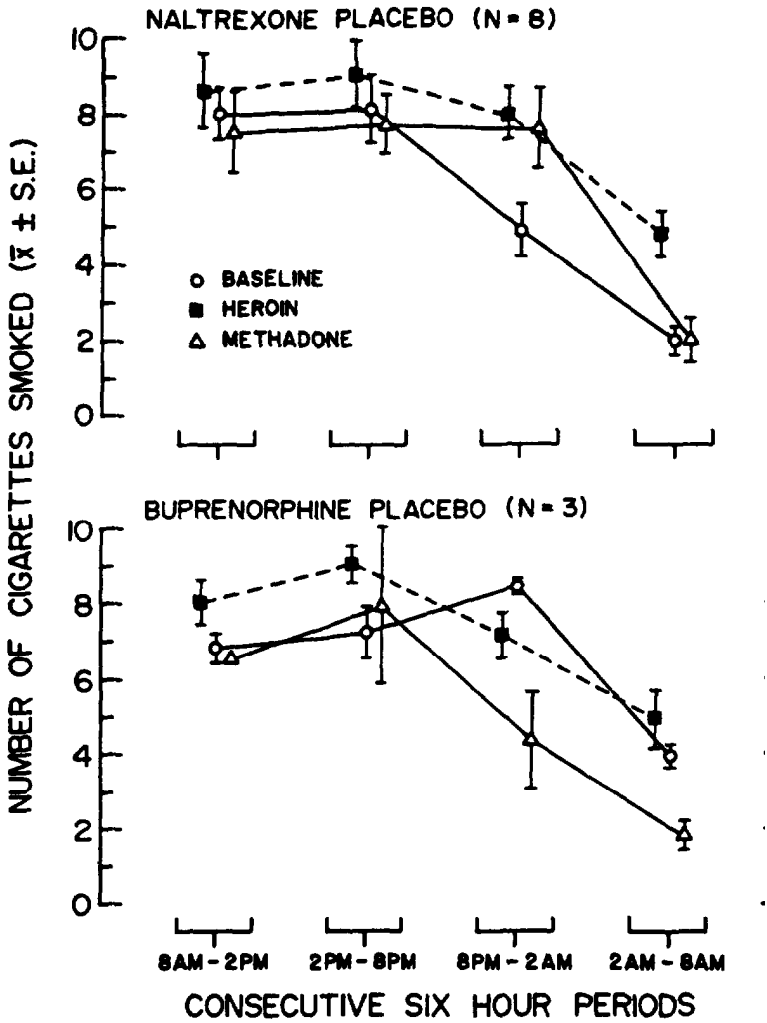

FIGURE 6

Cigarettes smoked as a function of time of day. The number of cigarettes smoked ($\bar{X}$ + S.E.) are shown on the ordinate and consecutive 6-hour periods are shown on the abscissa. The top row shows the number of cigarettes smoked by the naltrexone placebo group (N=8) during the drug-free baseline (open circle), the 10 days of heroin availability (closed square), and the methadone detoxification period (open triangle). The second row shows the number of cigarettes smoked by the buprenorphine placebo subjects (N=3) during the drug-free baseline (open circle), heroin availability (closed square), and methadone detoxification (open triangle). Reprinted with permission from Mello et al. 1980b.

comparison of hours slept during baseline, heroin self-administration, and methadone detoxification revealed no significant differences by t test analysis. Consequently, there were equivalent waking hours available for smoking during each condition.

The temporal distribution of smoking by the buprenorphine placebo group was also analyzed as a function of consecutive 6-hour periods during the drug-free baseline, buprenorphine placebo, and heroin availability conditions. These data are shown in the lower panel of figure 6. Heroin injections occurred three times a day, at 9:00 a.m., 5:00 p.m., and 1:00 a.m. Although more cigarettes were smoked during heroin use in the evening and at night than during the drug-free baseline, these differences were not statistically significant. There were also no significant differences in hours of sleep during baseline and heroin self-administration. However, these subjects did sleep significantly more during methadone detoxification than during heroin self-administration ($p < .05$).

Intercigarette Interval Analysis. In order to determine if there were marked changes in the overall rate of cigarette smoking as a function of heroin self-administration, the distribution of intervals between successive cigarette requests was examined for three representative placebo naltrexone subjects. The number of cigarette requests occurring at intervals of less than 15 minutes, 16 to 30 minutes, 31 to 45 minutes, and so on were tabulated for the drug-free baseline condition and for the period of heroin self-administration for individual subjects. The percent of the total number of cigarettes smoked during each condition at each intercigarette interval was calculated. The distributions of intersmoking intervals are shown in figure 7.

Subject 3-HT-1 increased cigarette smoking during heroin self-administration by an average of 17 cigarettes per day or 113% (cf. figure 3). The peak intercigarette Interval distribution fell between 16 and 30 minutes during both baseline and heroin conditions. However, during baseline, he smoked 19% more of the total number of cigarettes at intervals of 46 to 60 minutes, 61 to 75 minutes, and 76 to 90 minutes than during heroin self-administration. When heroin became available, this subject smoked more cigarettes more frequently, i.e., 72% of all cigarettes were smoked at intervals between zero and 45 minutes. During baseline, he only smoked 50% of his total cigarettes at this rate and 6% of the cigarettes were smoked at intervals of 6 or more hours.

Subject 1-HA-1 smoked an average of 10 more cigarettes per day during heroin self-admlnistration than during baseline and averaged 45 cigarettes per day (cf. figure 3). The peak and form of the distribution of intercigarette intervals during baseline and heroin conditions were very similar. However, he smoked 12% more cigarettes at 0- to 30-minute intervals during heroin self-administration than during baseline.

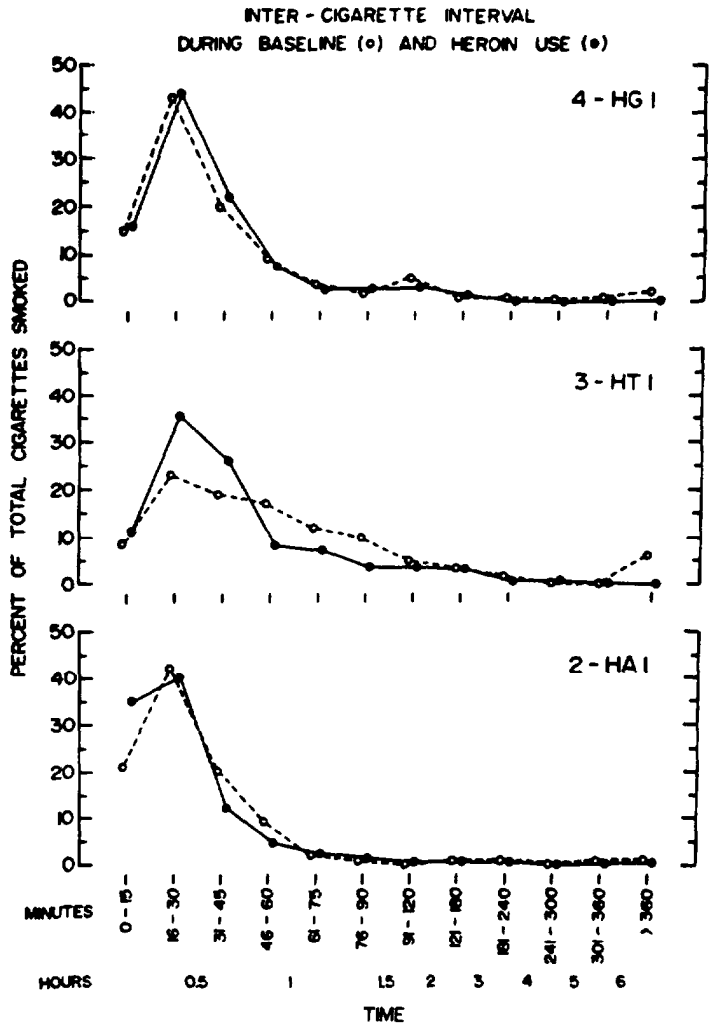

FIGURE 7

Distribution of intercigarette intervals during baseline and heroin use. The interval between successive cigarette requests is shown on the abscissa. The percent of the total cigarettes smoked during the 9-day baseline period and 10 days of heroin availability is shown on the ordinate. Intersmoking interval data are presented for three naltrexone placebo subjects who were moderate or heavy smokers. Reprinted with permission from Mello et al. 1980b. Copyright 1980, Springer-Verlag, Heidelberg.

Subject 4-HG-1 also smoked an average of 10 more cigarettes per day during heroin self-administration than during baseline and averaged 39 cigarettes per day during that period (cf. figure 3). However, there was no appreciable change in the distribution of intercigarette intervals, except that he smoked fewer cigarettes at intervals of 3 to 6 hours during heroin self-administration than during baseline.

These distributions of intercigarette intervals suggest that the increased smoking during heroin self-administration reflects a more rapid rate of smoking, rather than smoking more cigarettes at long intervals of 3 hours or more. The consistency of the peak of the distribution of intersmoking intervals within and across subjects and across conditions indicates that these moderate to heavy smokers usually smoke a cigarette every 15 or 30 minutes (Mello et al. 1980b).

Methadone Effects on Cigarette Smoking. These observations that intravenous heroin self-administration is associated with increased cigarette smoking have recently been extended to oral administration of another opioid agonist, methadone (Chait and Griffiths 1984). Five male volunteers with a history of opiate drug abuse, and maintained in a methadone maintenance treatment program, were studied. Dally 120-minute sessions were held five times each week. Ninety minutes before the smoking session, subjects were given the pretreatment drug (methadone, dextromethorphan, or placebo) and then allowed to smoke ad libitum for 60 minutes. A 30-minute period of cigarette deprivation preceded each smoking session. These subjects were maintained on 40 to 60 mg of oral methadone. The methadone pretreatment dose was 0.5, 1.0, or 2.0 times each individual subject's maintenance methadone dose (Chait and Griffiths 1984).

Figure 8 shows that methadone pretreatment resulted in dose dependent increases in cigarette smoking in four of the five subjects studied. Group data shows that the mean number of cigarettes smoked during the two-hour session increased twofold after the high dose methadone in comparison to placebo. Pretreatment with placebo or dextromethorphan had no consistent appreciable effect on cigarette smoking. A number of other smoking related measures also increased with increasing methadone doses. Subjects changed their smoking behavior to increase their smoke intake, i.e., both the number and duration of puffs per session increased at higher methadone doses. Moreover, the total time spent puffing during the session increased 2.8-fold after the high dose of methadone in comparison to placebo. Correlated increases in expired air CO levels indicated that subjects were actually inhaling more smoke during the high methadone dose smoking sessions. Similarly, there was a decrease in the latency to the first puff of the session as well as the mean intercigarette interval with increasing methadone doses (Chait and Griffiths 1984).

these findings that methadone pretreatment can produce substantial increases in cigarette smoking are concordant with previous

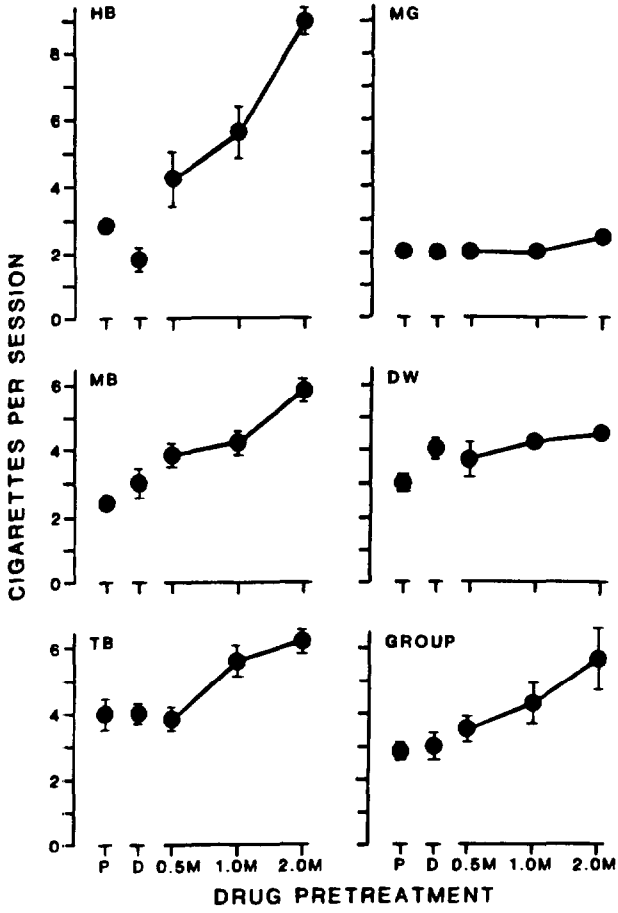

FIGURE 8

The number of cigarettes smoked per session as a function of drug pretreatment for individual subjects and for the group (bottom right panel). Bars show ±1 S.E.; P, placebo; D, dextromethorphan; M, methadone. Reprinted with permission from Chait and Griffiths, 1984. Copyright 1984, American Society for Pharmacology and Experimental Therapeutics.

observations of the effects of methadone detoxification. As the daily methadone maintenance dose was decreased, the number of cigarettes per day also gradually decreased (Bigelow et al. 1981).

One possible implication of the association between opioid agonist administration and increased cigarette smoking is that endogenous opioids may contribute to the reinforcing effects of cigarette smoking . Pomerleau and coworkers (1983) have reported that after cigarette smoking, increased plasma nicotine levels were significantly correlated with increased beta-endorphin levels, with no change in ACTH levels. These findings suggest the importance of examining the effects of opioid antagonists on cigarette smoking.

Opiate Antagonist Effects on Cigarette Smoking

Unfortunately, studies of the effects of opioid antagonists on cigarette smoking have yielded inconsistent and contradictory findings. Nal trexone, a long acting opioid antagonist, did not change cigarette smoking in one heroin addict subject (Mello et al. 1980b). The naltrexone-maintained (50 mg/day p.o.) subject smoked an average of 25 cigarettes per day during a 9-day drug free baseline and a 10-day period of naltrexone maintenance (Mello et al.) The effects of administration of a short acting opioid antagonist, naloxone (10 mg s.c.), on cigarette smoking was studied in three men and four women under ordinary working conditions (Karras and Kane 1980). Subjects were offered a cigarette every 30 minutes for 3 hours following naloxone administration and asked to report their desire for a cigarette, their mood, and their satisfaction with the cigarette (if smoked). Subjects were allowed to smoke a cigarette only for 2 minutes and were requested to abstain from cigarettes except during the smoking trials. The experimenters recorded the number of puffs taken and weighed the butts of the cigarettes. Subjects took 32% fewer puffs and smoked 30% less often after naloxone administration than after placebo administration. The amount of each cigarette smoked, inferred from the weight of the remaining cigarette butt, was also reduced by 33%. Karras and Kane (1980) interpreted these data as consistent with the hypothesis that beta-endorphin is released during smoking and may be partially responsible for smoking maintenance.

These findings were not replicated under laboratory conditions in subjects given a range of naloxone doses (0.625, 0.25, 1.0, and 4.0 mg/kg i.m.) when a number of smoking related measures including expired carbon monoxide levels were also examined (R.R. Griffiths, Personal Communication, 1984). Naloxone or placebo was administered 60 minutes before the 120-minute smoking sessions in seven normal subjects. Each subject was used as his own control in three treatment conditions with at least 48 hours between smoking sessions. Naloxone administration had no effect on any smoking related measures including carbon monoxide levels in expired air across the naloxone dose range studied.

At present, most of the evidence suggests that narcotic antagonists do not significantly alter cigarette smoking under both acute and chronic administration conditions. However, the effects of opiate antagonists have been studied in a total of 15 smokers in three different laboratories and findings have been inconsistent. Additional studies should provide a more definitive answer to this question.

Opioid Mixed Agonist-Antagonist Effects on Cigarette Smoking

Since opioid agonists consistently increase cigarette smoking (Mello et al. 1980b; Chait and Griffiths 1984) and opiate antagonists either have no effect or decrease smoking behavior, it is interesting to consider the effects of an opioid that has both agonist and antagonist properties. Buprenorphine is a potent opioid agonist with respect to analgesia, physiological, and subjective reactions in man and is also a long acting opiate antagonist like naltrexone (Houde 1979; Jasinski et al. 1978; Levis et al. 1983). Buprenorphine has been shown to produce opiate agonist-like subjective effects comparable to morphine and methadone. A comparison of the effects of single doses of buprenorphine (0.2 to 2.0 mg), morphine (15 to 40 mg), and methadone (30 mg) showed similar euphoria and liking scores on several self-report measures. An 8 mg/day dose of buprenorphine produced subjective effects and euphoria equivalent to that produced by 120 mg/day of morphine (30 mg q.i.d.) or 40 to 60 mg of methadone (Jasinski et al. 1978).

The agonist and antagonist components of buprenorphine appear to have different durations of action (Lewis et al. 1983). Buprenorphine can antagonize high doses of morphine (60 to 120 mg) for almost 30 hours (Jasinski et al. 1978), whereas an analgesic dose of buprenorphine effectively relieves pain for about 6 hours (Houde 1979).

The effects of huprenorphine on heroin self-administration and cigarette smoking were evaluated under clinical research ward conditions (Mello and Mendelson 1980; Mello et al. 1982). Nine heroin addict subjects were cigarette smokers. Three were sssigned to buprenorphine treatment and two to buprenorphine placebo treatment. Four subjects participated in two separate studies and received both buprenorphine and placebo in a counterbalanced order; i.e., two received buprenorphine first and two received placebo first. Consequently, final data are reported for seven subjects assigned to buprenorphine and six subjects assigned to placebo under double blind conditions.

After a 5-day drug free baseline, subjects were given ascending doses of buprenorphine or its placebo for 14 days at 8 a.m. each day. An initial subcutaneous buprenorphine dose of 0.5 mg/day was gradually increased by 0.5 mg per day for 12 days and by 1 mg per day for 2 days to a final dose of 8 mg/day s.c. The volume of placebo and buprenorphine injections was equivalent at each dose level. Subjects were maintained on 8 mg/day of buprenorphine (or

placebo) for 10 days during which they could work for i.v. heroin at a simple operant task. They were then gradually withdrawn from buprenorphine over 5 days in a dose reduction schedule of 7, 6, 5, 3, and 1 mg/day. All subjects assigned to placebo buprenorphine used heroin and were detoxified with methadone in progressively decreasing doses (25 to 5 mg/day p.o.) over 5 days.

Heroin self-administration was significantly suppressed by bupre norphine treatment, whereas placebo maintained subjects self-administered 93% to 100% of all the heroin available (Mello and Mendelson 1980; Mello et al. 1982). Placebo maintained subjects increased cigarette smoking significantly during heroin self-administration (Mello et al. 1980b).

Buprenorphine treatment was associated with a significant increase in tobacco smoking in comparison to the drug free baseline. During the 14-day ascending dose phase, buprenorphine doses of 2.0 mg/day s.c. and above were associated with significant increases in cigarette smoking ($p < .01$). During the 10-day period of buprenorphine maintenance at 8 mg/day, the significant increase in smoking observed during buprenorphine induction was sustained. Subjects smoked significantly more cigarettes during the period of high dose buprenorphine maintenance than during the buprenorphine induction phase ($p < .01$). As the daily buprenorphine dose was decreased from 7 to 1 mg/day, cigarette smoking also decreased and returned to baseline levels during the postbuprenorphine drug free period. Subjects in the buprenorphine treatment group and the placebo treatment group smoked an equivalent number of cigarettes during the predrug and postdrug free baseline periods (Mello et al. 1985).

These data suggest that the agonist properties of buprenorphine remained salient in terms of its effects on cigarette smoking over 29 days of chronic administration. These findings are interesting in view of the fact that the antagonist component of buprenorphine appears to last for almost 30 hours (Jasinski et al. 1978), whereas the agonist analgesic effects persist for about 6 hours (Houde 1979). Tolerance to most of the opioid agonist-like side effects developed within 21 days of chronic buprenorphine maintenance in most subjects (Mello et al. 1982).

Buprenorphine appears to act primarily like an opioid agonist in its effects on cigarette smoking (Mello et al. 1985). Buprenorphine also acts primarily like an agonist rather than an antagonist on male pituitary hormones (Mendelson et al. 1980). chronic buprenorphine maintenance was associated with the suppression of luteinizing hormone (LH) and prolactin (PRL) levels, a finding comparable to that previously observed in heroin users and heroin addicts treated with methadone and with LAAM (Mendelson and Mello 1975, 1982; Mendelson et al. 1974, 1975 a,b,c). In contrast, opioid antagonists such as naltrexone have been shown to be associated with an increase in LH in normal adult males (Mendelson et al. 1980; Ellingboe et al. 1982), and naloxone is frequently used to stimulate LB for endocrine studies in the males of several species (Moult et al. 1981; Mirin et al. 1976; Cicero et al. 1979, 1982).

In summary, the facilitatory effects of opiofd agonists on cigarette smoking appears to be a robust finding consistently observed under different experimental conditions (Mello et al. 1980b; Chait and Griffiths 1984). The decrease in cigarette smoking associated with gradual decreases In daily methadone maintenance doses (Bigelow et al. 1981) was also seen during both buprenorphine and methadone detoxification (Hello et al. 1985). However , despite these converging findings, it is difffcult to account for the apparent effects of opioid agonists on smoking. It is not clear if more cigarettes were smoked during opioid use because they were more reinforcing, or because their effects were attenuated by opioid intoxication and more cigarettes were required (cf. Hello et al. 1980b). Chait and Griffiths (1984) suggested that methadone might block or attenuate the aversive effects of cigarette smoking such as throat irritation which could limit smoking under drug free conditions.

The possible contribution of endogenous opioids to cigarette smoking is a provocative hypothesis, but still quite speculative. The notion that an opiofd antagonist such as naloxone or naltrexone might lower cigarette smoking by antagonizing smoking related increases in plasma beta-endorphin levels (cf. Karras and Kane 1980; Pomerleau et al . 1983) has been challenged by studies showing that opioid antagonists have no effects on cigarette smoking (Mello et al . 1980b; R.H. Griffiths, Personal Communication, 1984). The fact that the opioid mixed agonist-antagonist buprenorphine significantly increased cigarette smoking is also inconsistent with the hypothesis that opioid antagonists might antagonize cigarette smoking through related changes in endogenous opioids. Since buprenorphine effectively antagonized both the subjective and physiological effects of heroin and decreased heroin self-administration by heroin addicts over 10 days (Mello and Mendelson 1980; Hello et al. 1982), it is likely that buprenorphine antagonized endogenous opioid levels as well . Alternatively, if increases in beta-endorphin levels associated with increased nicotine levels following smoking (Pomerleau et al. 1983) are important for the reinforcing properties of cigarette smoking, it could be argued that more cigarettes were smoked during buprenorphine treatment because they were less reinforcing.

MARIJUANA EFFECTS ON CIGARETTE SMOKING

In contrast to alcohol, opiates, and certain stimulants, marijuana does not appear to alter tobacco smoking in any systematic way (Hello et al. 1980a; Hello and Mendelson, in press). Examination of cigarette smoking in a study of the covariation between alcohol and marijuana use (see Hendelson et al., this volume) showed that there were no dose related changes in cigarette smoking during marijuana availability. The introduction of marijuana did not change average cigarette smoking in comparison to the drug free baseline, except in one occasional tobacco smoker who smoked more during both alcohol and marijuana availability (Hello et al. 1980a).

Recently, we have examined cigarette smoking during marijuana smoking in women (Mello and Mendelson, in press). Sixteen of 21 women studied were cigarette smokers. Cigarettes were freely available upon request. Women could earn one 1-gram marijuana cigarette or 50¢ in 30 minutes of performance at a simple operant task on a second order FR 300 (FI 1 sec:S) schedule of reinforcement. A 7-day drug free baseline was followed by 21 days of marijuana availability and a postmarijuana drug free period of 7 days. The amount and temporal pattern of tobacco cigarette smoking observed during drug free conditions were not changed during concurrent marijuana use by either heavy or moderate marijuana smokers (Mello and Mendelson, in press).

Although it might be expected that smoking marijuana and tobacco would be antithetical, in fact, these drugs usually were smoked in close temporal contiguity by both men and women (Mello et al. 1980a, Mello and Mendelson,in press). These data have unfortunate implications for one medical consequence of marijuana and tobacco smoking, impaired pulmonary function. Adverse effects of marijuana smoking on pulmonary function have been consistently demonstrated in numerous studies with men (Tashkin et al. 1973, 1976, 1980; Vachon et al. 1973; Bernstein et al. 1976). Studies of pulmonary function in these female marijuana users have shown that single breath carbon monoxide diffusion capacity was signifcantly lower than in tobacco cigarette smokers and nonsmoker control subjects (Tlllea et aL,in press). These data were interpreted to suggest that marfjuana smoking may cause significant impairment of pulmonary function associated with the gas exchange surface of the lungs.

TOBACCO SMOKING AND DRUG INTERACTIONS

Alcohol, opioid agonists, and mixed agonist-antagonists as well as certain stimulants (Schuster et al. 1979; Henningfield and Griffiths 1981) have been shown to be associated with increased cigarette smoking. Since these drugs have a broad spectrum of actions, it is difficult to construct a plausible hypothesis concerning specific pharmacological effects on cigarette smoking.

Nicotine appears to be the primary pharmacological reinforcer in cigarette smoking (Jaffe and Jarvik 1978; Russell 1976; Gritz 1980), but it has been difficult to separate the effects of nicotine from other constituents of tobacco smoke. The pharmacokinetics of nicotine make it an almost ideal drug reinforcer. Nicotine inhaled from cigarettes reaches the CNS within seconds and appears to produce rapid behavioral effects which diminish over 30 to 40 minutes (Jaffe and Jarvik 1978). There is increasing evidence that subjects adjust their smoking behavior to maintain constant nicotine levels when low nicotine content or short cigarettes are provided (Benowitz and Jacob 1984; Herning et al. 1981; Gritz 1980; Chait and Griffiths 1982; Robinson et al. 1983). But, analysis of several aspects of the microtopography of smoking behavior, such as puff duration (Nemeth-Coslett and Griffiths 1984) and puff frequency (Griffiths et al. 1982), has not shown significant effects of nicotine dose. Consequently, the role of

nicotine in maintaining cigarette smoking is continually under evaluation (Jarvik et al. 1977; Kumar et al. 1977).

In experimental animal studies, intravenous nicotine can be a positive or a negative reinforcer depending upon the schedule of nicotine reinforcement and the behavioral history of the animal (cf. Goldberg et al. 1983 for review). Similar results have been obtained in human studies of the reinforcing properties of intravenous nicotine (Henningfield and Goldberg 1983). These studies Illustrate the complexity of analyzing the reinforcing properties of nicotine alone.

The interactions between cigarette smoking and other drugs from various classes presents an even greater challenge. This problem illustrates aome as yet unresolved questions concerning the nature of the reinforcer in polydrug use. The simultaneous use of drugs which appear to have contradictory pharmacological effects is especially puzzling. We have suggested elsewhere that polydrug use may have less to do with the pharmacological properties of the drugs or the anticipated effects than with the capacity to produce some change in subjective states (Mello 1977, 1978, 1983). Change, rather than any particular direction of change, may be the goal of the polydrug user. It appears that any drug or drug combination that has definite stimulus properties and behavioral effects for the user may have abuse potential. Since multiple drug use appears to be an increasingly common pattern, the way in which drugs interact to modulate use patterns is an important area for further study.

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Drug Combinations in Pleasure and Pain

Conan Kornetsky, Ph.D.

The use of more than one drug simultaneously is not new. Drugs are combined for both medical and nonmedical use, e.g., codeine and aspirin for the relief of pain, heroin and cocaine for the enhancement of euphoria. In this essay, I will describe a series of experiments from my laboratory on the effects of various combinations of drugs on the threshold for brain-stimulation reward (pleasure) and brain-stimulation escape (pain).

We, as well as others (e.g., Kelly and Reid 1977; Wise 1980), have suggested that many abuse substances increase the sensitivity of animals to rewarding brain stimulation and, by inference, these substances cause an activation of those areas of the brain that are involved in brain-stimulation reward. Olds and Milner (1954) were the first to report that animals would work in order to receive electrical stirmlation to various areas of the brain. Although animals will work for stimulation to many midbrain and cortical sites, the most reliable site commonly used for eliciting self-stimulation behavior is the medial forebrain bundle/lateral hypothalamic area. The phenomenon has been called intracranial self-stimulation (ICSS) as well as brain-stimulation reward. For the most part, but not exclusively, the former term has been used when the animals are in an operant paradigm and the dependent variable is rate of lever pressing for the rewarding stimulation. We have used the term brain-stimulation reward to designate threshold determinations.

We (Marcus and Kornetsky 1974) first demonstrated that morphine will lower the threshold for brain-stimulation reward and raise the threshold for brain-stimulation escape. The dose-effect curve for the brain-stirmlation reward is U-shaped, while it is a monotonic positive dose-effect curve for escape from aversive brain stimulation. For a review of this work see Kornetsky and wheeling (1982) and Kornetsky (1985).

REWARDING BRAIN STIMULATION

METHOD

Bipolar stainless steel electrodes (0.013cm in diameter and insulated except at the tips) are stereotaxically implanted bilaterally in the lateral hypothalamic region of the medial forebrain bundle of male rats (300 g, CDF, Charles River Laboratories, Wilmington, MA). Surgical anesthesia is produced by systemic administration of Equi-Thesin (0.3 ml/100 g of body weight). After surgery, animals are given at least 1 week for postoperative recovery before behavioral testing is instituted. Animals are maintained on a 12-hour light/dark cycle, housed in standard steel cages, and have ad libitum access to food and water.

During the initial phase of animal training, each electrode is tested to determine the current intensity needed to produce appetitive behavior with little or no motor artifact. The electrode which produces appetitive behavior at the lowest current intensity and has the least or no motor artifact is used in the subsequent study. Animals are trained and tested on a rate independent threshold procedure in a plastic chamber (20 by 20 by 35 cm) A wheel manipulandum is located within one wall of the test chamber. Four equally spaced cams on one endplate of the wheel manipulandum operate a microswitch which results in immediate delivery of a stimulation when the wheel is rotated one-quarter of a turn. A constant current stimulator (Sunrise System, Pembroke, MA) is used to deliver the biphasic symmetrical pulses. Each stimulus consists of a 500 milliseconds (msec) train with a pulse width of 0.2 msec and a delay of 0.2 msec between the positive and negative pulses at a frequency of 160 Hz.

Thresholds are determined by a procedure involving the use of discrete trials systematically presented over a range of stimulus intensities. A trial begins with the delivery of a non-contingent stimulus. A response of one-quarter wheel turn within 7.5 seconds (sec) of this stimulus results in the delivery of a contingent stimulus, identical in all parameters to the non-contingent stimulus, and terminates the trial. Failure to respond has no scheduled consequences and the trial is terminated after 7.5 sec. The interval between trials varies around an average of 15 sec, and responses made during the intertrial interval (error responses) result in a 15 sec delay before the start of the next trial.

Stimulus intensities are varied using a modification of the classical psychophysical method of limits. Stimuli are presentd in an alternating descending and ascending series with a step size of 5 or 10μA (depending on the sensitivity of the individual animal) with five trials presented at each intensity level before the next lower or higher intensity is presented. Subjects complete four series (i.e., descending, ascending, descending and ascending) prior to injection, then four or eight series postinjection, with the entire pre-, post-session lasting 2.5 to 3 hours. All experimental data are collected and stored by an on-line micro-

computer. Each series' threshold value is defined as the midpoint in microamperes between the level at which the animal makes three or more correct responses out of the five stimulus presentations (a plus score) and the level where less than three correct responses (a minus score) were made. The pre- and post-injection thresholds are defined by the respective series means.

Animals require approximately six 1-hour training sessions to learn the task and approximately four additional sessions for the establishment of a stable threshold level whereupon saline injections are begun. Animals are tested with saline injections for five days before drug administration is initiated. Also, saline days are interspersed with drug treatment day so that animals receive a drug only twice weekly.

Threshold values are calculated for both the preinjection and the postinjection sessions, with the difference between the two scores taken as the dependent measure. These difference scores are transformed to standard scores (Z-scores) based on the mean and standard deviation of the difference scores for all saline days. A Z-score of ±2.0 or greater (95% confidence limits) is preselected as the level for significance.

TRIPELENNAMINE AND PENTAZOCINE

Because of the street use of this combination, called "T's and Blues," we determined the effect of these drugs alone and in combination on the threshold for rewarding brain stimulation. In previous studies, we had already found that pentazocine would lower the threshold by itself (Kometsky et al. 1979) and, to our surprise, we found that tripelennamine would also lower the threshold by itself (Unterwald et al. 1984). This finding is in agreement with those of Jasinski (personal communication), who found that tripelennamine causes an increase in euphoria as measured by the Addiction Research Center Inventory. Although both tripelennamine and pentazocine significantly lower the threshold for reward, the effect is minimal and considerably less than that seen after morphine.

Figure 1 (top) shows the mean effect (in Z-soorss) of five animals after various doses of tripelennamine. The bottom panel of the figure shows the effects of 2.5 mg/kg of tripelennamine administered simultaneously with various doses of pentaxocine (Unterwald and Kometsky 1984). As can be seen, the 2.5 mg dose of tripelennamine has no significant effect by itself, but when combined with ineffective doses of pentazocine, the effect is clearly and markedly significant. It is important to note that the results suggest a real synergistic effect, for were the effect only due to increasing the amount of pentazocine available at receptor sites, then the dose/response curve simply would have moved to the left. By combining the two drugs, however, the mamximum effect, or efficacy, is clearly enhanced.

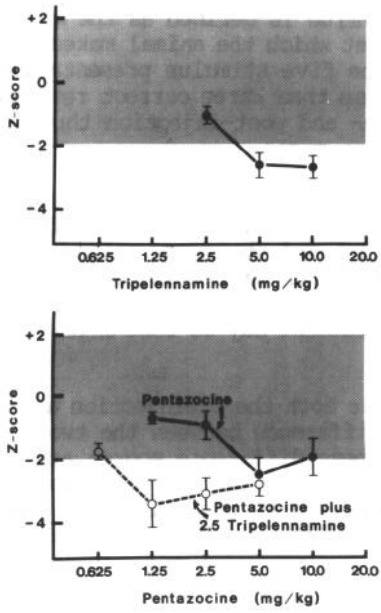

FIGURE 1
Mean Z-score Effects of Various Doses of Tripelennamine (top panel) and Pentazocine (bottom panel). TheBottom Panel also shows the Effects of 2.5mg/kg of Tripelennamine with Various Doses of Pentazocine. Error Bars Indicate the Standard Error of the x Z-score. A Z-score of ±2 Indicates the 95% Confidence Limits. (Adapted from Unterwald and Kometsky 1984) Copyright 1984, ANKHO International, Inc.

NALBUPHINE AND TRIPEPENNAMINE

In order to further examine the effects of tripelennamine with a mixed agonist-antagonist, we studied the simultaneous administration of tripelennamine with nalbuphine. Nalbuphine is currently available in injectable form for clinical use as an analgesic. Jasinski and Mansky (1971) reported that it has significantly less abuse potential than morphine, although it does increase the euphoria score on the Addiction Research Center Inventory. Also, animals will self-administer nalbuphine (Steinfels et al. 1982). Figure 2 shows the results obtained with an ineffective dose of tripelennanine combined with various doses of nalbuphine in the rat. As can be seen, although nalbuphine alone will significantly lower the threshold for rewarding brain stimulation, the addition of tripelennamine causes a highly significant increase in efficacy, and moves the We-effect curve to the left.

Figure 3 presents sane idea of the relative effects of these tripelennamine mixtures as compared to morphine, cocaine, or amphetamine.As can be seen,the combinations put tripelennamine, with pentazocine and nalbuphine, in the same class with the latter highly favored and abused substances.

MORPHINE AND D-AMPHETAMINE ON REWARD

Two experiments with morphine and d-amphetamine were carried out by Hubner et al (1983). In the first one, a minimally effective dose of morphine was given simultaneously with various doses of d-amphetamine. In the second experiment, the procedure was reversed;

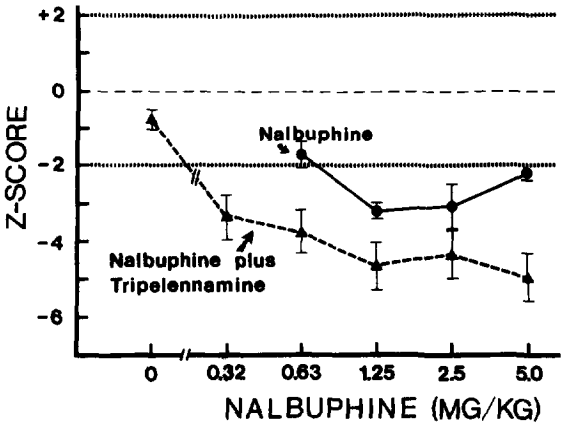

FIGURE 2
Mean Effect of Various Doses of Nalbuphine Alone and in Combination with 2.5 mg/kg of Tripelennamine

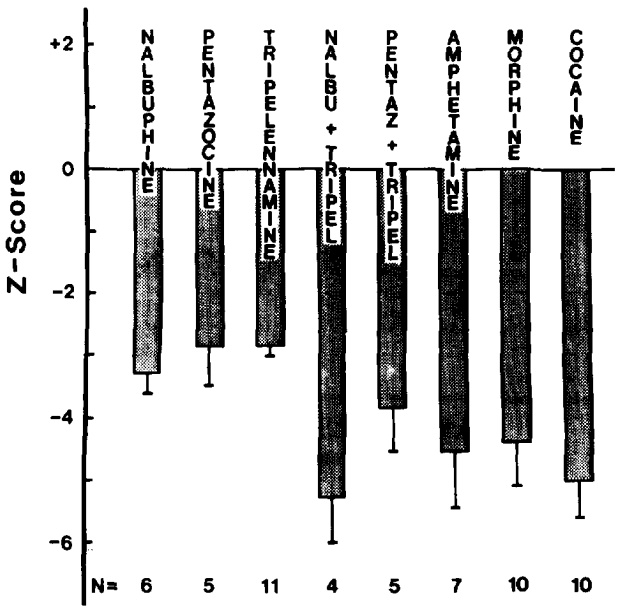

FIGURE 3
Mean Maximal Lowering Effect on Rewarding Stimulation for Several Drugs. As in Previous Figures, Data are Presented in Z-scores with Error Bars. (Data from Unterwald and Kometsky 1984)

an ineffective dose of d-amphetanine was given simultaneously with various doses of morphine. The procedure used in these experiments was similar to that used in the previously described studies. In both cases, there was clearly a greater effect of these two drugs when given together than when given separately. However, it is not clear whether the effect was simply additive or synergistic. A summary of the effects of the combination in the three animals used in the second experiment is shown in figure 4. The figure shows doses of morphine from 0.25 to 2.0 mg/kg alone and with a nonsignificant threshold-lowering dose of d-amphetamine. The dose of d-amphetamine used varied between animals. In each case, a non-significant dose was selected. The doses were 0.063, 0.125, and 0.5 mg/kg, respectively. Although the effect of morphine alone, as represented in the figure, indicates no significant effect at the 2.0 mg/kg dose, doses up to 1.0 mg/kg rarely show a significant lowering of the threshold in an individual animal.

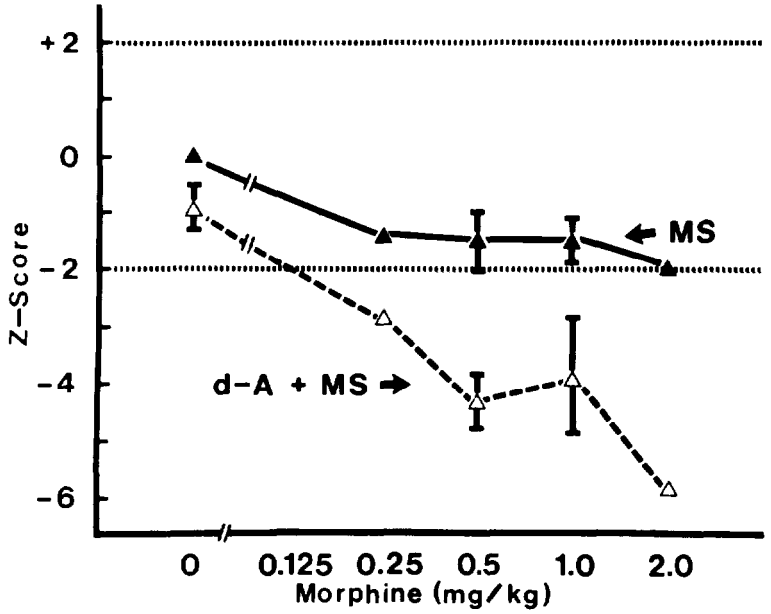

FIGURE 4

Mean Effects of Morphine Sulfate Alone (N=3) and in Combination with d-Amphetanine. (Data from Hubner et al. 1983)

AVERSIVE BRAIN STIMULATION

METHOD

The experimental chamber, the manipulandum, and the characteristics of the electrical stimulation are identical to those we use in determining the threshold for brain-stimulation reward. However,

in these experiments, the electrodes are stereotaxically implanted into a brain site that, when stimulated, is only aversive. The brain site that we use is the mesecephalic reticular formation (MRF). The rat quickly learns to escape from such stimulation by rotating the manipulandum a quarter turn. A trial is initiated by the onset of the electrical stimulation. A response within 7.5 sec immediately terminates the shock and the trial. If no response occurs within 7.5 sec, the stimulus is automatically terminated. Stimulus intensities are varied according to a modification of the classical psychophysical method of limits. Stimuli are presented in an alternating ascending and descending series with a step size of 1 or 2μA, depending on the sensitivity of the animal. An ascending series is initiated at a previously determined sub-threshold intensity. Three trials are given in succession at each intensity. Two or more escape responses at a particular intensity are scored as a plus, while less than two responses are scored as a minus. An ascending series is conducted until plus scores are achieved in two successive steps. A descending series is then initiated at one step size lower and current intensity continuously decreased until two successive minus scores are achieved. The threshold for a particular ascending or descending series is defined as the midpoint between those intensities which delimited the transition from plus to minus scores.

Four series, two ascending and two descending, comprised a session. A session threshold is computed as the mean of the four series thresholds. Immediately after the first session is completed, animals are injected subcutaneously with the test drug or saline, and a second session of four series is conducted.

Threshold differences between pre- and post-injection sessions on a drug test day are expressed as a Z-score based on the standard deviation of the mean threshold differences for all saline test days. As in the case of brain-stimulation reward, a Z-score of ±2.0 or greater (95% confidence limits) is preselected as the level for significance.

Using this method, we have found that morphine (Wheeling et al. 1981), cyclazocine and pentazocine (Sasson and Kometsky 1986) and ethylketocyclazocine (Sasson and Kometsky 1984) all raise the escape threshold. Naloxone lowers the threshold (Sasson and Kometsky 1983), and amphetanine either lowers it or has no effect (Sasson et al. 1983).

AMPHETAMINE AND MORPHINE

It has been previously demonstrated that amphetamine combined with morphine results in a greater degree of analgesia in man than morphine alone (Forrest et al. 1977). In order to test whether our model would also show a potentiation of the analgesic effect of morphine by amphetamnine, we tested various doses of amphetamine in combination with a dose of morphine that was ineffective in raising the escape threshold (Sasson et al. 1983).

Four animals were tested. As in previous experiments, we found that morphine alone in doses from 1.0 to 16.0 mg/kg (i.p.) caused

a dose-related increase in the escape threshold d-Amphetamine at doses from 0.06 to 4.0 mg/kg (i.p.) either had no effect or lowered the escape threshold. Figure 5 show the interaction of a minimally effective or ineffective dose of morphine in combination with various doses of d-amphetamine in two of the four animals tested. Similar results were obtained in the other two animals As shown, the d-amphetam ine clearly potentiated the antinociceptive effect of the morphine

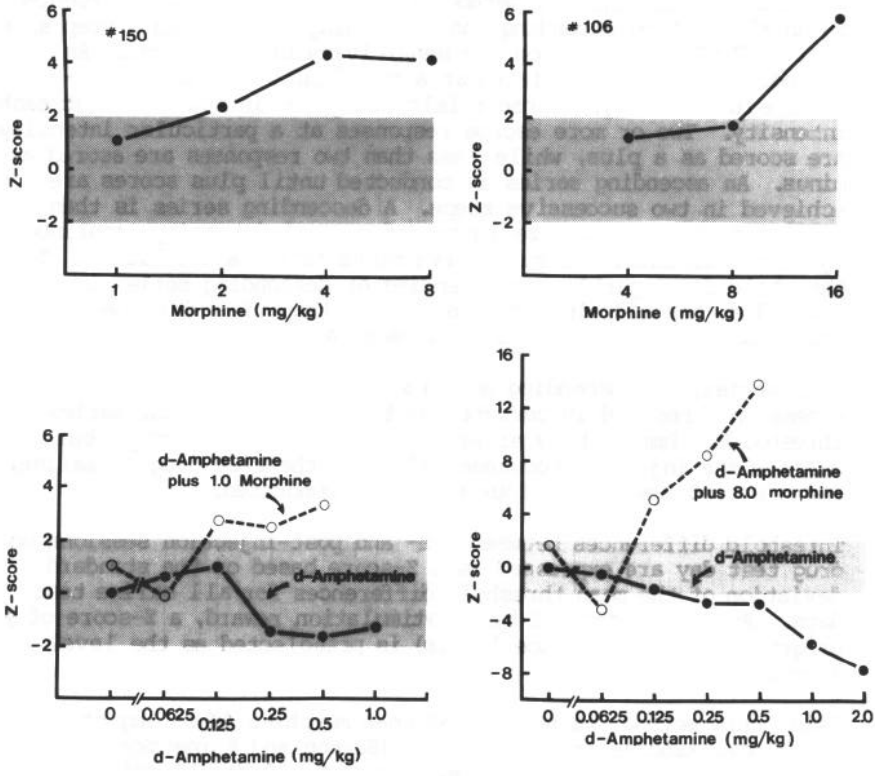

FIGURE 5

Effects of Morphine Alone and in combination with d-Amphetamine in Two Separate Animals, Left and and Right Two charts, Respectively. As in Previous Work, Data is Expressed as Z-score charges. (Data from Sasson et al. 1983)

DISCUSSION

These experiments show that combinations of drugs often lead to effects that exceed the simple algebraic sum of the actions of the individual drugs. This complex interaction seems to exceed what might be seen if one drug simply increased the amount of the other

drug's availability at the receptor. These synergistic or potentiation effects are manifested not only in the euphoriant action of drugs, but also in their analgesic action.

The combining of the antihistmine tripelennamine with the mixed agonist-antagonist raises sane interesting questions regarding the role of histamine in the effects of these opiate drugs. The effect is not confined to the euphoriant action, for Tagashira et al. (1982) reported that tripelennamine enhanced the analgesic response of pentaxocine in the mouse using the hot/plate method. Also, Shannon and Su (1982) found that tripelennamine enhanced the morphinelike discriminative stimulus effects of pentaxocine in rats trained to discriminate morphine from saline.

Shannon and Su (1982) argued that the interaction seen at the behavioral level is not due to a molecular interaction at the opiate receptor. This conclusion is based on their finding that tripelennamine did not alter the response of the stimulated guinea pig ileum to pentazocine, did not modify the Ke for naloxone in antagonizing pentaxocine, and did not change the inhibition of specific (3H)-naloxone binding by pentazocine. However, other evidence suggests that a central histamine system may account for the interaction Mazurkiewicz-Kwilecki and Henwood (1976) found that, in the rat, chronic treatment with morphine causes a decrease in histamnine in the CNS. Also, Eroglu (1979) reported that naloxone can reverse or block these effects of chronic morphine treatment on brain histamine. Fran the above mentioned studies, the mechanism involved in the synergistic effect of tripelennamine with the mixed agonist-antqonist is not clear. It is clear, however, that the role of histamine in the response of opiates is still not understood.

The mechanisms involved in the enhancement of a putative analgesic response of morphine by d-amphetamine and the drugs' combined increaesd effect on brain-stimulation reward are certainly not apparent. It is highly possible that different mechanisms are involved since, in the case of rewarding brain stimulation, each drug independently will increase the animal's sensitivity. However, in the case of brain-stimulation escape, there is clearly no similarity in the effects of these two compounds.

Despite a great deal of evidence that dopaminergic pathways are involved in the reward system (Fibiger 1978), some recent data suggest that there may not be a close correspondence between the boundaries of the reward system and those of the dopamine terminal fields (Prado-Alcala and Wise 1984; Prado-Alcala et al. 1984). However, the finding that naloxone will attenuate the threshold lowering effect of d-amphetamine on brain-stimulation reward (Esposito et al. 1980) suggests an interaction between the dopaminergic and an endogenous opiate system. This is supported by the finding that opiate receptors have been localized on dopaminergic presynaptic neurons in the mesolimbic system and the striatum (Pollard et al. 1977a, 1977b). However, the role that these endogencus opiates play in the behavior of the dopamine neuron is not clear. Some investigators have proposed that opiates

facilitate (Chesselet et al. 1981) the release of dopamine, while other suggest inhibition (Pollard et al.).

Clearly, these experiments suggest that the neuronal mechanisms of drug interactions require understanding of a greater magnitude than does the action of either drug alone. There is, however, sane advantage to studying drug combinations. First,of course, the abuse liability of new drug combinations may be predicted,based on animal models. Equally important, the study of combinations may be helpful in understading the underlying mechmisms involved in the action of each of the drugs alone. For example, the use of the combination of the antihistamine with opiates has helped to elucidate the role of histamine in the action of the opiate drugs. Thus, while gathering information to understand more fully the synergistic effects of drug combinations, we gain information valuable in its own right.

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Drug Interactions With Methadone in Humans

Mary Jeanne Kreek, M.D.

In a rigorous consideration of the desirable strategies for research on the interactions of drug abuse, and also interactions with drugs used to treat drug abuse, it becomes evident that despite the usefulness of animal models and *in vitro* models, both for delineation of mechanisms of observed interactions and for screening for possible interactions, ultimately, controlled studies must be carried out in normal human volunteer subjects, or patient volunteer subjects, because of the profound dispositional, pharmacokinetic, and pharmacodynamic differences with respect to drug fate and action in humans as contrasted to other species. Also, because of the enormous number of theoretically possible drug interactions of various kinds which might occur, it is essential first to explore what kinds of drugs are being used and/or abused in combination by humans using both wide-scale epidemiological techniques as well as small-scale, careful clinical observational techniques. These findings could then direct both clinical research, animal model and *in vitro* model research. By this approach, priorities with respect to which potential drug interactions should be studied first can be more logically established.

Research on potential drug interactions should include not only studies of the possible interactions between drugs or chemical agents which are documented to be used (or abused) concomitantly, but also interactions between similar new drugs or chemical agents which might be, in the near future, so used in combination. Studies of model compounds which might elucidate mechanisms of drug interactions -- such as compounds known to alter drug disposition by specific mechanisms, compounds known to alter receptor site actions by antagonism or which may effect augmentation of action, and, finally, drugs which may

have dynamic actions that either compliment or counteract some of the diverse actions of the primary drug of interest -- should also be encouraged, both in animal models and, when appropriate and possible from both a regulatory and ethical standpoint, in humans. For legal, ethical, and scientific reasons, studies of many model compounds, of combinations of new drugs,and of combinations of new and old drugs probably should be carried out initially in animal model; and/or in vitro systems. However, studies of possible interacts of those drugs of use and/or abuse which are already known by clinical observations to be used in combination by active drug-abusing, or former drug-abusing humans, in treatment, and studies of drugs which must be used together in the treatment of former drug-abusing humans, should be carried out in controlled human studies at the earliest possible time.

The use of human subjects, both volunteer subjects and patient subjects, for studies of interactions of drugs of use and/or abuse presents many diverse types of ethical, feasibility-related, and methodological problems. Studies of drugs of abuse in normal volunteer subjects are frequently not acceptable on ethical grounds. Similarly, the administration of large doses of drugs of abuse, such as the amounts actually taken in street drug abuse situations, may not be easily accepted by ethical review committees, even when studies are to be carried out in subjects who themselves are substance abusers using those very drugs in large amounts. However, as in other scientific-clinical-ethical considerations, thoughtful development of risk/benefit factor analysis will undoubtedly facilitate the approval for performance of needed research.

Feasibility is a second extremely important issue when clinical studies are to be carried out for any purpose. Although problems of feasibility will not be discussed in detail here, it should be made clear that the most ideal, scientifically and method-ologically rigorous type of drug interaction studies, such as the most desirable types of studies using animal models designed to determine the time course of action and pharmacokinetics of each drug alone and in combination, as well as the full dose response curve of each drug alone and in combination, are not feasible in humans. Also, diverse factors which may influence drug interactions--such as circadian variations of drug disposition, sex and age of subject, environment, route of drug administration-- and the various diverse pharmacodynamic effects of each drug alone and in combination--such as the

effects on neurotransmitter or neuroendocrine systems--obviously cannot be fully considered in even the most basic clinical research. From a purely scientific standpoint, however, it is not absolutely clear that it would be desirable to carry out such rigorous testing in humans since a relatively narrow range of doses of each drug is used and abused in humans and careful clinical observational studies may promptly identify these dose ranges for each drug when used alone and in combination. Similarly, the approximate time course of action of most drugs used or abused can be established by careful clinical observations with respect to time of maximal clinical effect. Also, the time of peak drug levels in plasma may be determined and, therefore, the possible time of maximum action at receptor sites predicted.

On the other hand, many of the criteria demanded for excellent animal model research in drug interaction studies certainly can and should be demanded of human research as well. Perhaps the most important issue to be addressed in appropriate rigorous clinical research is patient selection and characterization, coupled with appropriate subset analyses when a heterogeneous population of subjects is to be included in the study. Many factors, including circadian factors, effects of food and other drugs, and effects of environment, can be controlled by the environment selected for the clinical research studies. For instance, in-patient clinical research in a formal Clinical Research Center setting is far preferable for such work than outpatient studies conducted in outpatient clinics, which in turn are preferable to studies carried out in a nonresearch clinical setting. In human studies, when feasibility must be a major consideration (despite the views of many pharmacologists and pharmacokineticists), it is most appropriate to study drugs by the routes of administration which are used both in clinical medicine and in abuse settings, rather than to demand, purely for study purposes, one specific route of administration (e.g., intravenous route with the misconception that this is essential for pharmacokinetic studies), or to demand studies following drug administration by all possible routes of administration which is clearly the most desirable way to carry out the studies in an animal model, but is not necessarily feasible or desirable to be done in human subjects. Increasingly, it is being appreciated that the route of administration used may significantly alter drug disposition, pharmacokinetics, and pharmacodynamics; and, again, careful consideration of possible species differences in each of these parameters is extraordinarily

important in interpretation of data. In human studies, appropriate statistical analysis of data should be demanded, and the end-point to be studied should be chosen in advance of controlled studies.

The technological methods to be used in human research will be addressed to some extent in this report by giving examples of those methadologies which have been used in studies of methadone interaction with other drugs, which have allowed scrutiny of such indices as dispositional pharmacokinetics of both racemic methadone and each of the enantiomers of methadone following oral dosing in the setting of chronic drug administration.

Methadone is an orally effective opioid agonist which, because of its long-acting properties in humans (but not in any animal model, where it is always a short-acting drug with rapid clearance), can be effectively used to treat narcotic addiction in humans. Methadone may also be used effectively in the management of chronic pain, either by providing analgesia for which the dosages used must exceed the degree of tolerance developed by the individual, or by preventing signs and symptoms of narcotic withdrawal (effects similar to one of the effects desired in the treatment of narcotic addiction) for which the doses used should be less than the degree of tolerance developed by the individual. In the case of chronic pain patients, additional use of short-acting narcotics is required to provide the desired analgesic effects per se.

Methadone has been used in chronic maintenance treatment of addiction of several hundreds of thousands of patients in the United States as well as an increasing number abroad. To a limited extent, methadone has remained a minor drug of abuse on the street, just as it was prior to the introduction of methadone maintenance treatment in 1964. Because of the wide-spread clinical use and dramatic efficacy of methadone in the maintenance treatment of addiction, it has been essential to determine any significant interactions between other drugs of use, and of abuse, with methadone, since it is the steady state of plasma levels and effects of methadone in chronically treated individuals which allows normalization of physiological functions, including neuroendocrine functions, which are significantly perturbed by chronic abuse of short-acting narcotics, such as heroin.

Two general types of interactions between any two drugs or chemical agents may occur: first, disposi-

tional or pharmacokinetic interactions, which either increase or decrease the actual amount of drug available at sites of action; and, secondly, interactions which alter the pharmacodynamics of either or both drugs by competition at sites of action, such as at specific receptor sites, or by a variety of actions of each drug which may augment or counteract the primary desired actions of each. Appropriate studies of the first kind of interactions should include as "end-points" the determination of the disposition of one drug alone, and then with the addition of a second drug. Observations should be made of clinical symptoms of increased or decreased action of the first drug, which may occur as a result of dispositional interactions when the second drug is added. The end-points for study with respect to the second type of drug interactions could be of a wide variety of types depending upon the primary and secondary actions of each drug.

Most studies of drug interactions with methadone in humans have dealt with dispositional drug interactions. The most obvious, though not always fully recognized, interaction of the second type, which will be considered briefly, is the interaction of methadone with a specific opioid antagonist, naloxone. Studies were carried out to determine whether the addition of naloxone to a methadone formulation had any significant effect on methadone disposition (Kreek 1973B). In these studies, naloxone was administered orally along with methadone in a 1 to 10 dose ratio. Naloxone has very limited oral bioavailability; thus any dispositional interactions would have to occur at the intestinal wall sites of binding, absorption, or metabolism prior to the sites of hepatic uptake, biotransformation, and clearance of naloxone as its major glucuronide metabolite. Naloxone's poor oral bioavailability is due not to failure to absorb the drug but rather to extensive metabolism to the inactive naloxone glucuronide after initial up-take by the liver, or the classical "first pass" effect. The studies which we carried out to determine whether any dispositional interactions occurred showed that naloxone, added to the oral formulation of methadone, did not alter either plasma levels of methadone or urinary excretion of methadone in its major pyrrolidine metabolite. However, when oral naloxone was given with the oral methadone formulation to narcotic-tolerant and -dependent individuals, profound gastrointestinal signs and symptoms of narcotic withdrawal were observed, presumably due to antagonist effects of naloxone at opiate receptor sites within the intestinal wall (Kreek 1973B). These gastrointestinal signs and

symptoms were associated with only minimal systematic signs and symtoms of narcotic withdrawal, reflecting the very small percentage of naloxone administered which reached the systemic circulation in a chemically active unmetabolized form (Kreek 1973B; Kreek et al. 1976B, 1983B). In this case, there was no dispositional interaction between the opiate agonist methadone and the opiate antagonist naloxone, but rather a profound pharmacodynamic interaction -- i.e.,precipitation of gastrointestinal narcotic abstinence syndrome--was observed, probably due to interaction at the opiate receptor sites within the intestinal wall.

Studies of factors which may significantly alter methadone disposition in humans have been carried out to address hypotheses which we have developed concerning the action of methadone in the treatment of addiction. Our hypotheses state that a narcotic drug must be available to critical receptor sites (or binding sites) for finite and definable periods of time for tolerance and physical dependence to develop: that drug-seeking behavior follows as a natural consequence when the symptoms resulting from narcotic drug withdrawal in a tolerant and physically dependent individual (the abstinence syndrome) are identified by that individual as being related to drug withdrawal and are observed by that individual to be relieved when a narcotic drug is readministered; that constant availability of a narcotic drug (in this case, methadone) to critical receptor sites is essential for the steady-state maintenance of a tolerant and dependent stage; and, finally, that availability of drugs to critical receptor sites depends in part on various factors which may affect overall drug disposition, pharmacokinetics and excretion. We have shown that three types of factors may significantly alter methadone disposition in humans: 1) altered drug disposition in a setting of chronic disease, including liver and renal disease: 2) altered drug disposition in a setting of the altered physiological state of pregnancy; and 3) altered drug disposition due to interaction with other drugs or hormones (Kreek, Gutjahr, Garfield et al. 1976B).

When methadone is administered orally on a chronic basis, a steady state is achieved with relatively steady plasma levels over a 24-hour dosing interval. A small increment of methadone plasma levels is found after oral dosing, with a peak reached in 2 to 4 hours (Kreek 1973B; Kreek, Gutjahr et al. 1976B). After oral dosing, the peak plasma levels of methadone rarely exceed a doubling of the nadir or steady-state

plasma levels and then these slowly decline to a steady-state plateau level over the remainder of the 24-hour dosing interval (see figure 1). Using a conventional model of analysis, the specific and sensitive technique of gas liquid chromatography, it has been shown that the apparent plasma terminal half-life of methadone in humans receiving methadone orally on a chronic basis ranges from around 18 to 28 hours (Kreek 1973B; Kreek et al. 1979).

One of the major problems encountered when animal models are used in attempts to study methadone disposition or methadone interactions with other agents is that the pharmacokinetics of methadone in amimal models is entirely different from that in humans. Using gas chromatographic techniques, we have determined that the apparent plasma terminal half-life of racemic methadone in the rat is 90 minutes after chronic oral administration of drug and 70 minutes after chronic parenteral subcutaneous (s.c.) administration of drug. The clearance of methadone in the mouse is similarly very rapid: 112 minutes after chronic parenteral s.c. administration. Therefore, the most commonly used rodent models are very poor models to use for studies of methadone interactions unless either a constant infusion of methadone is given or, more realistically, the profound differences in pharmacokinetics are

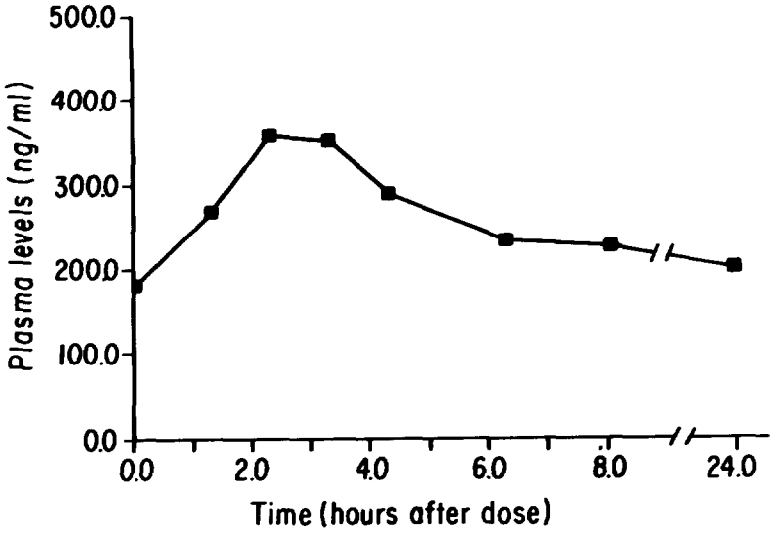


Figure 1
Plasma Levels of Methadone Over a 24-Hour Dosing Interval in an Individual Maintained on 100mg/day

appreciated and drug interactions are studied only during the first 1 hour following methadone administration (Burstein et al. 1980; Kreek 1979) (see figure 2).

To be able to rigorously determine the dispositional fate and pharmacokinetics of a single dose of orally administered methadone against a background of chronic methadone dosage, a new technology has been developed and used in basic clinical research studies. For this purpose, various stable isotope-labeled species of methadone have been specially synthesized. These include: dl(SR)- pentadeutero-methadone, d(S)-trideuteromethadone, l(R)-pentadeu-teromethadone, and dl(SR)-octadeuteromethadone (Hachey et al. 1977; Kreek et al. 1979; Nakamura et al, 1982) (see figures 3 and 4).

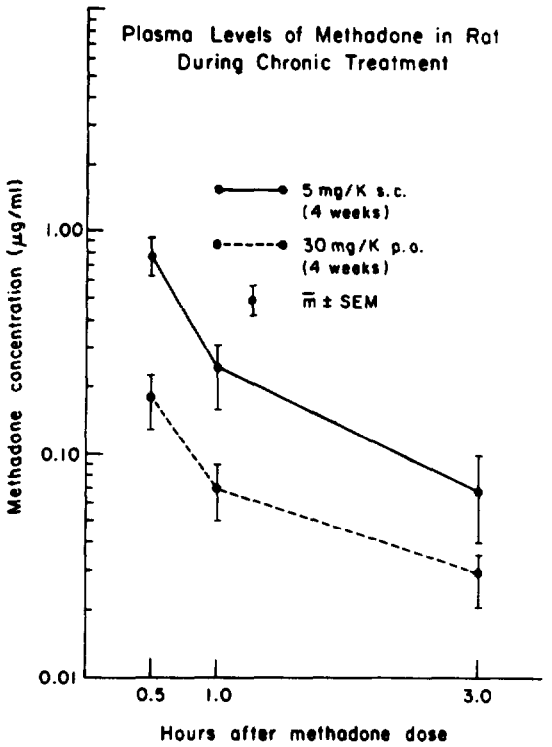


Figure 2
Plasma Levels of Methadone in the Rat During Chronic Treatment Using the Oral or Subcutaneous Routes of Administration. Copyright 1979, Phar Biochem Behav, ANKHO Int. Inc. Kreek 1979.

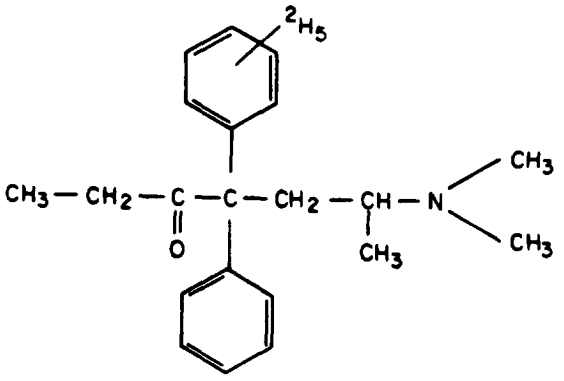


Figure 3
Structure of Pentadeuteromethadone (Methadone-d_5, i.e., $^2H_5$-Methadone). Copyright 1979, Life Sci, Pergamon Press, Ltd. Kreek et al. 1979.

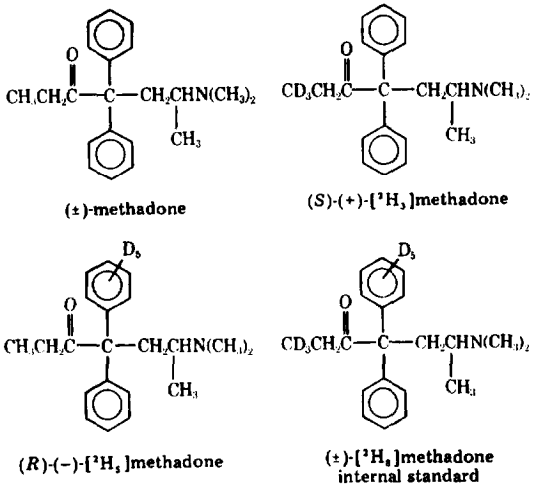


Figure 4
Four Different Species of Stable Isotope Labeled Methadone. Copyright 1982, J of Pharm Sci, American Pharmaceutical Association. Nakamura et al. 1982.

In some studies, the entire daily dose of methadone has been administered to chronic methadone-maintained patients as the racemic dl(SR)-pentadeuteromethadone. Using gas chromatography-chemical ionization mass spectrometry with selected ion monitoring, the enrichment of the labeled over the unlabeled species of methadone has been determined over a period of several days following administration of the single, stable isotope-labeled oral dose. In other studies, a single, stable isotope-labeled species of one enantiomer of methadone has been administered along with equal amounts of the other enantiomer in unlabeled form and the fate of the single-labeled enantiomer was determined, again using gas chromatography-chemical ionization mass spectrometry, with selected ion monitoring to determine the amounts of the single-labeled species against a background of unlabeled methadone. Finally, and most recently, the technique has been significantly modified so that each of the two enantiomers of methadone may be given simultaneously as separate, stable isotope-labeled species. Thus, the full daily dose of methadone can then be given as racemic methadone, but with each enantiomer labeled separately so that the fate of each enantiomer may be determined simultaneously in a single study. For these studies, dl(SR)-octadeuteromethadone is used as an internal standard in the gas chromatography-chemical ionization mass spectrometry measurements, so that the absolute amounts, as well as the ratios of labeled to unlabeled species, of methadone may be determined in a single analytical procedure (Hachey et al.1977; Kreek et al. 1979; Nakamura et al. 1982) (see figures 5 and 6).

Radioisotope-labeled species of methadone could not be used in such studies because of the very wide distribution and tissue binding of methadone in the body; the resultant low plasma levels of methadone which ensue; and the appropriate ethical limits on amounts of radioisotope-labeled compound which can be given to human subjects. The ethically acceptable amounts would be insufficient to obtain a sufficiently high specific activity of labeled methadone in plasma for pharmacokinetic studies. Using the stable isotope technology, it has been determined that the plasma apparent terminal half-life of methadone ranges from 19 to 38 hours and that the plasma apparent terminal half-life of the active l(R)-enantiomex is significantly greater than that of the inactive d(S)-enantiomer. Using this stable isotope technique, it has been shown that mean half-times for disappearance of the two enantiomers of methadone in urine are 34 hours for the inactive d(S) and 57 hours for the active l(R)-enantiomers, respectively.

If studies of drug interactions between drugs of abuse, or drugs for treatment of drug abuse and other agents of use or abuse are to be carried out in human subjects, appropriate subject selection, characterization of the health status of each subject, and appropriate sub-group analysis are essential. The very high prevalence of liver disease in substance abusers, in general, necessitates a consideration of the effects of liver disease on the disposition of each drug to be studied, as well as on the effects of drugs ox agents used concomitantly. We have carried out extensive studies of the effects of liver disease of various types and degrees of severity on the disposition of methadone in humans. This was absolutely essential because of the very high prevalence of liver disease in both heroin addicts and former heroin addicts in methadone maintenance treatment. Several prospective studies by our group, as well as similar studies by others (Beverly et al. 1980; Hartman et al. 1983; Kreek et al. 1972; Kreek 1973A; Kreek 1978A; Kreek 1981,; Novick et al. 1985A;

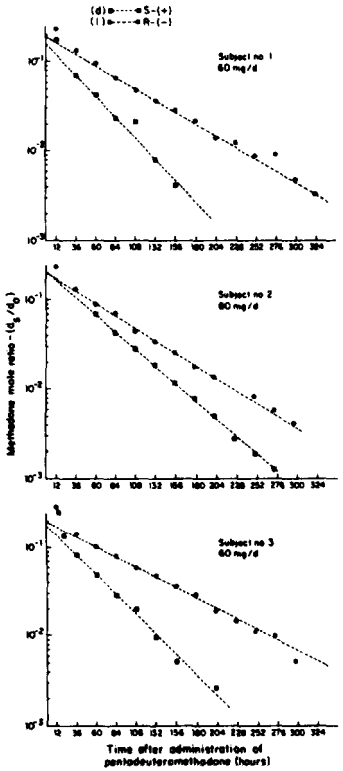
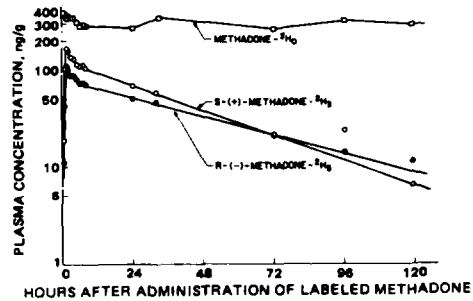
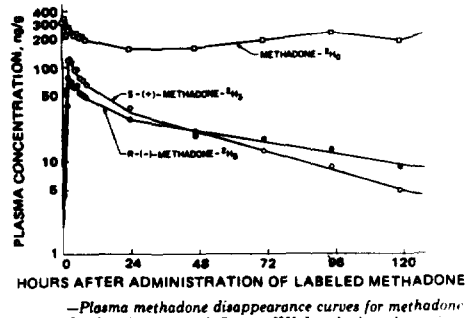


Figure 5
Urine Disappearance Curves of d - and 1 - Methadone in 3 Patients (After Separate Oral Administration of Pentadeuteromethadone: Time in Hours). Copyright 1979, Life Sci, Pergamon Press, Ltd. Kreek et al. 1979.

Novick et al. 1985B), have shown that over 60% of all heroin addicts have biochemical, with or without clinical, evidence of chronic liver disease and that approximately the same percentage of patients continue to have biochemical with or without clinical evidence of chronic liver disease during chronic long-term methadone maintenance treatment. It has been shown that chronic liver disease in former heroin addicts and in methadone maintenance treatment patients is due to: 1) chronic sequelae of hepatitis B virus infection, delta agent infection, and, undoubtedly, also sequelae of non-A/non-B hepatitis virus infection: and 2) alcohol-induced hepatotoxicity, with alcohol-induced liver disease (Kreek et al. 1972). In many patients, liver disease has been documented to be of a mixed type, due both to viral sequelae of hepatitis virus infection and to alcohol-induced injury (Beverly et al. 1980; Hartman



—Plasma methadone disappearance curves for methadone, (R)-(−)-[$^2H_3$]methadone, and (S)-(+)-[$^2H_3$]methadone determined in Patient 1.



—Plasma methadone disappearance curves for methadone (R)-(−)-[$^2H_3$]methadone, and (S)-(+)-[$^2H_3$]methadone determined in Patient 2.

Figure 6

Plasma Disappearance Curves of the Separate d - and l - Enantiomers of Stable and Plasma Levels of dl - Methadone (After Simultaneous Oral Administration of Separate Stable-Labeled Species). Copyright 1982, J of Pharm Sci, American Pharmaceutical Association. Nakamura et al. 1982.

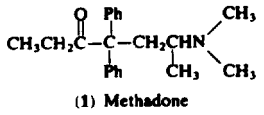
et al. 1983; Kreek 1978A; Kreek 1978B; Kreek 1984; Novick et al. 1985A; Novick et al. 1985B).

In one prospective study, it was shown that 20% of all heroin addicts entering methadone maintenance treatment were also chronic abusers of alcohol and that approximately the same percentage of these patients continued to abuse alcohol on a chronic basis during methadone maintenance treatment (Kreek 1978A). In other studies, it has been shown that from 20 to 50% of heroin addicts entering treatment for narcotic addiction and chronic methadone maintained patients, including both youthful drug abusers who have become chronic long-term heroin addicts and thus have been admitted to methadone maintenance treatment and adult heroin addicts who have been entered into methadone maintenance treatment, remain chronic abusers of alcohol (Beverly et al. 1980; Hartman et al.1983; Novick et al.1985A). Several studies have shown that the prevalence of all hepatitis B markers in heroin addicts and methadone maintenance patients is around 95% and that about 12% of heroin addicts and patients in the early years of methadone maintenance treatment are chronic carriers of hepatitis B antigen. (Kreek 1973A; Kreek 1978A; Kreek et al. 1972; Novick et al.1981A).

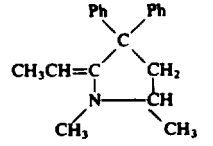
Studies of methadone disposition have been carried out in patients with moderately severe, but fully compensated, chronic liver disease of a cirrhotic type. Each of these patients had been treated with chronic methadone maintenance for extended periods of time. In these studies, it was shown that the apparent plasma terminal half-life of methadone was prolonged to 35.5 +/- 7.6 hours in patients with compensated alcoholic and/or viral cirrhosis, as compared to 18.8 +/- 3.0 hours in the contrast group (Novick et al.1981B). It was also found that plasma levels of methadone were not increased in cases of severe liver disease, as had been anticipated from studies of the effects of chronic liver disease on the disposition of other drugs. In more recent studies of patients with very severe liver disease, performed to determine the disposition of methadone in that setting, the plasma levels of methadone appear to be even lower than those in otherwise healthy patients receiving similar doses of methadone (Novick et al.1985C). These findings are of considerable interest because they are the opposite of what might have been anticipated.

Methadone is metabolized primarily by the hepatic P450-dependent microsomal drug-metabolizing enzymes. Methdone is first N-demethylated to form an inactive

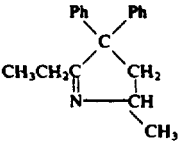
pyrrolidine metabolite--the major metabolite of methadone --which in turn undergoes, in part, a second N-demethylation to form a second inactive metabolite, a pyrroline. There are also several minor metabolites of methadone, only two of which, accounting for less that 2% of the administered dose, are pharmacologically active compounds (see figure 7). The liver plays two important roles in the disposition of methadone: first, it is the major site of biotransformation of methadone: and, second, it has been shown to be an important site for non-specific storage and release of unchanged methadone. The liver thus serves as a reservoir for methadone, probably accounting in large part for the long-acting pharmacokinetic properties of methadone (Kreek et al. 1978). Using an isolated perfused rabbit liver preparation, it has been found that methadone is avidly extracted by the liver, but after extraction, it is extensively bound non-specifically to plasma membranes where it is stored for subsequent release in an unchanged form (Kreek et al. 1978). Only a small proportion of methadone is metabolized during its first pass through the liver (Kreek et al. 1978). Therefore, although methadone is avidly extracted by the liver, it does not undergo the classical "first pass" effect, implying uptake followed at once by



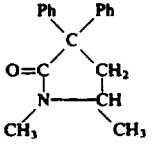
(1) Methadone



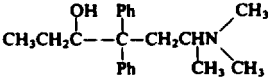
(2) Pyrrolidine (2-ethylidin 1,5-dimethyl-3, 3-diphenyl pyrrolidine)



(3) Pyrroline (2-ethyl-5-methyl-3, 3-diphenyl pyrroline)



(4) Pyrrolidone (1,5-dimethyl-3, 3-diphenyl pyrrolidone-2)



(5) Methadol

Figure 7

Structures of Methadol, Methadone, Pyrrolidine, Pyrroline, Pyrrolidone Metabolite of Methadone. Copyright 1983, Biomedical Mass Spec, John Wiley & Sons Ltd. Kreek et al. 1983.

biotransformation usually to inactive forms, and excretion. Similarly, using a whole rat model, it has been shown that a single dose of methadone may persist in various tissues for up to 6 weeks and that, at all time points studied, the liver contains both the highest concentrations and the highest total amounts of methadone (Harte et al. 1977; Siring et al. 1981A; Ziring et al. 1981B). Thus, the liver appears to be the major reservoir for methadone storage in tissue and subsequent release. In the setting of very severe chronic liver disease (such as severe cirrhosis), the profoundly decreased hepatocellular mass with resultant decreased reservoir capacity plays an even greater role in altering methadone disposition than does the reduction in hepatic P450-dependent microsomal drug-metabolizing enzyme capacity, which, though probably very compromised in a setting of severe chronic liver disease, may remain adequate to carry out the biotransformation of methadone, since this drug is metabolized very gradually by the liver over a 24-to-48-hour period, as contrasted to short-acting drugs which are very rapidly metabolized by the hepatic microsomal P450 drug-metabolizing enzymes.

Other studies have been carried out to determine the effects of chronic liver disease of varying types and degrees of severity on the urine and fecal excretion of methadone and its metabolites. For this work, techniques have been developed using direct probe chemical ionization mass spectrometry, in which the stable isotope-labeled methadone octadeuteromethadone is used as an internal standard for the quantitation of unlabeled methadone and its metabolites, but without the administration of stable isotope-labeled compounds for use as *in vivo* tracers in these studies (Kreek et al. 1980A; Kreek et al. 1983A). In these studies, it was shown that from 46 to 55% of an oral daily dose of methadone is excreted in urine as the sum of unchanged methadone and its metabolites; the major pyrrolidine metabolite accounts for 24 to 29% of urine clearance of the daily methadone dose, whereas unchanged methadone accounts for 10 to 26% of the total amount (Kreek et al. 1980A). In otherwise healthy patients, a mean of 48% of the daily dose of methadone is excreted by the urinary route of methadone plus all methadone metabolites; whereas, in patients with chronic liver disease of varying types and degrees of severity, there was a significant decrease in the total amounts of methadone and metabolites excreted in urine, with a mean of 31% of the daily dose being excreted by that route (Kreek et al. 1980A) (see figure 8). In additional studies which also used direct probe chemical mass

spectrometry, it was shown that, in a setting of chronic liver disease, increased amounts of both unchanged methadone and its metabolites are excreted in feces. This suggests that, in the setting of decreased hepatic reservoir capacity, methadone is either more extensively biotransformed or passed as unchanged methadone into the bile after hepatic uptake and, thus, eliminated in feces (Kreek et al. 1983A) (see figure 9). In all of these studies, no patients were observed to have any symptoms of relative narcotic overdose. This fact is of clinical importance, since patients who have stable chronic liver disease may thus be treated with methadone without undue concern about accumulation of drug in plasma and, therefore, excessive amounts of active compounds at various receptor sites. Thus, any possible adverse central nervous system effects would not be expected to occur in the setting of severe chronic liver disease. These findings also should be considered when planning and conducting studies of drug interactions in narcotic-dependent persons, or other parenteral drug abusers, in whom chronic liver disease of one or more types is known to be of high prevalence.

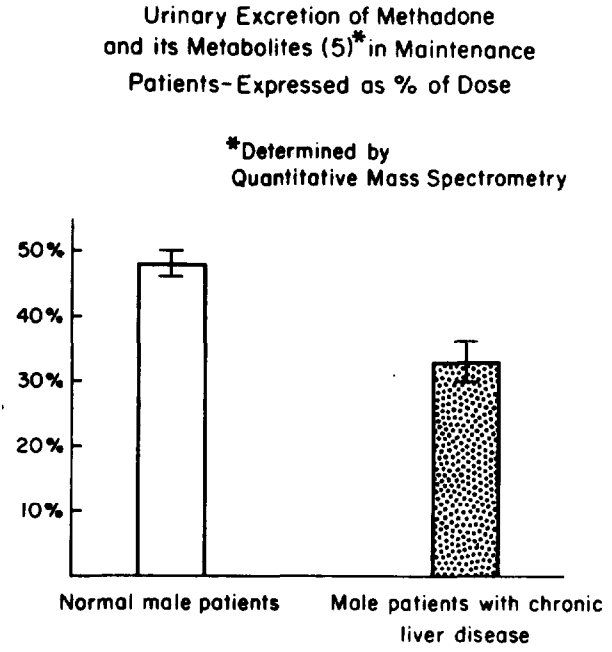


Figure 8
Urinary Excretion of Methadone and Its Metabolites in Humans as Studied by Direct Probe Chemical Ionization Mass Spectrometry

Limited studies have also been carried out to determine the effects of compromised renal function on methadone disposition. In these limited studies, it has been shown that both in a setting of oliguria in a patient maintained on hemodialysis, as well as following renal transplantation, there was no evidence of accumulation of methadone in plasma (Kreek et al. 1980B). Plasma levels of methadone in those settings were found to be within the range expected in otherwise healthy subjects for the dose of methadone administered. Also in these studies it was found that there were marked increases in the fecal excretion of methadone, which accounted for essentially the total elimination of methadone in patients with oliguria or anuria.

Controlled clinical studies have also shown that methadone disposition becomes significantly altered during late pregnancy (Kreek et al. 1974; Kreek 1979; Pond et al. 1985). In early observations and study

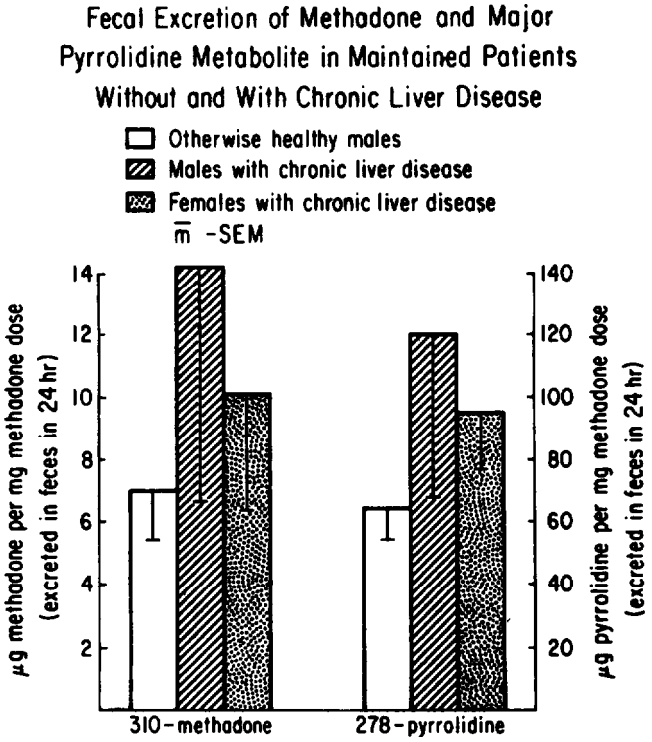


Figure 9
Fecal Excretion of Methadone and Its Metabolites in Humans, as Studied by Direct Probe Chemical Ionization Mass Spectrometry

of one case, it was found that, for a given dose of methadone, the plasma levels of methadone during the third trimester of pregnancy were significantly lower than would be expected for the dose administered and, yet, the levels returned to anticipated levels for dose shortly following delivery (Kreek et al. 1974). Subsequently, prospective studies have been carried out in several methadone-maintained patients who were documented to be free of any alcohol or polydrug abuse and who had minimal to no evidence of chronic liver disease (Kreek 1979) Pond et al. 1985). In these studies, it was shown that, during the last trimester of pregnancy, the plasma levels of methadone become progressively lowered with concomitant lowering of the area under the plasma concentration time curve coupled with increased nonrenal clearance of methadone (Kreek 1979; Pond et al. 1985).

Although albumin levels are normally lowered in late pregnancy, globulin levels become increased. Methadone binds to both albumin and globular fractions. Specific binding studies were performed which showed that the percentage of free methadone did not change significantly and, thus, could not account for the observed lowering of plasma levels and enhanced clearance of methadone during late pregnancy (Pond et al. 1985). In these studies, it was also shown that, in the postpartum period, plasma levels of methadone resulting from administration of a constant dose increased promptly back to the normal anticipated range (Pond et al. 1985). Each patient served as her own control in this study, thus minimizing any interindividual variation. In these studies, as well as in all of our other controlled studies, we have shown that both in otherwise normal healthy subjects and in patients with chronic liver disease and altered physiological states, there is very little intraindividual variation of plasma levels of methadone when studies are carried out on different days but in a clinical research setting, where time of day, time of dosing, and circadian factors, along with careful monitoring of patients for use and abuse of other substances which might alter drug disposition, can all be controlled. However, all of our studies have indicated that there is highly significant interindividual variation with respect to plasma levels of methadone after any given dose. Both the lowering of plasma levels of methadone in drug interactions discussed below, and the lowering of plasma levels of methadone during late pregnancy, exceeded what one would expect to see, even given the range of interindividual variations in levels and, far beyond expectation, given the very limited range

of intraindividual variation. In these studies, since each patient served as her own control, it was possible to see both the progressive lowering of plasma levels and the area under the plasma concentration time curve as pregnancy progressed and, then, a return to normal range of these indices in the postpartum period (Kreek 1979; Kreek et al. 1974; Pond et al. 1985). It is assumed, though not proven, that the hormonal milieu of pregnancy resulting in an enhanced biotransformation of methadone is a major factor accounting for the reduction in plasma levels of methadone. This formulation is supported in part by the finding of increased urinary excretion of the major pyrrolidine metabolite relative to the excretion of unchanged methadone during pregnancy. It has been shown by others that progestins, which are present at very high levels during late pregnancy, may enhance the hepatic microsomal P450-dependent enzyme activities for some substrates. Also, the biotransformation of methadone to inactive compounds by the placenta and the fetal liver may have contributed in part to the apparent enhancement of methadone metabolism and lowering of plasma levels observed during late pregnancy.

The first clinical observations and documentation of interaction of any other drug with a narcotic drug were the observations of the profound interactions between the antituberculosis drug, rifampin, and the long-acting narcotic methadone, being used on a chronic basis in the maintenance treatment of addiction (Kreek et al. 1976A). Rifampin has been shown to have several effects on the liver, including a hepatocellular toxic effect resulting in non-specific hepatitis in some cases and an effect on hepatic uptake and biliary clearance of a variety of substances. Also of specific importance for this discussion, it has been shown that rifampin is a potent enhancer of hepatic microsomal P450-dependent drug-metabolizing enzyme activities. Based on knowledge of this action of rifampin, it was postulated that this drug, and also phenobarbital, which similarly is a potent enhancer of hepatic microsomal P450-dependent drug-metabolizing enzyme activities, might result in acceleration of metabolism of a drug such as methadone, which normally is dependent upon the hepatic P450 microsomal enzymes for its biotransformation. The first clinical observations of such an interaction were made in a special clinic for the simultaneous management of heroin addiction, by use of chronic methadone maintenance treatment, and tuberculosis, by use of a variety of anti-tuberculosis agents. Severe signs and symptoms of narcotic withdrawal ensued when

the then experimental new drug rifampin was added to the therapeutic regimen of some of the methadone-maintained patients who, up to that point, had been successfully stabilized on both methadone maintenance and anti-tuberculosis treatment, but who needed additional antituberculosis treatment because of far advanced resistant disease. Thirty of the 86 patients in this special treatment program for tuberculosis and narcotic addiction were treated with rifampin and, of these, signs and symptoms of narcotic withdrawal developed in 21 cases, or 70%. Of the 21 patients who developed narcotic withdrawal symptoms, 14 had mild symptoms of withdrawal whereas, in 7, severe withdrawal symptoms ensued. Mild withdrawal symptoms included abdominal cramps, rhinorrhea, lacrimation, yawning, and irritability: in the severe cases, additional symptoms included nausea, vomiting, anorexia, joint pains, chills, tremulousness, insomnia, and severe anxiety (Kreek et al. 1976A). Most of the severely affected patients developed withdrawal symptoms within the first week of combined rifampin and methadone treatment.

Studies were carried out to determine whether there were any dispositional or pharmacokinetic interactions between methadone and rifampin in six of these patients with severe narcotic withdrawal symptoms during combined treatment (Kreek et al. 1976A). Each patient was studied while receiving methadone alone, and while receiving methadone plus rifampin. A highly significant lowering of plasma levels of methadone, along with a decreased area under the plasma concentration time curve, was observed in each of the six patients studied during the combined rifampin and methadone treatment as compared to the period of treatment with methadone alone (see figure 10). Also in each case, the symptoms of narcotic withdrawal reappeared when rifampin treatment was reinstituted for study purposes. The apparent plasma terminal half-life of methadone was not significantly altered during combined rifampin treatment, despite the fact that the plasma levels and area under the plasma concentration curves were significantly lowered. Further studies showed increased urinary excretion of the N-demethylated pyrrolidine metabolite in urine and great increases in fecal excretion of the N-demethylated inactive metabolites during combined rifampin and methadone treatment (Kreek et al. 1976A; Kreek et al. 1976B). The results of these studies indicate that when rifampin must be added to the antituberculosis therapeutic regimen of a patient receiving methadone on a chronic basis for treatment of addiction or for the management of chronic pain, the patient should be carefully

observed; increases in doses of methadone and/or increases in frequency of doses will probably be needed to sustain the desired effects of methadone in this observed and documented interaction between rifampin and methadone. The effectiveness of careful clinical observations, followed by controlled clinical research studies which elucidate both the phenomena and the probable mechanisms of the drug interaction, was demonstrated in this observed and documented interaction between rifampin and methadone. This is a kind of approach which may be most effective from all standpoints in identifying and elucidating interactions between drugs of abuse or between drugs, such as methadone, used to pharmacologically treat drug abusers and other drugs of abuse or therapeutic agents, such as rifampin.

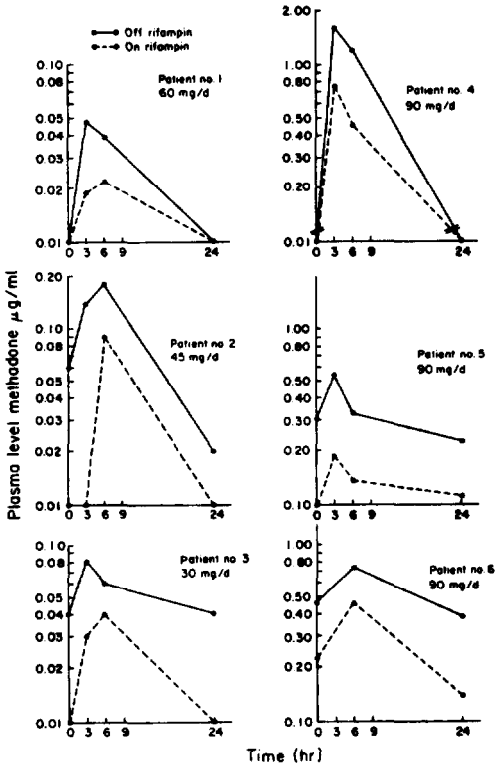


Figure 10

Plasma Concentration-Time Curves for Methadone During Treatment with Methadone Alone and During Concomitant Treatment with Methadone and Rifampin in 6 Patients. Copyright 1976, New England Journal of Medicine 294:1104-1106, 1976. Kreek et al. 1976.

A second clinically very significant drug interaction with methadone has also been observed clinically and then studied in a controlled setting (Tong et al. 1981). It was noted that when the anticonvulsant drug phenytoin (Dilantin) was added to the therapeutic regimen of patients receiving methadone on a chronic basis, symptoms of narcotic withdrawal would frequently appear within 1 to 4 days, suggesting that phenytoin enhances methadone metabolism. A study was carried out in volunteer chronic methadone-maintained patients without polydrug abuse, alcohol abuse, or significant liver disease. The disposition and pharmacokinetics of methadone were studied in these volunteer subjects while being treated with methadone alone and, then, while also receiving the anticonvulsant drug phenytoin in therapeutic doses (1000 mg in two divided doses on the first day, followed by a single daily dose of 300 mg on the second through fifth day). Moderate to severe symptoms of narcotic withdrawal appeared in each of these subjects by the third or fourth day of concomitant phenytoin and methadone administration. The drug disposition studies showed that plasma levels of methadone became significantly reduced during concomitant phenytoin treatment as compared to treatment with methadone alone (Tong et al. 1981) (see figure 11). Quantitative analyses of methadone and its metabolites in urine documented that, during concomitant phenytoin treatment, there was a very significant increase in the relative amount of the inactive N-demethylated pyrrolidine metabolite of methadone, thus showing enhanced urinary excretion of the biotransformation products of methadone during phenytoin treatment (Tong et al. 1981) (see figure 12). Thus, both in clinical observations and in controlled studies carried out in a clinical research setting, it was shown that phenytoin enhances methadone clearance, resulting in lower plasma levels of methadone at all time points and a reduction in the the area under plasma concentration time curves. These changes in methadone disposition are accompanied by highly significant clinical signs and symptoms of moderate to severe narcotic withdrawal. Thus, again, as recommended in the case of rifampin, when phenytoin is added to the therapeutic regimen of a patient receiving methadone treatment on a chronic basis, whether for the maintenance treatment of addiction or for the management of chronic pain, it is essential to observe the patient carefully and adjust the dose or dosing intervals of methadone as needed (Kreek et al. 1976A; Kreek et al. 1976B; Tong et al. 1981).

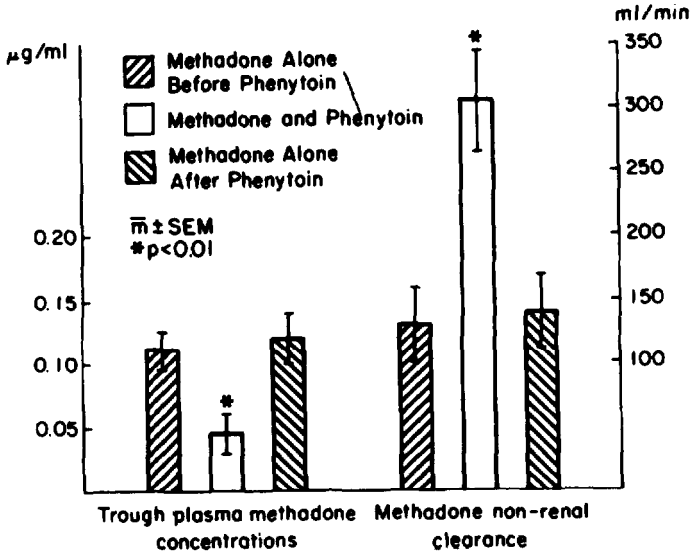


Figure 11
Effects of Phenytoin (Dilantin) on Plasma Levels of Methadone

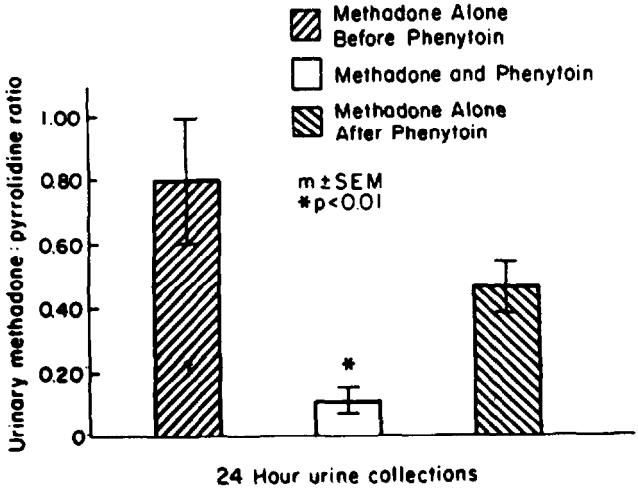


Figure 12
Effects of Phenytoin (Dilantin) on Urinary Excretion of Methadone and its Major N-Demethylated Pyrrolidine Metabolite

Other clinical observations have suggested that possibly the pharmacological agent used in an attempt to manage alcohol abuse, disulfiram (Antabuse), might cause dispositional interactions with methadone. A study was carried out in seven male volunteer subjects, all of whom were receiving chronic methadone maintenance treatment and none of whom had any alcohol or polydrug abuse or significant liver disease (Tong et al. 1980). Dispositional studies of methadone metabolism were carried out first while subjects received methadone alone and, then, while they received methadone plus disulfiram in therapeutic doses. There were no significant changes in plasma levels of methadone during combined disulfiram treatment, and the areas under the plasma concentration time curves were not altered in the setting of combined treatment (Tong et al. 1980). However, quantitative analyses of the excretion of methadone and its metabolites in urine showed that there was a relative increase in urinary excretion of the N-demethylated pyrrolidine metabolite of methadone during concomitant disulfiram treatment as compared to treatment with methadone alone, suggesting that some minor dispositional interaction between methadone and disulfiram had occurred. There were no clinical signs and symptoms of narcotic withdrawal in the study subjects (Tong et al. 1980). However, with the suggestion that some minor dispositional interaction might have occurred, it will probably be necessary to carry out similar studies to determine whether there are any significant dispositional interactions between disulfiram and methadone in patients who are former alcohol abusers in chronic methadone treatment and, thus, might be receiving this combination of drugs, including both those subjects without and also with alcohol-induced liver disease or mixed type of liver disease of varying degrees of severity.

Studies have also been carried out in humans to determine whether the acute social use of alcohol would have any effect on either methadone disposition or action (Cushman et al. 1978). For these studies, chronic methadone-maintained volunteers without a history of either alcohol abuse or polydrug abuse and without significant chronic liver disease were selected. Plasma levels of methadone were determined during treatment with methadone alone and during administration of an acute dose of 90 ml of ethanol in juice solution. There were no significant changes in plasma levels of methadone during combined treatment as compared to treatment with methadone alone (Cushnan et al. 1978). Also, there were no unexpected or enhanced effects of either ethanol or methadone observed clinically in this setting (Cushman et al. 1978).

Studies are currently in progress to determine if there are any significant interactions between methadone and ethanol in the setting of chronic alcohol abuse by chronic methadone-maintained patients (Kreek 1984). Based on studies carried out for other drugs, primarily in animal models, with respect to possible interactions with ethanol, it has been suggested that two types of dispositional interactions may occur during chronic ethanol use or abuse. When ethanol is administered in high doses (probably doses too high to be tolerated by any animal or human who is not already tolerant and dependent on ethanol), inhibition of the metabolism of a second drug may occur at the hepatic microsomal P450-dependent enzyme activity level, since ethanol, to an extent of approximately 30% of an administered dose undergoes biotransformation by that system and since the microsomal system is more extensively utilized in the metabolism of alcohol in the setting of high blood levels resulting from consumption or administration of large amounts of ethanol. Conversely, it has been well documented that chronic ethanol administration causes enhancement of the hepatic microsomal P450-dependent enzyme activities; therefore, when alcohol itself has been cleared from the body, drugs which are normally metabolized by the hepatic microsomal P450-dependent enzymes are metabolized more rapidly than normal because of this enhancement by ethanol. Thus, a biphasic effect of ethanol on the metabolism of another drug occurs. Whether or not each of these types of dispositional drug interactions occur when large amounts of ethanol are ingested by chronic alcohol-abusing methadone-maintained patients has yet to be established and is currently under study by our laboratory group.

In each of these examples, it has been amply demonstrated that studies of drug interactions between methadone and a second drug may be carried out in a controlled clinical research setting and that the results have immediate and enormous clinical relevance. However, it is essential sometimes either to conduct pilot studies using an animal model or to use an animal model to elucidate mechanism of action of such drug interactions. In our laboratory, we have used both whole animal models, primarily involving administration of one or two drugs to rats, as well as isolated perfused liver preparations. Using organ models, we have shown, for instance, that acute perfusion with ethanol does not significantly affect the hepatic uptake of methadone, nor does it affect the immediate metabolism of methadone (Kreek et al. 1981).

We have also shown that hepatic perfusion with ethanol does not affect the immediate hepatic uptake of other narcotics, including morphine (Kreek et al. 1981). Thus, the observed inhibition of drug metabolism by ethanol is probably due to a sustained action of competitive inhibition by ethanol of the second drug at the hepatic microsomal drug-metabolizing enzyme. In studies carried out in the whole rat, we have shown that, when animals have been treated with both ethanol and methadone, or with methadone alone on a chronic basis, and determination of plasma levels of methadone is carried out 24 hours following the last dose of ethanol and 1 hour following dosing with methadone (a time point which conforms with what is now known about the pharmacokinetics of methadone in the rat), significant reductions in plasma levels of methadone are observed in the animals which have been treated with both ethanol and methadone as compared to animals treated with methadone alone (see figure 13). Thus, chronic ethanol treatment does result in acceleration of methadone metabolism in the whole rat model. However, if other time points had been selected for study, other interpretations might have ensued simply

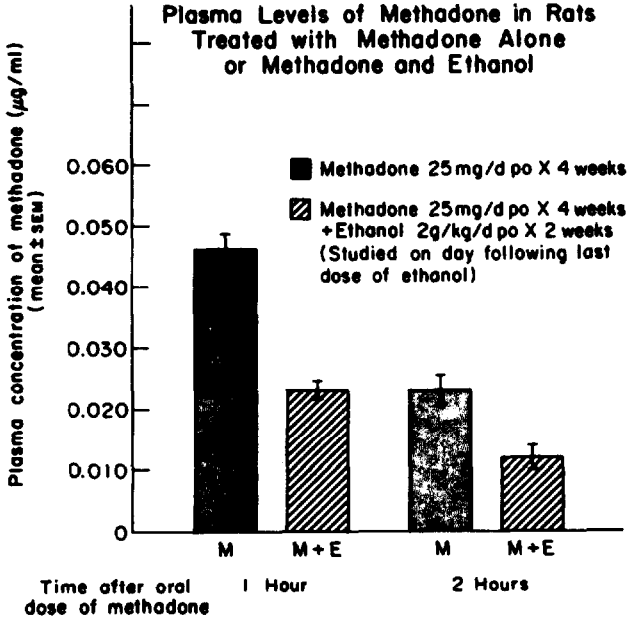
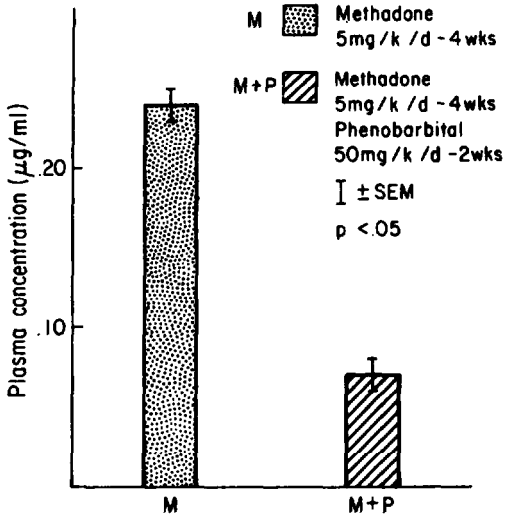


Figure 13

Plasma Levels of Methadone in Rats Treated with Methadone Alone as Compared with Methadone and Ethanol on Chronic Basis

because of the pharmacokinetic properties of methadone in a rat, i.e., the very rapid metabolism of methadone in this animal (Kreek 1981, Kreek 1978).

Similarly, studies have been carried out using the whole rat model to determine possible interactions between phenobarbital and methadone. Again, in these studies, animals are treated chronically with methadone plus phenobarbital or with methadone alone (Kreek 1978B). These studies have shown that plasma levels of methadone at 1 hour after dose administration are significantly lower in animals treated with methadone plus phenobarbital than in animals treated with methadone alone (Kreek 1978B) (see figure 14). It was also shown that the fecal excretion of methadone plus metabolites was significantly enhanced in phenobarbital-treated animals as compared to animals treated with methadone alone. Furthermore, it was critical to fully appreciate the pharmacokinetics of both methadone and phenobarbital in the rat model before this interaction could be properly studied.



Plasma levels of methadone at one hour after last subcutaneous dose in rats treated with methadone alone (5 mg/kg/d, s.c., for 3 weeks), or with methadone (5 mg/kg/d, s.c., for 3 weeks) and phenobarbital (50 mg/kg/d, s.c., for 1 week); determinations by gas liquid chromatography

Figure 14

Plasma Levels of Methadone in Rats Treated with Methadone Alone as Compared with Methadone and Phenobarbital on a Chronic Basis. Copyright 1978, Raven Press, N.Y. Kreek 1978B.

These studies were carried out because phenobarbital is the most potent enhancer of hepatic microsomal P450-dependent drug-metabolizing enzyme activity of all agents categorized as enhancers or "inducers" of hepatic P450-dependent drug-metabolizing enzyme systems.

This is an example of the use of animal models to study the effect of a model drug, with a known type of mechanism of action, on the disposition of a second drug. Prom these studies, it was predicted that, should any patient be placed on phenobarbital treatment, or abuse phenobarbital, while on chronic methadone treatment, methadone plasma levels probably would be significantly reduced and, probably, narcotic withdrawal symptoms would ensue. Thus, it was predicted that a drug interaction between methadone and phenobarbital would occur similar to that clinically observed and documented to occur between methadone and rifampin, and between methadone and phenytoin, with the same resultant precipitation of the narcotic abstinance syndrome. The first clinical report of such an interaction between phenobarbital and methadone in a chronically maintalned patient was published recently (Liu and Wang 1984). In this report, careful clinical observations, coupled with multiple determinations of methadone plasma levels, were made in a single patient observed to develop symptoms of narcotic withdrawal while in chronic methadone maintenance treatment, first unexplained, and later documented and verified to be due to chronic phenobarbital abuse. In this patient, it was shown that, during the period of phenobarbital abuse, plasma levels of methadone and the area under the plasma concentration time curve of methadone were significantly reduced as compared to similar indices of methadone disposition when that same patient was studied both before and some time following cessation of phenobarbital abuse, while taking methadone alone (Liu and Wang 1984).

In developing a strategy to identify, define, and elucidate the mechanisms of any drug interactions between drugs of abuse, or drugs of use and abuse, or agents used therapeutically in the treatment of drug abuse with other agents of use or abuse--although it may often be appropriate and suitable to use animal models or *in vitro* models--clearly, the most urgently needed studies are those which can be carried out in human beings and, thus, directly document the presence or absence of any pharmacokinetic or pharmacodynamic interactions of clinical significance in the human species. Such work is extremely difficult to carry out and is frustrating for a multitude of

reasons; this type of clinical research frequently is not perceived by critics, at least in advance of performance of such studies, to be of merit. Nevertheless, it is quite clear that once performed, especially when positive findings are made, clinical studies are the basis for not only more appropriate therapeutic management, or prevention, of the effects of concomitant use of two interacting agents, but also serve as the basis for making predictions of future drug interactions which may be of clinical significance in humans. Thus, properly conducted studies of drug interactions in humans using rigorously and appropriately selected study subjects should be encouraged and supported.

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